No. 10-844

IN THE

Supreme Court of the United States

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,

Petitioners,

v.

NOVO NORDISK A/S AND NOVO NORDISK INC.,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF IN OPPOSITION

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QUESTION PRESENTED

The Hatch-Waxman Act includes a narrow counterclaim under which, if a listed "patent does not claim … an approved method of using the drug," a district court may order the patentee "to correct or delete the patent information submitted … under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii). Petitioners concede that the patent here *does* claim an approved method of use, and they seek judicially ordered revision of information that was *not* submitted under the specified subsections of the statute and that is, in any event, correct. Thus, the "question presented" in the petition does not exist. Rather, the question presented is:

Whether the court of appeals correctly concluded, in a case of first impression, that neither the cause of action nor the remedy provided for by the Hatch-Waxman Act's counterclaim provision is available to petitioners on the particular facts of this case.

RULE 29.6 STATEMENT

Pursuant to this Court's Rule 29.6, undersigned counsel state that:

Novo Nordisk Inc. is a wholly owned subsidiary of Novo Nordisk US Holdings, Inc. No publicly held company owns 10% or more of Novo Nordisk Inc.'s stock. Novo Nordisk US Holdings, Inc. is a wholly owned subsidiary of Novo Nordisk A/S, a public limited liability company. Novo Nordisk A/S is the only publicly held company that owns 10% or more of Novo Nordisk US Holdings, Inc.'s stock.

Novo A/S, a private limited liability company, is Novo Nordisk A/S's controlling shareholder. No publicly held company owns 10% or more of Novo Nordisk A/S's stock. Novo A/S is a wholly owned subsidiary of the Novo Nordisk Foundation, a Danish self-governing institution. No publicly held company owns 10% or more of Novo A/S's stock.

Novo Nordisk Foundation has no parent company, and no publicly held company owns 10% or more of its stock.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Regulations

Other Authorities

BRIEF IN OPPOSITION

Respondents Novo Nordisk A/S and Novo Nordisk Inc. respectfully submit that the petition for a writ of certiorari should be denied.

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-52a) is reported at 601 F.3d 1359. The order denying rehearing (Pet. App. 53a-64a) is reported at 615 F.3d 1374. The district court's decisions on the counterclaim issue (Pet. App. 67a-72a & 73a-103a) are reported at 656 F. Supp. 2d 729 and 649 F. Supp. 2d 661. Its injunction (Pet. App. 65a-66a) is available at 2009 U.S. Dist. LEXIS 88551. Subsequent decisions of the district court on subject-matter jurisdiction (App., *infra*, 1a-10a) and validity and enforceability (App., *infra*, 11a-106a) are available at 2010 U.S. Dist. LEXIS 106729 and 2011 U.S. Dist. LEXIS 4889, respectively.

JURISDICTION

The court of appeals entered an interlocutory judgment on April 14, 2010, and denied rehearing on July 29, 2010. On October 18, 2010, the Chief Justice extended the time to file a petition for a writ of certiorari to and including December 23, 2010. No. 10A380. Petitioners invoke the jurisdiction of this Court under 28 U.S.C. § 1254(1).

The federal courts lack subject-matter jurisdiction over this dispute as a result of petitioners' election in April 2008 to withdraw their certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV"), on which jurisdiction previously rested (*see Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678 (1990)), and to replace it with a statement under 21 U.S.C.

§ 355(j)(2)(A)(viii) ("section viii"), which does not support federal jurisdiction. *Compare Novo Nordisk Inc.* v. *Mylan Pharms. Inc.*, 2010 U.S. Dist. LEXIS 32569 (D.N.J. Mar. 31, 2010) (so holding), *with* App., *infra*, 1a-10a (contra). As explained below, this jurisdictional issue has not yet been reviewed by the Federal Circuit.

STATUTORY PROVISIONS INVOLVED

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly known as the Hatch-Waxman Act, amended various provisions of the Federal Food, Drug, and Cosmetic Act, including 21 U.S.C. § 355 (Pet. App. 104a-195a), and the Patent Act, including 35 U.S.C. § 271(e)(2) (App., *infra*, 108a-109a). The counterclaim provision at issue here (Pet. App. 145a-146a) states in full:

> **(ii) Counterclaim to infringement action**
>
> **(I) In general**
>
> If an owner of the patent or the holder of the approved application under subsection (b) of this section for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the [generic] applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) of this section on the ground that the patent does not claim either—
>
> (aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) No independent cause of action

Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

21 U.S.C. § 355(j)(5)(C)(ii) (added by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066).

STATEMENT

The district court entered a "mandatory injunction" under the Hatch-Waxman Act's counterclaim provision, ordering respondents to alter the entirely correct "use code narrative" previously submitted to, and accepted by, the Food and Drug Administration in connection with a patented method of diabetes drug therapy. Pet. App. 65a-66a. The Federal Circuit—in the first appellate decision construing the Hatch-Waxman counterclaim since it was enacted by Congress in 2003—ruled that "[b]ecause [petitioners do] not have a statutory basis to assert a counterclaim requesting such injunctive relief, this court reverses and vacates the injunction." Pet. App. 2a-3a.

1. The Hatch-Waxman Act governs many aspects of the intense competition among makers of branded and generic drugs, including patented drug products and methods. *See generally Janssen Pharmaceutica, N.V.* v. *Apotex, Inc.*, 540 F.3d 1353, 1355-57 (Fed. Cir. 2008). In particular, Section 505 of the Federal Food, Drug, and Cosmetic Act, as amended by the Hatch-Waxman Act, regulates the process by which drug makers can secure FDA approval of new drugs, as well as the avenues of judicial relief avail-

able to patent holders and their generic competitors. *See* 21 U.S.C. § 355.

Section 505(a) prohibits the sale of a new drug "unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) requires a pioneer company seeking to manufacture a new drug to file a new drug application (NDA), together with a variety of information on the safety and effectiveness of the drug. *See id.* § 355(b)(1)(A)-(G). Subsection (c) addresses amendments to and approval of NDAs, and authorizes certain lawsuits by the NDA holder to enforce its rights. *Id.* § 355(c)(1)-(3).

Section 505(b) requires the NDA applicant to "file ... the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug," and requires FDA to "publish information submitted under [that requirement]." 21 U.S.C. § 355(b)(1)(G). FDA publishes a list of patents claiming approved drug products or methods, along with the statutory "patent information" and other information required by regulation, in the "Orange Book." *See Janssen*, 540 F.3d at 1355.

Section 505(j) allows a generic competitor to file an abbreviated new drug application (ANDA) with FDA, relying on the research into safety and effectiveness previously conducted by a pioneer drug maker. It requires generic companies making ANDA filings to include a certification that (I) no patent covering the listed drug has been listed in the Orange Book; (II) the patent has expired; (III) the patent will expire on a particular date and approval of

the ANDA should be deferred until expiration; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. 21 U.S.C. § 355(j)(2)(A)(vii). If the applicant does not seek approval for a use that is patented, it may instead file a "section viii statement," and seek to "carve out" of its proposed label any patented uses. *Id.* § 355(j)(2)(A)(viii); *see Purepac Pharm. Co.* v. *TorPharm, Inc.*, 354 F.3d 877, 880 (D.C. Cir. 2004) ("whereas applicants use paragraph IV certifications to challenge the validity of admittedly applicable patents, they use section viii statements to assert that patents do not apply").

The Hatch-Waxman Act provides that the filing of a Paragraph IV certification by an ANDA applicant is an act of patent infringement. 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S 661, 678 (1990). If the pioneer company brings suit within 45 days of receiving notice of the Paragraph IV certification, the FDA may not approve the ANDA for 30 months. 21 U.S.C. § 355(j)(5)(B)(iii). As an incentive for generic companies to bear the cost of such an infringement suit, the Hatch-Waxman Act grants the first company to submit a Paragraph IV certification for a particular drug a 180-day period of generic marketing exclusivity, during which time FDA will not approve a later-filed Paragraph IV ANDA based on the same NDA. *Id.* § 355(j)(5)(B)(iv).

In 2001, the Federal Circuit held that a generic competitor could not resist a Paragraph IV infringement suit on the ground that the asserted patent was improperly listed in the Orange Book. *Mylan Pharms., Inc.* v. *Thompson*, 268 F.3d 1323 (Fed. Cir. 2001). There, the ANDA applicant for generic BuSpar (buspirone hydrochloride) argued

that the patent listed in the Orange Book "did not claim BuSpar or an approved method of using BuSpar." *Id.* at 1331. The Federal Circuit held that the statute did not authorize judicial delisting of an improperly listed patent. *Id.* at 1332.

In 2003, the Hatch-Waxman Act was amended to respond to the *Mylan* decision by authorizing a limited counterclaim for ANDA filers in Paragraph IV lawsuits. The counterclaim (echoing the language of *Mylan*) requires the generic applicant to prove that the patent "does not claim ... the drug ... or ... an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I). If the generic applicant can carry this burden, it may "seek[] an order requiring the [patentee] to correct or delete the patent information submitted ... under subsection (b) or (c) of this section." *Ibid.*

Section 505(b) requires NDA filers to provide FDA with specified "patent information": "The applicant shall file with the application the *patent number* and the *expiration date* of any patent which claims the drug … or which claims a method of using such drug." 21 U.S.C. § 355(b)(1)(G) (emphases added). Section 505(c) states that "[i]f the patent information described in subsection (b) of this section could not be filed with the submission of an application," the holder of an approved application "shall file with the Secretary the *patent number* and the *expiration date* of any patent which claims the drug … or which claims a method of using such drug." *Id.* § 355(c)(2) (emphases added).

Separate and apart from the "patent information" specifically required of NDA filers by subsections (b) and (c) (*i.e.*, the patent number and expiration date), FDA has promulgated regulations that

require NDA applicants to provide additional information not mandated by statute. *See* 68 Fed. Reg. 36,676, 36,703-05 (June 18, 2003) (codified at 21 C.F.R. pt. 314) (Pet. App. 196a-210a); 72 Fed. Reg. 21,266, 21,268-69 (Apr. 30, 2007). This information is provided to FDA on Form 3542 (Pet. App. 211a-214a), and includes "the description of the approved indication or method of use" for a drug. Pet. App. 213a; *see also* 21 C.F.R. § 314.53(c)(2)(ii)(P). This description (provided in Box 4.2b of the form) is popularly known as the "use code narrative." FDA includes use code narratives with the statutory "patent information" in the Orange Book.

2. Respondents sell the drug repaglinide under the brand name PRANDIN®. Repaglinide is approved for treating diabetes when used alone (monotherapy) or in combination with other specified drugs. C.A. App. A464; A821-A839. In 2004, respondents were issued U.S. Patent No. 6,677,358, Claim 4 of which claims a method for using repaglinide in combination with metformin to treat type 2 diabetes. C.A. App. A69-A79. Following the issuance of the '358 patent, respondents submitted a proposed use code narrative to FDA (C.A. App. A801-A803), which published the following use code in the Orange Book: "U-546—Use of repaglinide in combination with metformin to lower blood glucose." C.A. App. A888; A1234-A1235.

In 2005, petitioners filed an ANDA for generic repaglinide that included a Paragraph IV certification that the '358 patent was invalid or would not be infringed by the sale of generic repaglinide. C.A. App. A239-A242. Respondents sued for infringement under the provisions of the Hatch-Waxman Act. Petitioners eventually stipulated that its ANDA for repaglinide would infringe the '358 patent if it "in-

clude[d] a label that discusses the combination of metformin and repaglinide." C.A. App. A236; *see also* Pet. 19 n.10.

In April 2008, petitioners amended their ANDA and, with respect to Claim 4, replaced their Paragraph IV certification with a section viii statement that would "carve out" repaglinide-metformin combination therapy from its otherwise infringing label. C.A. App. A257-A260. In December 2008, the FDA indicated that this carve-out would be permitted. C.A. App. A625-A643. Shortly thereafter, respondents moved for reconsideration on the ground that allowing this carve-out would render generic repaglinide less safe and effective. C.A. App. A644-A657; *see also* C.A. App. A658-A663.

During the same time period, respondents revised the PRANDIN® label pursuant to an FDA directive "requesting changes to the professional labeling of all oral anti-diabetic drugs." C.A. App. A667. This FDA directive required respondents to "[r]eplace all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) with the following sentence: 'Prandin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.'" C.A. App. A667-A668.

In May 2009, respondents submitted an amended FDA Form 3542, which included an updated use code narrative to reflect precisely the new FDA-mandated indication for PRANDIN®. C.A. App. A670-A674. Respondents explained to FDA that "[t]he information being submitted is to amend the use code relating to [the '358 patent] to correspond with the change in labeling required by FDA in [its directive]." C.A. App. A670. FDA published the following use code in

the Orange Book: "U-968—A method for improving glycemic control in adults with type 2 diabetes mellitus." C.A. App. A912; A840.

FDA then determined that respondents' request for reconsideration was "moot" in light of the new use code, as the "factual predicate" on which FDA's permissive carve-out decision had rested no longer applied. C.A. App. A664-A666. Despite repeated entreaties from petitioners, FDA declined to allow their section viii carve-out. C.A. App. A810-A814; A815-A820. Petitioners are thus required to include repaglinide-metformin combination therapy in their labeling, which is stipulated to infringe Claim 4 of the '358 patent, the only claim at issue in this case. C.A. App. A236-A238.

3. After FDA declined to allow petitioners to proceed under section viii, they sought in the district court "an order requiring [respondents] to correct the use code information submitted by [respondents]." C.A. App. A1259. As a statutory basis, they cited the counterclaim added by the 2003 amendments to the Hatch-Waxman Act. *Ibid.* Respondents resisted on the ground that both the cause of action asserted and the relief sought were not authorized by that counterclaim provision.

The district court denied respondents' motion to dismiss the "use code" counterclaim (Pet. App. 73a-103a) and later granted summary judgment to petitioners on this counterclaim (Pet. App. 67a-72a). The district court directed respondents by "mandatory injunction" to "submit[] to FDA an amended Form FDA 3542 that reinstates its former U-546 listing for Prandin and describes claim 4 of the '358 patent in section 4.2b as covering 'the use of repaglinide

in combination with metformin to lower blood glucose.'" Pet. App. 65a-66a.

4. On respondents' interlocutory appeal, the Federal Circuit vacated the injunction in the 2-1 decision that is the subject of this petition. Pet. App. 1a-52a.

The majority, "detect[ing] no ambiguity in the statutory language," held that "the Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug." Pet. App. 12a. This result, the majority explained, was compelled by the text, structure, and history of the counterclaim provision, including the Federal Circuit's *Mylan* decision. Pet. App. 11a-14a. Because petitioners conceded that the listed patent "*does* claim an approved method of use" (C.A. Stay Opp. 13), the counterclaim was not available to petitioners.

The majority also held that "the terms of the counterclaim provision do not authorize an order compelling the patent holder to change its use code narrative." Pet. App. 14a-15a. That is because the counterclaim provision only authorizes an order compelling the patentee "to correct or delete *the patent information* submitted ... under subsection (b) or (c)" (21 U.S.C. § 355(j)(5)(C)(ii)(I) (emphasis added)), and "the Act defined the term 'patent information' as 'the patent number and the expiration date.'" Pet. App. 15a (citing *Valley Drug Co.* v. *Geneva Pharms. Inc.*, 344 F.3d 1294, 1296-97 (11th Cir. 2003)). Thus the counterclaim, even if available, did not authorize the injunction that the district court issued.

Concurring, Judge Clevenger "agree[d] with Judge Rader's analysis of the relevant statutory provisions in this case and therefore join[ed] the opinion

he writes for the court." Pet. App. 19a. Judge Clevenger wrote separately to emphasize that "Novo did nothing that was illegal or forbidden" and that "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 19a, 21a.

Judge Dyk dissented, urging adoption of petitioners' expansive reading of the counterclaim provision and arguing that "[a]n error in an Orange Book use code" should be "subject to correction" under the counterclaim provision. Pet. App. 43a; *see also* Pet. App. 57a-64a (Gajarsa, J., dissenting from denial of rehearing).

5. Following the Federal Circuit's interlocutory decision, proceedings on the remaining issues resumed in the district court.

Respondents renewed their motion to dismiss the lawsuit for lack of subject-matter jurisdiction, arguing that petitioners' decision to convert from a Paragraph IV certification to a section viii statement defeated the jurisdictional basis for suit. The district court, however, denied that motion. App., *infra*, 1a-10a.

On January 19, 2011, after a bench trial, the district court issued a decision concluding that Claim 4 is both invalid for obviousness and unenforceable for inequitable conduct. App., *infra*, 11a-106a. Respondents have filed a notice of appeal from the judgment entered contemporaneously with that decision.

REASONS FOR DENYING THE PETITION

The decision below is correct and does not conflict with any decision of this Court or any court of appeals. Moreover, the interlocutory nature of the decision and an antecedent jurisdictional problem make this case an inappropriate one in which to re-

solve the scope of the Hatch-Waxman Act's counterclaim provision.

I. THIS IS AN INAPPROPRIATE VEHICLE IN WHICH TO REVIEW THE SCOPE OF THE HATCH-WAXMAN COUNTERCLAIM

This is the first case in which any court has substantively construed or applied the Hatch-Waxman Act's counterclaim in a published or electronically available decision. Although petitioners assert that the issue is "recurring" (Pet. 17), they cannot identify any other case in which it has arisen in the past, and there is nothing to suggest that it will arise again any time soon. That is reason enough to deny the petition. *Boag* v. *MacDougall*, 454 U.S. 364, 368 (1982) (Rehnquist, J., dissenting) ("'To remain effective, the Supreme Court must continue to decide only those cases which present questions whose resolution will have immediate importance far beyond the particular facts and parties involved'") (quoting Chief Justice Vinson, Address before the American Bar Association (Sept. 7, 1949)).

Although petitioners and their *amici* suggest that the decision below has implications for the entire generic pharmaceutical industry, it is actually limited to the narrow, and perhaps unique, circumstances of this case, where a method (not product) claim recites some (but not all) FDA-approved uses of a drug, FDA has mandated a broad approved indication for the drug that includes both patented and non-patented uses, and the brand manufacturer has submitted a use code for its patented method that precisely tracks the FDA-mandated indication.

The leading generic companies and their trade association have all filed briefs in this Court, but they have not identified a single other patent listed in the Orange Book with these characteristics. On

the contrary, they ask the Court to "assume" that hypothetical (and unlikely) scenarios might be affected by the decision below. *See* Apotex Br. 4 ("assume" a scenario involving "drug X"); Mylan Br. 9 ("assume" a scenario involving "disease 1" and "disease 2").

Petitioners' bid to make the issue sound more important than it is rests on their hyperbolic assertion that the Federal Circuit's construction of the counterclaim, which is available only in Paragraph IV infringement proceedings, somehow "eviscerates" the section viii procedure, which is an *alternative* to Paragraph IV. Pet. 19. This is every bit the *non sequitur* it appears to be. Section viii and Paragraph IV are mutually exclusive—the ANDA applicant must choose one or the other. *Purepac Pharm. Co.* v. *TorPharm, Inc.*, 354 F.3d 877, 882 (D.C. Cir. 2004). If the generic proceeds via section viii, the counterclaim is *never* available under *any* circumstances: By its terms, the counterclaim applies *only* in infringement suits brought in response to a Paragraph IV certification. 21 U.S.C. § 355(j)(5)(C)(ii). The counterclaim was enacted in response to *Mylan*, a Paragraph IV case, and section viii was not even on the congressional radar screen. Indeed, the counterclaim has *nothing to do* with section viii carve-outs, rendering many of the arguments advanced by petitioners and their *amici* entirely irrelevant.

The counterclaim issue arose in this case only because petitioners first submitted a Paragraph IV certification, provoking an infringement suit by respondents; then, *after stipulating to infringement*, converted to a section viii statement that sought to carve out the patented methods of use; and then proceeded to assert the counterclaim in the (Paragraph IV) infringement litigation. To the extent the deci-

sion below precludes such an applicant from invoking the counterclaim, it simply ensures a level playing field with generics who attempt to avoid litigation by proceeding under section viii.

Moreover, the unusual arc of this litigation gives rise to two case-specific issues that are independent impediments to immediate review of the counterclaim issue: Caraco's conversion from Paragraph IV to section viii deprived the federal courts of jurisdiction, and the district court's ensuing judgment (if not *ultra vires*) could effectively moot the issue relating to the counterclaim.

A. The Federal Courts Lack Jurisdiction Over The Dispute

This Court must satisfy itself of its jurisdiction at the threshold before proceeding to the merits. *Steel Co.* v. *Citizens for a Better Env't*, 523 U.S. 83, 88-89 (1998); *Permoli* v. *New Orleans*, 44 U.S. (3 How.) 589, 609 (1845). Accordingly, certiorari will be denied in the absence of federal jurisdiction. *Good Shot* v. *United States*, 179 U.S. 87, 88-89 (1900) ("the writ of certiorari cannot properly be issued to require the court to send up a cause over which it has no jurisdiction for determination on the merits"); *see also*, *e.g.*, *California* v. *Gordon*, 420 U.S. 938 (1975) ("Certiorari denied, there being no present case or controversy such as to confer jurisdiction on this Court"); *Lawrence* v. *Arizona*, 269 U.S. 585 (1926) (per curiam).

In this case, respondents raised a substantial jurisdictional challenge in the district court—*viz.*, that petitioners deprived the federal courts of subject matter jurisdiction over the case when they converted from a Paragraph IV certification to a section viii statement as to Claim 4 of the '358 patent. This

jurisdictional issue was decided by the district court only after the Federal Circuit issued the decision that petitioners ask this Court to review. *See* App., *infra*, 1a-10a. As a result, the jurisdictional issue has not yet been reviewed by the Federal Circuit.

The Hatch-Waxman Act provides for jurisdiction in ANDA cases if and only if the generic applicant maintains a Paragraph IV certification with regard to the patent claim(s) at issue. *See Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 678 (1990) (Section 271(e)(2) of the Patent Act, 35 U.S.C. § 271(e)(2), creates "a highly artificial act of infringement that consists of submitting an ANDA ... containing *the fourth type of certification* that is in error as to whether commercial manufacture, use, or sale of the new drug (none of which, of course, has actually occurred) violates the relevant patent") (emphasis added). If the generic applicant's ANDA does not contain an effective Paragraph IV certification with respect to the patent claim-in-suit, there is no federal jurisdiction.

Although petitioners originally filed a Paragraph IV certification with respect to Claim 4 of the '358 patent, initially creating jurisdiction for this lawsuit, they subsequently amended their ANDA by withdrawing the Paragraph IV certification and replacing it with a section viii statement. *See* 21 C.F.R. § 314.94(a)(12)(viii) ("Once an amendment … is submitted, the [ANDA] application will no longer be considered to contain the prior certification").

The Hatch-Waxman Act does not provide for jurisdiction where an ANDA applicant files a section viii statement. *See Purepac Pharm. Co.* v. *Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C. 2002), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004). The Declaratory

Judgment Act includes express statutory limitations on declaratory judgment actions in the patent context (*see* 28 U.S.C. § 2201(b); 35 U.S.C. § 271(e)(5)) and, in any event, "is not an independent source of federal jurisdiction." *Schilling* v. *Rogers*, 363 U.S. 666, 677 (1960). Thus, there is no basis for federal jurisdiction in a lawsuit involving a patent claim subject only to a section viii statement, as this one is.

Elementary principles of federal jurisdiction require that a justiciable controversy exist not only at the initiation of a lawsuit but throughout. *Arizonans for Official English* v. *Arizona*, 520 U.S. 43, 67 (1997). Thus, petitioners' strategic choice to proceed under section viii rather than Paragraph IV divested the federal courts of jurisdiction over any challenges involving Claim 4 of the '358 patent—the only patent claim at issue in this litigation.

Another district court considering a different manufacturer's ANDA for the same drug (generic repaglinide) has squarely held that the absence of a Paragraph IV certification as to Claim 4 of the '358 patent means that there is no federal jurisdiction. *Novo Nordisk Inc.* v. *Mylan Pharms. Inc.*, 2010 U.S. Dist. LEXIS 32569, at *26-31 (D.N.J. Mar. 31, 2010). To be sure, the district court in this case reached the directly contrary conclusion (App., *infra*, 1a-10a); but that conflict will be presented to the Federal Circuit for resolution on appeal from the final judgment in this case. That appeal, however, has yet to be briefed, argued, or decided.

Thus, if the Court were to grant certiorari to review the scope of the Hatch-Waxman counterclaim, it would first have to resolve the jurisdictional issue without benefit of the court of appeals' analysis. *See DTD Enters.* v. *Wells*, 130 S. Ct. 7, 8 (2009) (state-

ment of Kennedy, J., respecting denial) ("If [the Court] were to grant the petition [it] would be required to ... confront a procedural obstacle unrelated to the question presented"); *see also*, *e.g.*, *Wrotten* v. *New York*, 130 S. Ct. 2520, 2520 (2010) (statement of Sotomayor, J., respecting denial) ("Granting the petition for certiorari at this time would require [the Court] to resolve the threshold [jurisdictional] question"). "Under these circumstances, it is best to deny the petition." *DTD*, 130 S. Ct. at 8 (statement of Kennedy, J.).

B. The Counterclaim Issue Would Be Reviewable After Final Decision

Furthermore, following the decision of the Federal Circuit challenged in the petition, the district court proceeded to resolve petitioners' challenges to the validity and enforceability of Claim 4 of the '358 patent. Those issues too remain to be decided by the Federal Circuit.

Where "[t]he decree that was sought to be reviewed by certiorari … was not a final one, [that] fact … alone furnishe[s] sufficient ground for the denial of the application." *Hamilton-Brown Shoe Co.* v. *Wolf Bros. & Co.*, 240 U.S. 251, 258 (1916). This is because "a mere denial of the writ to an interlocutory ruling of the Circuit Court of Appeals does not limit [the Court's] power to review the whole case when it is brought here by … certiorari on final decree." *Toledo Scale Co.* v. *Computing Scale Co.*, 261 U.S. 399, 418 (1923); *see also Hamilton-Brown Shoe*, 240 U.S. at 258.

Thus, if the Court declines interlocutory review and waits for a petition for certiorari from a final judgment, it is able to evaluate all of the issues, presented together on a fully developed record, with no

attendant prejudice to any party. This approach also alleviates the risk that the issue will become moot or otherwise of diminished significance in light of the final disposition. *Am. Constr. Co.* v. *Jacksonville, Tampa & Key West Ry. Co.*, 148 U.S. 372, 384 (1893) ("many orders made in the progress of a suit become quite unimportant by reason of the final result, or of intervening matters"). Therefore, as a matter of course, and regardless of the importance of the legal issues presented, this Court traditionally declines review of interlocutory decisions. *Va. Military Inst.* v. *United States*, 508 U.S. 946 (1993) (Op. of Scalia, J., respecting denial) ("We generally await final judgment in the lower courts before exercising our certiorari jurisdiction").

Petitioners seek review of an interlocutory injunction, from which respondents took an interlocutory appeal to the Federal Circuit. Subsequent to the filing of the petition for a writ of certiorari, the district court decided petitioners' invalidity and unenforceability counterclaims. Respondents have noticed an appeal to the Federal Circuit. Rather than reviewing this case piecemeal, the better course is for this Court to decline certiorari now. It can then review, if necessary, any issues that the parties may wish to bring to its attention, in a single proceeding, after the Federal Circuit decides the remaining issues in this case.

Moreover, if either the invalidity or unenforceability holding were affirmed (assuming, *dubitante*, the existence of federal jurisdiction), the counterclaim issue could be rendered of little or no continuing importance to petitioners. It makes little sense for this Court to invest its resources, or the parties theirs, on an issue that might be rendered inconsequential by the pending appeal.

II. THE FEDERAL CIRCUIT CORRECTLY CONSTRUED THE SCOPE OF THE HATCH-WAXMAN COUNTERCLAIM

Although petitioners complain that the Federal Circuit "violated numerous precedents of this Court, including precedent interpreting the Hatch-Waxman Act itself" (Pet. 17), they concede that this Court "has never addressed the Act's provisions governing approval of generic marketing" (*id.* at 5). The claimed conflict with this Court's decisions—like their prediction of impending "disaster" (*id.* at 35)—is, to put it mildly, wildly overstated.

The counterclaim provision states that, if the generic company defendant in a Paragraph IV lawsuit proves that "the patent does not claim … an approved method of using the drug," the court may order the patentee "to correct or delete the patent information submitted … under subsection (b) or (c) of this section." 21 U.S.C. § 355(j)(5)(C)(ii). The Federal Circuit construed this provision by applying well-settled principles of statutory construction. *See*, *e.g.*, *Hughes Aircraft Co.* v. *Jacobson*, 525 U.S. 432, 438 (1999) ("statutory construction … begins with the language of the statute") (internal quotation marks omitted); *Barnhart* v. *Thomas*, 540 U.S. 20, 26 (2003) (construction favored that is "quite sensible as a matter of grammar"); *Envtl. Def.* v. *Duke Energy Corp.*, 549 U.S. 561, 574 (2007) (identical words used in the same act are presumed to have the same meaning).

Using these unchallenged tools, the court of appeals held that the text and structure of the Hatch-Waxman Act establish that the counterclaim is not available if the patent-in-suit *does* claim "an approved method of using the drug," even if other ap-

proved methods are not patented; and that the "patent information" subject to correction or deletion is limited to the patent number and expiration date—the only "information" required by (or even mentioned in) Section 505(b) and (c). Pet. App. 11a-16a.

Petitioners acknowledge, as they must, that the construction of the counterclaim provision adopted by the majority below is consistent with the statutory language. Pet. 30 (conceding "that 'an,' when qualified by a negative, *can* mean 'any'") & 35 (conceding that "§ 505(b) and (c) mention only the patent number and expiry"). That should end the matter, since the Judiciary's "charge is to give effect to the law Congress enacted." *Lewis* v. *City of Chicago*, 130 S. Ct. 2191, 2200 (2010). *All* of the policy arguments advanced by petitioners and their *amici* suggest, at most, "a problem for Congress, not one that federal courts can fix." *Ibid.*

A. The Counterclaim Is Not Available Where The Patent Claims An Approved Method Of Use

The majority in the court below explained that the counterclaim was enacted to "correct the specific issue raised in *Mylan*, *i.e.*, to deter pioneering manufacturers from listing patents that were not related at all to the patented product or method" (Pet. App. 13a), and it is undisputed that the construction of the counterclaim adopted in this case entirely addresses the *Mylan* situation.

In *Mylan*, the Federal Circuit held that a generic competitor could not obtain judicial relief to delist an improperly listed patent because it "did not claim ... an approved method of using [the drug]." 268 F.3d 1323, 1331 (Fed. Cir. 2001). Because a delisting cause of action was not explicitly authorized by the Hatch-Waxman Act, the court reasoned that Mylan's

suit was "an impermissible attempt by a private party to enforce the [Federal Food, Drug, and Cosmetic Act]." *Id.* at 1329-30 (citing *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001)). In response, Congress enacted a narrow provision authorizing a counterclaim to delete or correct patent information where "the patent does not claim …. an approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii)(I)(bb). The majority's construction ensures that the counterclaim is available in the *Mylan* situation, and thus fully effectuates the 2003 amendment. Petitioners' argument that the majority unduly limited the counterclaim is nothing other than a policy-based plea to extend it *beyond* the *Mylan* situation that Congress set out to address. *See* Pet. App. 21a (Clevenger, J., concurring) ("The counterclaim statute, which the dissent would expand beyond its literal reach, was designed to cure the situation presented in *Mylan*.").

Under the counterclaim, *if* a patent was improperly listed because it does not claim an approved method of using the drug, *then* the court may order the deletion or correction of the "patent information." In this case, however, petitioners have conceded that respondents' '358 patent "is properly listed in the Orange Book" because it "covers an FDA-approved method of using the referenced drug." C.A. App. A675; *see also* C.A. Stay Opp. 13 (petitioners' concession that the '358 patent "*does* claim an approved method of use"). There is thus nothing to delete or correct.

The operative language of the counterclaim provision requires the generic competitor to prove that the listed patent "does not claim ... an approved method" of using the drug. In light of their concession, petitioners argue that "an approved method" should be interpreted as "all approved methods" or "every approved method." As the majority explained,

however, "[w]hen an indefinite article is preceded and qualified by a negative, standard grammar generally provides that 'a' means 'any.'" Pet. App. 12a (citing dictionary definitions). Indeed, that is the *only* definition dictionaries provide where, as here, the article is preceded and qualified by a negative ("does not claim"). *See* Random House Webster's Unabridged Dictionary 1 (2d ed. 2001) (defining the indefinite article "a" as "any" in the example "not a one"); American Heritage Dictionary of the English Language 1 (4th ed. 2006) (defining "a" solely as "[a]ny" in the example "not a drop to drink").

Petitioners further concede that "'an,' when qualified by a negative, *can* mean 'any.'" Pet. 30. That concession is fatal: The majority made an interpretative decision, applying a clearly accepted definition of the word "an." It did not "rewr[i]te the statute" or "change[] the statute's meaning," in contravention of the principles of statutory interpretation, as petitioners allege. Pet. 30-31.

Petitioners' objection that "an approved method" does not *necessarily* mean "any approved method" (*see* Pet. 30-31) is unsupported by any authority and irreconcilable with the doctrine that statutes are to be read *in pari materia*. The Hatch-Waxman Act requires listing of patents that claim "*a* method of using such drug" (21 U.S.C. § 355(b)(1)) and the counterclaim is available if the owner of a patent "for the drug ... *a* use of which is claimed by the patent" initiates an infringement action (*id.* § 355(j)(5)(C)(ii)(I)) (both emphases added). In both instances it is clear from context that the indefinite article "a" means *any*, as petitioners have previously acknowledged. Pet. C.A. Br. 38 n.2 ("an NDA holder may list a patent if it covers any approved use"). Reading "an approved method" the same way is the only way to harmonize the statute as a whole, as the majority correctly recognized. Pet. App. 12a ("Therefore, the

Hatch-Waxman Act authorizes a counterclaim only if the listed patent does not claim any approved methods of using the listed drug").

The dissenting judge below acknowledged that adopting petitioners' alternative construction would require reading into the statute a word—"associated"—that Congress did not include. *See* Pet. App. 42a-43a (suggesting that the counterclaim provision be judicially amended to read "does not claim ... an [associated] approved method"). But adding a term to a statute "from which it is conspicuously absent more closely resembles inventing a statute rather than interpreting one." *Hardt* v. *Reliance Standard Life Ins. Co.*, 130 S. Ct. 2149, 2156 (2010) (internal quotation marks omitted).

Petitioners contend, however, that the majority "'render[ed] superfluous' the term 'correct.'" Pet. 32 (citing *Astoria Fed. Sav. & Loan Ass'n* v. *Solimino*, 501 U.S. 104, 112 (1991)). Not so: If a patent was improperly listed because it does not claim an approved method of using the drug, then the court may order either delisting or correction of the patent number and expiration date. In most cases in which a generic competitor proves that the listed patent does not claim an approved method, the appropriate remedy will be delisting. *See* 21 U.S.C. § 355(b)(1) (listing requirement applies to "any patent ... which claims a method of using such drug"). But there may also be instances in which the NDA holder lists the wrong patent: A brand-name company with a large portfolio of patents, with several patents in similar fields of use, could well have multiple NDA applications on related drugs and methods. If an error were made in listing a patent (for example, the wrong patent number were given), the Hatch-Waxman counterclaim authorizes the court to order correction of the listed patent number without requiring a resubmission by the NDA holder. In this way, Congress

completely addressed the *Mylan* situation that prompted the 2003 amendment.

There is good reason to restrict the counterclaim to the *Mylan* situation under this Court's precedents. The counterclaim is an *exception* to the rule that private litigants may not challenge submissions to FDA (*Buckman*, 531 U.S. at 348-51), and must be construed narrowly to avoid swallowing that rule. (Tellingly, petitioners do not cite *Buckman* or attempt to address this point.) If the counterclaim is to be extended beyond *Mylan*, then such an extension is a task for Congress, not this Court. *See Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437, 457 (2007) (any such "'loophole' ... is properly left for Congress to consider, and to close if it finds such action warranted"); *Cardiac Pacemakers, Inc.* v. *St. Jude Med., Inc.*, 576 F.3d 1348, 1362-65 (Fed. Cir. 2009) (en banc) ("it is Congress's right, not the courts', to extend the statute beyond the ... problem it was designed to fix").

Contrary to petitioners' contention (Pet. 1, 27-29), the decision below is not "inconsistent" or in "conflict" with *Teva Pharm. USA, Inc.* v. *Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010). The D.C. Circuit did not construe the Hatch-Waxman counterclaim; rather, it referenced the provision in passing in construing an entirely different provision of the Hatch-Waxman Act, in a manner that is entirely consistent with the Federal Circuit's reading of the counterclaim provision. *See id.* at 1315 n.4 ("The purpose of this [counterclaim] procedure, says Teva, is to offer generics a means of combating brand companies' practice of delaying generic competition by listing 'sham patents,' baiting a generic into filing a paragraph IV certification, and then filing an infringement suit").

Moreover, both *Teva* and the decision below make clear that it is *Congress's* role to balance the interests of brand and generic manufacturers, and that FDA and the courts must respect and adhere to such congressional determinations (including the compromises they inevitably reflect). *Compare Teva*, 595 F.3d at 1316 ("FDA may not … change the incentive structure adopted by the Congress," for "the agency is bound not only by the ultimate purposes Congress has selected but by the means it has deemed appropriate") (emphasis and internal quotation marks omitted), *with* Pet. App. 16a (agency interpretations that are "at odds with the plain language of the statute itself" serve to "upset the careful balance" of the statute and must be rejected). Both courts are in full agreement that the statute must be enforced as written. That is of course this Court's view too. *Lewis*, 130 S. Ct. at 2200.

The supposed "inconsistent[cy]" is simply that the D.C. Circuit interpreted the statutory language at issue in *Teva* in the manner urged by the generic manufacturer, while the Federal Circuit interpreted the entirely different language of the counterclaim provision in the manner proposed by the branded company. This is not the kind of "obvious conflict with any other Circuit" that would constitute "special circumstances that justify the exercise of our discretionary certiorari jurisdiction to review the Court of Appeals' [review] of the interlocutory order entered by the District Court." *Office of Senator Dayton* v. *Hanson*, 550 U.S. 511, 515 (2007). Rather, it simply reflects that the Hatch-Waxman Act, like most complex federal legislation, does not uniformly benefit any particular constituency, but instead strikes a balance between competing interests—here, branded and generic competitors. Petitioners and their *amici*

obviously would prefer that the balance be tipped toward the generic industry, but that is a policy argument appropriately addressed only to Congress, not this Court.

B. The Remedy Is Limited To Correction Or Deletion of Patent Numbers And Expiration Dates

Even if the counterclaim were available to petitioners, the relief they seek—a judicial order requiring respondents to withdraw the current use code narrative and replace it with one approved by petitioners—is not authorized by the Hatch-Waxman Act.

The only relief authorized by the Hatch-Waxman counterclaim is an order requiring the NDA holder "to correct or delete the patent information submitted by the holder under subsection (b) or (c)." 21 U.S.C. § 355(j)(5)(C)(ii)(I). The incorporated provisions require the submission (and publication) of very specific "patent information"—the "patent number" and its "expiration date." *Id.* § 355(b), (c). As the majority recognized, "the Act defined the term 'patent information' as 'the patent number and the expiration date,'" and "to maintain consistency in the statutory terms, 'the patent information' in the counterclaim provision must also mean the patent number and the expiration date." Pet. App. 15a.

Importantly, petitioners do not dispute that the Federal Circuit's construction *of the statute* is permissible. On the contrary, they recognize that "§ 505(b) and (c) mention *only* the patent number and expiry." Pet. 35 (emphasis added). Accordingly, they do not take issue with the majority's statutory exegesis, which is entirely consistent with the legislative history of the counterclaim provision as well as

its underlying purpose (*i.e.*, allowing challenges to improperly listed patents).

Rather, petitioners maintain that FDA has by regulation interpreted the term "patent information" to include use code narratives in addition to the patent number and expiration date, and that this interpretation is entitled to deference. Pet. 34-35. Indeed, petitioners go so far as to say that certiorari is warranted because the majority's ruling that statutory "patent information" is limited to the patent number and expiration date, and not use codes—which are nowhere mentioned in the statute—"violates *Chevron [U.S.A. Inc.] v. NRDC, Inc.*, 46[7] U.S. 8[3]7 (1984)." Pet. 34.

Petitioners' "deference" argument rests on the premise that FDA promulgated a regulation in 2003 "defini[ng]" "patent information" to include "use code narratives," and that Congress acted "with full awareness of the agency's interpretation," effectively "adopt[ing]" and "implement[ing]" this "definition." Pet. 34. That premise, however, is false.

The FDA regulation on which petitioners rely is entitled "[s]ubmission of patent information" and requires the submission of certain information, including use code narratives. *See* 21 C.F.R. § 314.53; 68 Fed. Reg. 36,676, 36,703-05 (June 18, 2003). But petitioners fail to inform the Court of the rest of the story. In 2006, an industry group challenged FDA's regulatory authority to require use code narratives. In response, FDA did *not* justify this requirement as an interpretation of "patent information" in subsection (b) or (c); rather, FDA said—in a formal statement not cited by petitioners or any of their *amici*—that it was authorized to require use code narratives under its general rulemaking authority and subsection (j). 72 Fed. Reg. 21,266, 21,268-69 (Apr. 30, 2007) (describing submission of use codes as a "regu-

latory requirement"). In other words, FDA acknowledged that use code narratives are *not* "patent information" under Section 505(b) or (c), and it does not purport to have offered the "interpretation" that petitioners posit. Courts need not defer to an interpretation that the agency itself denies making.

Moreover, even if (counterfactually) FDA *had* interpreted "patent information" to include use code narratives, "'no deference is due to agency interpretations at odds with the plain language of the statute itself.'" Pet. App. 16a (quoting *Pub. Emps. Ret. Sys.* v. *Betts*, 492 U.S. 158, 171 (1989)). The statute, by defining "patent information" as including just two things, precludes any regulatory effort to include a third thing. And nothing in the counterclaim provision purports to alter that preexisting statutory definition. On the contrary, the counterclaim provision repeats that it is "the patent information submitted by the holder under subsection (b) or (c)" that may be corrected or deleted. 21 U.S.C. § 355(j)(5)(C)(ii)(I).

Where, as here, the statutory text and structure unambiguously limit "patent information" to the patent number and expiration date, there is no "gap" for the agency to fill. *Chevron*, 467 U.S. at 843. But even if Congress had been silent on this issue, FDA is not "entrusted to administer" a statutory provision establishing a judicial counterclaim for private plaintiffs—and thus FDA's purported interpretation of the terms of this statutory provision is of no help to petitioners. *Id.* at 844. It "is most certainly incorrect to say that language in a regulation can conjure up a private cause of action that has not been authorized by Congress. Agencies may play the sorcerer's apprentice but not the sorcerer himself." *Alexander* v. *Sandoval*, 532 U.S. 275, 291 (2001).

Congress specifically required two pieces of "patent information," and provided a counterclaim to cor-

rect or delete that information; had Congress wanted instead for the counterclaim to reach any other information that might be required by FDA (now or in the future), it would not have tied the counterclaim so specifically to the "patent information" submitted "under subsections (b) or (c)." *See*, *e.g.*, *Blue Chip Stamps* v. *Manor Drug Stores*, 421 U.S. 723, 734 (1975) ("When Congress wished to provide a remedy … , it had little trouble in doing so expressly"). Moreover, reading the statute as broadly as petitioners propose would render the express limitation superfluous, in contravention of another canon of construction. *TRW Inc.* v. *Andrews*, 534 U.S. 19, 31 (2001).

Petitioners rather breathlessly maintain that the decision below "expressly invalidates" the FDA's regulations requiring NDA holders to submit a broad range of information beyond the minimum required by the statute, including use codes. Pet. i, 23-27. According to petitioners, the decision therefore "throws a wrench in the FDA's ability to enforce provisions essential to the [Act's] operation." Pet. 23-24 (internal quotation marks omitted).

In truth, the majority decision does not invalidate any regulation, nor does it call into question FDA's authority to require the submission of use codes (or any other data) under its general rulemaking authority. And it does not in any way impact or undermine FDA's ability to enforce the Act's patent listing provisions. The same FDA regulations that were implemented and enforced before the decision continue to be implemented and enforced now. The same Form 3542 that was used by FDA to collect information from NDA holders then is used now, and must be completed by each NDA holder. It is simply not accurate to claim, as petitioners do, that the majority ruling "deprives the agency of information it 'must have' to expedite [its] review of ANDA … ap-

plications." Pet. 26 (quoting 68 Fed. Reg. at 36,682). The decision below does not preclude FDA from requesting (or publishing) any information, and the agency's authority to enforce the Act has not been threatened, much less bewrenched.

C. The Challenged Use Code Is Correct

Even if petitioners could convince this Court to adopt an expansive reading of both "an approved use" and "patent information," petitioners would also have to prove that respondents' current use code narrative is incorrect. As the concurrence below explained, however, "there is nothing illegal, or even incorrect, about Novo's current use code." Pet. App. 21a. The counterclaim gives the district court no license to force Novo to choose between two truthful alternatives. Indeed, if the statute were so construed it would give rise to serious First Amendment problems. *See Hurley* v. *Irish-Am. Gay, Lesbian & Bisexual Group of Boston*, 515 U.S. 557, 579 (1995). In addition, petitioners would be unable to justify the issuance of such an order under the traditional criteria for equitable relief. *eBay Inc.* v. *MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

The counterclaim places the burden of proof on the generic, and petitioners did not come close to proving that respondents' use code is incorrect. (The district court's conclusion in this respect was perforce vacated by the Federal Circuit.) Respondents explained at considerable length in the court below why their current use code narrative is accurate and entirely consistent with the Hatch-Waxman Act and all applicable regulatory guidance. Resp. C.A. Br. 34-41; Resp. C.A. Reply Br. 17-26; *see also* C.A. App. A679-A696. In short, FDA expressly allows a pioneer manufacturer to base its use code narrative on the approved method of use *or* indication for the

drug. 21 C.F.R. § 314.53(c)(2)(ii)(P)(1); *see also* Pet. App. 213a.

A use code that tracks the approved indication is entirely consistent with the Hatch-Waxman Act and its legislative history, which focus on indications. *See* H.R. Rep. No. 98-857, pt. 1, at 21 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2654. And there is no dispute that respondents' current use code narrative directly tracks the FDA-mandated indication for PRANDIN®. *Compare* C.A. App. A673 ("A method for improving glycemic control in adults with type 2 diabetes mellitus"), *with* C.A. App. A667-A668 (PRANDIN® is indicated for "improv[ing] glycemic control in adults with type 2 diabetes mellitus"). It therefore "alerts generics" such as petitioners to the existence of a patent that claims an approved use of repaglinide, discharging the notice function that is the objective of the patent listing requirements in the Hatch-Waxman Act. *See* Pet. 5-6. Because respondents' current use code narrative complies with all actual regulatory guidance, there is nothing for any court to "correct"—even if petitioners' construction of the statute were to be adopted.

As the majority and concurring opinions below recognized, petitioners' true grievance lies with FDA, not respondents. Pet. App. 14a, 20a. Petitioners' real complaint is that FDA rejected their section viii carve-out on the basis of its longstanding policy that an ANDA filer "must, despite any disagreement as to the correctness of the patent information, [submit] an appropriate certification for each listed patent." 21 C.F.R. § 314.53(f). They also disagree with FDA's regulatory decision to allow use codes that track approved indications. And petitioners are dissatisfied that FDA has elected to conserve its financial and experiential resources by declining to "police" most Orange Book submissions. *See ibid.*

Petitioners try to blame respondents for these regulatory determinations, but FDA decisions cannot be challenged or resolved in the context of a Hatch-Waxman counterclaim. Rather, petitioners must challenge FDA policies, including FDA's decision to deny their attempted section viii carve-out, by proceeding against FDA, in the appropriate forum, under the Administrative Procedure Act. *See Andrx Pharms., Inc.* v. *Biovail Corp.*, 276 F.3d 1368, 1379 (Fed. Cir. 2002). Petitioners concede that they *could* have challenged FDA's refusal to authorize their section viii carve-out (Pet. 20), but—for reasons they have never explained—petitioners have elected not to bring an APA suit against FDA. Nonetheless, the admitted availability of such a suit destroys the argument, advanced by petitioners and echoed by their *amici*, that the decision below "leav[es] generics without any [judicial] remedy." Pet. 3.

The court below ruled only that the Hatch-Waxman counterclaim is not available to petitioners on the peculiar facts of this particular case, which is not an issue that warrants this Court's attention.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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February 25, 2011

APPENDIX

APPENDIX A

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN SOUTHERN DIVISION

NOVO NORDISK A/S and NOVO NORDISK, INC., Plaintiffs,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.

Case No. 05-40188
HON. AVERN COHN

* * *

MEMORANDUM AND ORDER DENYING PLAINTIFFS' MOTION TO DISMISS FOR LACK OF JURISDICTION[1]

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[1] Ordinarily, the Court would hold a hearing on this matter. However, upon review of the parties' papers, the Court finds that oral argument is not necessary. *See* E.D. Mich. LR 7.1(f)(2).

I.

This is a patent case. It involves the diabetes drug repaglinide marketed by plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc. (Novo) under the trade name Prandin. Novo's patent for repaglinide, U.S. Pat. No. RE37,035 (the '035 patent), expired on March 14, 2009. Novo also holds a patent on the combination of repaglinide and metformin, U.S. Pat. No. 6,677,358B1 (the '358 patent) which does not expire until 2018. As will be explained, this case began in 2005 when Novo sued Caraco Pharmaceutical Laboratories, Ltd. (Caraco) and Sun Pharmaceutical Industries, Inc. (Sun) claiming infringement of the '358 patent when Caraco applied to the FDA to market a generic version of repaglinide. Caraco and Sun countersued for declaratory relief, raising issues including validity, enforceability, and misuse.

After five years of litigation, one appeal, and a three-week bench trial on the issues of patent validity and enforceability, a decision on which is pending, Novo has moved to dismiss the case for lack of subject matter jurisdiction. Although Novo alleged in its complaint that an actual controversy existed because of Caraco's conduct before the FDA, it now says that jurisdiction is lacking because of Caraco's later actions before the FDA. For the reasons that follow, Novo's motion is DENIED.

II.

In analyzing jurisdictional questions in declaratory judgment actions, there is no bright-line rule. *MedImmune Inc. v. Genentech Inc.*, 549 U.S. 118, 127 S.Ct. 764, 771, 166 L. Ed. 2d 604 (2007). Instead, "the question in each case is whether the facts al-

leged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id*.

A party claiming declaratory judgment jurisdiction has the burden to establish the existence of such jurisdiction. *See Benitec Austl., Ltd. v. Nucleonics, Inc.*, 495 F.3d 1340, 1344 (Fed. Cir. 2007).

III.

The background of the case, including the process of certification of a generic drug, is described in several decisions of the Court reported at 450 F. Supp. 2d 757 (E.D. Mich. 2006) and 649 F. Supp. 2d 661, 2009 WL 2769855 (E.D. Mich. 2009). Background is also set forth in the Court of Appeals for the Federal Circuit's decisions reported at 601 F.3d 1359 (Fed. Cir. 2010) and 615 F.3d 1374, 2010 U.S. App. LEXIS 15611, 2010 WL 2990968 (Fed. Cir. July 29, 2010). What follows is background relevant to the instant motion.

A.

First, as to the statutory framework, this case falls under the Hatch-Waxman Act, which amended the Federal Food, Drug, and Cosmetic Act, Pub.L. No. 52-675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 et seq. (1994)) (the "FDCA"). Under the FDCA, the FDA is responsible for determining whether a generic drug product should be approved for sale to the public. 21 U.S.C. § 355(a). Under Hatch-Waxman, a pharmaceutical manufacturer, such as Caraco, seeking expedited FDA approval to market a generic version of a pat-

ented drug may submit an abbreviated new drug application ("ANDA"). 21 U.S.C. § 355(j). An applicant submitting an ANDA must certify one of four things: (1) that the drug for which the ANDA is submitted has not been patented (a "paragraph I" certification); (2) that any patent on such drug has expired (a "paragraph II" certification); (3) the date on which the patent on such drug will expire, if it has not yet expired (a "paragraph III" certification); or (4) that the patent on such drug "is invalid or that it will not be infringed by the manufacture, use, or sale of the new drug" for which the ANDA is submitted (a "paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV).

When an applicant submits an ANDA that contains a paragraph IV certification, it must give the owner of the relevant patent notice of the certification. 21 U.S.C. § 355(j)(2)(B). Importantly, inclusion of a paragraph IV certification in an ANDA is deemed an act of infringement. The statute, referring to an ANDA containing a paragraph IV certification, states: "It shall be an act of infringement" to submit an application under 21 U.S.C. § 355(j) "for a drug claimed in a patent . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of [the] drug . . . before the expiration of [the] patent." 35 U.S.C.A. § 271 (e)(2)(A).

If the ANDA contains a paragraph IV certification, and all applicable scientific and regulatory requirements have been met, approval of the ANDA "shall be made effective immediately" unless the patent owner brings an action for infringement under 35 U.S.C.A. § 271(e)(2)(A) within forty-five days of re-

ceiving the notice required by 21 U.S.C. § 355(j)(2)(B). 21 U.S.C. § 355(j)(4)(B)(iii). Hatch-Waxman further provides that, when a patent owner brings a section 271(e)(2)(A) infringement action, the FDA must suspend approval of the ANDA. *Id.* The suspension continues—and the FDA cannot approve the ANDA—until the earliest of three dates: (I) if the court decides that the patent is invalid or not infringed, the date of the court's decision; (ii) if the court decides that the patent has been infringed, the date that the patent expires; or (iii) subject to modification by the court, the date that is thirty months from the patent owner's receipt of notice of the filing of the paragraph IV certification. 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III); 35 U.S.C.[] § 271(e)(4)(A).

However, "the four types of certifications enumerated in 21 U.S.C. § 355(j)(2)(A)(vii) are not the only mechanisms by which an ANDA applicant can address a potentially relevant patent." *Apotex, Inc. v. Food & Drug Administration,* 393 F.3d 210, 213-14, 364 U.S. App. D.C. 187 (D.C. Cir. 2004). Rather than submit a paragraph IV Certification, an ANDA applicant may instead represent that it is not seeking approval for the patented method of use. 21 U.S.C. § 355(j)(2)(A) (viii). In what is commonly referred to as a "section viii statement", the ANDA applicant asserts that the "patent is inapplicable to the indication for which the drug product will be marketed." *In re Neurontin Antitrust Litigation,* No. 02-1390(FSH), 2009 U.S. Dist. LEXIS 77475, 2009 WL 2751029, [at] *2 n.11 (D.N.J. Aug. 28, 2009) (citing 21 U.S.C. § 355(j)(2)(A)(viii)).

In *Purepac Pharmaceutical Co. v. Thompson,* 354 F.3d 877, 880, 359 U.S. App. D.C. 319 (D.C. Cir.

2004), the D.C. Circuit explained the differences between a paragraph IV certification and a section viii statement as follows:

> A section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent. *See* 21 U.S.C. § 355(j)(2)(A)(viii). For example, if a brand-name manufacturer's patent covers a drug's use for treating depression, and the ANDA applicant seeks approval to use the drug to treat any other condition, then a section viii statement would be appropriate. Thus, whereas applicants use paragraph IV certifications to challenge the validity of admittedly applicable patents, they use section viii statements to assert that patents do not apply. The FDA has long required that for every patent ANDA applicants use either a paragraph IV certification or a section viii statement—they may not use both. As the FDA puts it, "either the applicant is seeking approval for the use claimed in the patent, or it is not." *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 77 (D.D.C. 2003) (quoting the record in that case) (internal quotation marks omitted).
>
> Paragraph IV certifications and section viii statements have quite different consequences. Applicants submitting section viii statements have no obligation to provide notice, nor must they wait thirty months for FDA approval. . . . "[T]he FDA may [thus]

> approve a section viii application immediately, making it an attractive route for generic manufacturers, even though a section viii statement does not entitle a successful applicant to the 180-day period of exclusivity bestowed on paragraph IV applicants."

354 F.3d at 880 (quoting *Purepac Pharmaceutical Co. v. Thompson*, 238 F. Supp. 2d 191, 195 (D.D.C[.] 2002)). Finally, a section viii statement, unlike a paragraph IV certification, does not constitute an act of infringement sufficient to invoke subject matter jurisdiction under Hatch-Waxman. *See Purepac*, 238 F. Supp. 2d at 195.

B.

Second, as to the facts of this case, in February 2005, Caraco submitted an ANDA, seeking to market a generic version of repaglinide. Caraco included in its ANDA a "paragraph IV certification" stating that all five claims of the '358 patent were invalid and thus not infringed by Caraco's attempt to manufacture a generic repaglinide.

On April 2, 2005, the FDA acknowledged receipt of Caraco's ADNA and Paragraph IV certification. *See* Ex. 16 of Joint Appendix. Caraco also notified Novo of the certification as required.

In June 2005, Novo sued Caraco for infringement and later added Sun as a defendant. Novo claimed that Caraco's anticipated manufacture of repaglinide would infringe the '358 patent because the label would suggest the use of repaglinide with metformin. Both Caraco and Sun counterclaimed that the '358 patent was invalid, unenforceable, and would not be infringed by the sale of generic repaglinide.

Meanwhile, in August 2007, the FDA notified Caraco that its ADNA had been "tentatively approved." In the correspondence, the FDA noted that because there was a patent dispute involving the '358 patent, Caraco's application could not be finally approved. The FDA specifically referenced the lawsuit filed by Novo against Caraco. Ex. 21 of Joint Appendix.

On April 2, 2008, Caraco submitted an amendment to its ADNA, proposing that it be allowed to redact references in its label to the combination of repaglinide with metformin. In this filing, Caraco was attempting to submit a split certification, encompassing both a paragraph IV certification and a section viii certification. As noted in the Federal Circuit's decision:

> . . . at the FDA's urging [Caraco] sought a paragraph IV certification as to the drug product claims of the '358 patent, *and* a section viii certification as to the method claim.

Novo v. Caraco, 601 F.3d at 1379 n.16 (Dyk, dissenting) (emphasis added). *See also* Ex. 10 of Joint Appendix.

This point is critical inasmuch as Novo's motion is grounded on the premise that in seeking the amendment with the section viii certification, Caraco "dropped" its paragraph IV certification and, in so doing, the basis for subject matter jurisdiction was lost. This is a faulty premise. Novo did not abandon, drop, replace or otherwise waive the paragraph IV certification. This is clear when the record is further examined.

In May 2009, Novo submitted an amended use code for the '358 patent which the FDA approved.[2] Specifically, Novo changed the use code from "U-546–use of repaglinide in combination with metformin to lower blood glucose" to "U-968–a method for improving glycemic control in adults with type 2 diabetes mellitus." As the case history shows, the propriety of Novo changing the use code was hotly litigated with Novo eventually prevailing in the Federal Circuit.

The FDA then notified Caraco that it would not approve a section viii statement in light of Novo's amended use code. The FDA later instructed Caraco to change its ADNA to add back in the information about the combination of repaglinide and metformin, which essentially mooted Caraco's efforts at a section viii statement.

All of this is spelled out in a May 26, 2010 letter from Caraco to the FDA in which Caraco states in relevant part:

> . . . it is Caraco's understanding that FDA has currently decided to reject the proposed section viii statement with regard to claim 4 of the '358 patent and, therefore the FDA is now deeming Caraco's ANDA to contain a

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[2] Shortly after Caraco sought the amendment, on July 9, 2008, Novo filed its first motion to dismiss for lack of subject matter jurisdiction. Following a status conference, Novo withdrew the motion. Novo refiled the motion after the proofs were submitted in the validity trial. The Court has already commented on the peculiar circumstances of Novo's filing in the Memorandum and Order of September 16, 2010. *See* Doc. No. 503.

> paragraph IV certification as of the time of tentative approval. Caraco may ultimately need to maintain its paragraph IV certification as to all claims of the '358 patent to obtain final approval. However, it is currently maintaining that certification under protest.

Ex. 4 of Joint Appendix. While Novo says that these statements mean Caraco was trying to "revive" its paragraph IV certification, that is not the case. Rather, these statements merely reconfirm that Caraco was pursuing both a paragraph IV certification and a section viii statement with respect to the '358 patent. When the section viii statement was rejected (because Novo was successful in obtaining an amended use code), the paragraph IV certification was still in place. At that point, Caraco's ANDA contained only the paragraph IV certification, which Caraco has continued to pursue.

C.

In the end, the fact is that there has always been a substantial controversy between the parties over the '358 patent. Caraco's paragraph IV certification is still pending before the FDA. Caraco's filing of the ANDA was an act of infringement sufficient to invoke subject matter jurisdiction. That dispute continues to date.

SO ORDERED.

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

Dated: October 6, 2010

APPENDIX B

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF MICHIGAN SOUTHERN DIVISION

NOVO NORDISK A/S and NOVO NORDISK, INC., Plaintiffs,
v.
CARACO PHARMACEUTICAL LABORATORIES, LTD. and SUN PHARMACEUTICAL INDUSTRIES, LTD., Defendants.

Case No. 05-40188
HON. AVERN COHN

* * *

DECISION

TABLE OF CONTENTS

I. INTRODUCTION

A. The Case

This is a patent case under the Hatch Waxman Act, 21 U.S.C. § 35[5], *et. seq*. The patent-in-suit, U.S. Patent No. 6,677,358B1, NIDDM REGIMEN (the '358 Patent) in the words of the abstract:

> . . . discloses a method of achieving improvement in glycemic control by combined use of repaglinide and metformin in NIDDM patients poorly controlled on metformin alone.

The patent is owned by assignment by plaintiffs Novo Nordisk A/S and Novo Nordisk, Inc. (Novo). Defendant, Caraco Pharmaceutical Laboratories, Ltd. (Caraco) asserts that Claim 4, the claim-in-suit of the '358 patent which reads

> A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising ad-

> ministering to a patient in need of such treatment repaglinide in combination with metformin

is invalid as obvious and anticipated, and is unenforceable because of inequitable conduct and patent misuse.

Proceedings against defendant Sun Pharmaceutical Industries, Ltd., the second defendant of which Caraco is a partially owned subsidiary, have been stayed until further order of the Court (Doc. 346).

The issues of obviousness, anticipation and inequitable conduct were tried to the Court in June and August of 2010. The issue of patent misuse is the subject of a separate proceeding before the Court.

B. The Decision

For the reasons which follow, which constitute the findings of fact and conclusions of law required by Fed. R. Civ. P. 52(a), the Court finds that:

- The '358 Patent is not invalid because of anticipation
- The '358 Patent is invalid because of obviousness
- The '358 Patent is not enforceable because of inequitable conduct

II. BACKGROUND

A. Overview

This case has a long and complicated history. It began with the filing of a complaint by Novo charging Caraco with infringement of the '358 Patent on July 21, 2005 (Doc. 1), and Caraco responding with an answer and counterclaim asserting [the] invalidity and

unenforceability of the '358 Patent (Doc. 7). Since filing, the case has generated over 500 docket entries.

B. History

The history of the case is generally described in the following decisions of the Court and the Court of Appeals for the Federal Circuit as follows:

On August 31, 2009, the Court held that Caraco could challenge the incorrect use code narrative furnished by Novo for placement in the Orange Book maintained by the Food and Drug Administration on its application for approval of the new drug covered by the '358 Patent, and that Caraco could assert an affirmative defense to the charge of infringement because of this. *Novo v. Caraco*, 649 F. Supp. 2d 661 (E.D. Mich. 2009).

On September 24, 2009, the Court found that Novo improperly filed a use code narrative in its application for approval of the new drug. *Novo v. Caraco*, 656 F. Supp. 2d 729 (E.D. Mich. 2009).

On September 25, 2009, the Court entered an Order and Injunction (Doc. 423) requiring Novo to correct the use code narrative in the Orange Book.

On April 14, 2010, the Federal Circuit reversed the Order and Injunction, holding that a counterclaim such as filed by Caraco challenging the Orange Book listing was not available under Hatch Waxman. *Novo v. Caraco*, 601 F.3d 1359 (Fed. Cir. 2010). On July 21, 2010, rehearing was denied. *Novo v. Caraco*, 615 F.3d 1374 (Fed. Cir. 2010). On December 23, 2010, Caraco applied to the Supreme Court for *certiorari*.

On June 9, 2010, the Court found that the relevant date for prior art in the challenge to validity of the '358 Patent was October 29, 1996. *Novo v. Caraco*, 2010 U.S. Dist. LEXIS 56752, 2010 WL 2403041 (E.D. Mich. June 9, 2010)

On October 6, 2010, in a Memorandum and Order, the Court denied Novo's motion to dismiss the case for lack of subject matter jurisdiction premised on the grounds that Caraco had changed the nature of its Application For A New Drug (ANDA) with the Food and Drug Administration (FDA). *Novo v. Caraco*, 2010 U.S. Dist. LEXIS 106729, 2010 WL 3492727 (E.D. Mich. Oct. 6, 2010).

On September 09, 2009, Caraco stipulated that its ANDA filed with the FDA infringed the '358 Patent (Doc. 309). On August 24, 2010, in a Notice of Lodging of Stipulation of Infringement, the stipulation was reaffirmed (Doc. 489).

III. THE TRIAL

On April 23, 2010, the Court entered an order (Doc. 459) reversing the order of proofs at trial. The trial extended over 11 days in June and August of 2010.

A. The Witnesses

Fourteen witnesses, as named in the List of Trial Witnesses (Doc. 490) filed by the parties post-trial, testified. The witnesses' direct testimony for the most part was presented in narrative form (*see* Doc. 459). A brief description by name and general nature of testimony of the witness follows.

1. Caraco

Name	General Nature of Testimony
Domenico Accili (Accili)	Expert in the field of endocrinology and diabetes research. Accili expressed the opinion that claim 4 of the '358 patent was invalid as obvious, and that there was a lack of unexpected results when repaglinide was combined with metformin.
Marcello Pagano (Pagano)	Expert in the field of biostatistics. Pagano expressed the opinion that there was a lack of statistical validity in Novo's studies with respect to the combination of repaglinide with metformin.

2. Novo

Name	General Nature of Testimony
Robert Moses, M.D. (Moses)	Medical Director of an Australian research institute. Moses was one of the principal clinical investigators of a study of the combination of metformin and repaglinide (Moses Study)[1]. His

[1] Appendix I contains a list of reports and articles referenced in this Decision, including the Moses Study, noted above. The appendix lists (1) the exhibit number for the report or article,

	research data and results were the foundation of the examples reported in the '358 [patent].
Peter Müller, M.D. (Müller)	A research associate in Novo's research department in Denmark. Müller is the named inventor of the '358 patent. He designed the Moses Study to test the combination of repaglinide and metformin.
Andreas Pfeiffer, M.D. (Pfeiffer)	A clinical specialist in the field of endocrinology. Pfeiffer conducted clinical research on the combination of repaglinide and metformin (Pfeiffer Study). He expressed the opinion that the results of the combination were unexpected.
Jeppe Sturis, Ph.D. (Sturis)	A principal scientist of Novo in Denmark. Sturis tested a combination of repaglinide and metformin in Zucker obese rats (Sturis Study). He expressed the opinion that the results of his testing were synergistic. The results were cited to the

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[Footnote continued from previous page]

(2) the full citation for the report or article, and (3) the Court's abbreviation for the report or article.

	Patent Office in support of patentability of the combination of repaglinide and metformin.
Howard Thaler, Ph.D. (Thaler)	An expert in biostatistics. Thaler reviewed the results of the Moses Study and the Sturis Study. He expressed the opinion that the studies showed synergistic results from the combination of repaglinide and metformin.
Peter Damsbo, M.D. (Damsbo)	Novo's chief medical advisor. Damsbo's early work with repaglinide provided a foundation for a therapeutic approach for the combination of repaglinide and metformin.
John Miller, M.D. (Miller)	Medical director of Novo in Australia. Miller coordinated and supervised the Moses Study. He described this work and said he was surprised by the results.
Michael Mark, Ph.D. (Mark)	A German scientist. Mark discovered repaglinide and attempted to commercialize it. He was involved in its transfer to Novo.
Arne Melander, M.D. (Melander)	Researcher in the clinical pharmacology of diabetes.

	Melander expressed the opinion that repaglinide was not interchangeable with sulfonylureas, and was not thought suitable for combination therapy with metformin.
Brian Reisetter, Ph.D. (Reisetter)	An expert in medical marketing. Reisetter expressed an opinion about the commercial success of the repaglinide-metformin combination therapy.
Alan Garber, M.D., Ph.D. (Garber)	An expert in clinical endocrinology and biochemistry. Garber expressed the opinion that claim 4 the '358 Patent is valid as nonobvious.
Bharati Nadkarni (Nadkarni)	A senior manager at Sun Pharmaceutical. Nadkarni described Sun's activities in India and Mynamar with repaglinide and sulfonylureas.

B. Exhibits

Roughly over 360 exhibits were introduced in evidence at trial. A consolidated list of trial exhibits (Doc. 494) was filed by the parties post-trial. The exhibits beyond the '358 Patent (JX 1) and an abbreviated File History (JX 2A), include correspondence, chains of e-mails, articles, abstracts of articles, clinical trials reports, curriculum vitaes of scientific witnesses, data compilations and various graphic com-

parisons, as well as a miscellany of other written material.

IV. THE LAW

A. Anticipation

Anticipation exists only if, within the four corners of a single prior art document, every element of the claimed invention is described, expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009).

B. Obviousness

A patent is presumed valid, 35 U.S.C. § 282, and a party challenging its validity bears the burden of proving the factual elements of invalidity by clear and convincing evidence. *Pfizer v. Apotex*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). Once the challenger has presented a prima facie case of invalidity, the patent owner has the burden of going forward with rebuttal evidence. *Id.* at 1360. This requirement "does not in substance shift the burden of persuasion, because the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation." *Id*. (case citations omitted).

Where the accused infringer relies only upon prior art considered by the patent examiner, the statutory presumption of validity includes deference to the examiner's decision based upon the Patent Office's expertise. *American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359-60 (Fed. Cir. 1984). In the Supreme Court's *KSR* decision, where the invalidity

defense was based on prior art not considered by the Patent Office, the Court observed that "the rationale underlying the presumption – that the PTO, in its expertise, has approved the claim – seems much diminished here."[2] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 426, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007).

A valid patent may not be granted or upheld when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The ultimate question of patent validity is one of law, based on an underlying factual framework laid out by the Supreme Court in *Graham v. John Deere Co.*:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved

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[2] On November 29, 2010, the Supreme Court granted *certiorari* in *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831 (Fed. Cir. 2010) on the question whether the clear and convincing standard must be applied to the invalidity defense under these circumstances. *Microsoft Corp. v. i4i Ltd*. Partnership, 131 S. Ct. 647, 178 L. Ed. 2d 476 (2010).

> needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).

Often, as here, it is necessary to utilize this framework to determine whether a patent claiming a combination of elements known in the prior art was obvious at the time of the claimed invention. Over the years, the Federal Circuit created and applied a test known as the "teaching, suggestion or motivation" (TSM) test. Under this test, a patent claim is proved obvious only if a motivation or suggestion to combine the prior art teachings can be found in the prior art. The Supreme Court in *KSR* held that the TSM test can provide a "helpful insight," but noted that

> [o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. . . . As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court

> can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

Continuing:

> The obviousness analysis cannot be confined by a formalistic conception of the words, teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends.

550 U.S. at 418-19.

Known disadvantages of prior art elements that might have taught away from the claimed combination may be taken into account in determining obviousness. *Id*. at 416, citing *United States v. Adams*, 383 U.S. 39, 51-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966).

In another step applicable here, *KSR* approved the selective use of the "obvious to try" test that had long been rejected by the Federal Circuit:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her

> technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421.

The Federal Circuit subsequently elaborated on the obvious-to-try "rule of thumb," identifying two factual situations where it was inappropriate:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *[In re] O'Farrell*, 853 F.2d [894,] 903 [(Fed. Cir. 1988)]. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble*, 566 F.3d at 996; *[In re] Kubin*, 561 F.3d [1351,] 1359 [(Fed. Cir. 2009)]. It is also consistent with our interpretation that KSR requires the number of options to be "small or easily traversed." *Ortho-McNeil Pharm., Inc. v. Mylan*

> *Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).
>
> Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421, 127 S.Ct. 1727; *see also Proctor & Gamble,* 566 F.3d at 996-97; *Kubin*, 561 F.3d at 1359-60.

Bayer Schering Pharma AG v. Barr Labs, Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009). The Federal Circuit has declined to "cabin" the "obvious to try standard" to the "predictable arts" (as opposed to the relatively unpredictable biotechnology arts). *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Where, as here, all the elements of the claimed invention are found in a combination of prior art references, the party challenging validity must show by clear and convincing evidence (1) that a skilled artisan would have had a reason or motivation to combine the teachings of the prior art to achieve the claimed invention combination, or would have found it obvious to try the claimed combination, and (2) that such person would have had a reasonable expec-

tation of success in doing so. *Pfizer v. Apotex*, 480 F.3d 1348, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 421.[3] The court in *Pfizer* elaborated on the "reasonable expectation of success":

> [C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success . . . [T]he expectation of success need only be reasonable, not absolute.

Id. at 1364.

A case of prima facie obviousness can be rebutted by "unexpected results," but "the results must be shown to be unexpected compared with the closest prior art." *Id.* at 1370. "[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected." *Id.* at 1371. But even unexpectedly superior results may not be sufficient to overcome a strong prima facie case of obviousness. *Id*. at 1372.[4]

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[3] *Pfizer* was decided one month before *KSR*. In *KSR*, the Supreme Court held that the "obvious to try" standard may be applied in appropriate circumstances, as quoted above. 550 U.S. 398, 421, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007).

[4] The parties have belabored the issue of whether the claimed combination produced synergistic, as well as unexpected and superior results. Synergy became part of the vocabulary in this case in an abstract written for publication describing the results of the Moses Study. *See*, DX 9; ¶ 96, *infra*.

The Supreme Court has endorsed the generally accepted definition of "synergistic," namely, "an effect greater than the sum of the several effects [of the constituent elements] taken separately." *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282, 96 S.

See also, Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010).

A strongly contested legal issue here is the relevance and meaning of *Asyst Techs. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008), which Caraco relies upon for its holding that "objective evidence of non-obviousness [e.g., unexpected results and commercial success] must be commensurate in scope with the claims which the evidence is offered to support." Evidence of unexpected results, though based upon subject matter that lies within the scope of a patent claim, will not support the unobviousness of a claim whose breadth extends far beyond that evidence unless "the probative value of a narrow range of data can be reasonably extended to prove the unobviousness of a broader claimed range." *In re Clemens*, 622 F.2d 1029, 1036 (CCPA 1980); *see also* the MPEP § 716.02(d), which cites *Clemens; In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (cited in *Asyst*); *In re Tiffin*, 448 F.2d 791, 792, 58 C.C.P.A. 1420 (CCPA 1971) (cited in *Asyst*).

Prima facie obviousness can also be rebutted by evidence of commercial success of the claimed invention. *Graham, supra*, 383 U.S. at 17-18.

[Footnote continued from previous page]

Ct. 1532, 47 L. Ed. 2d 784 (1976). The Manual of Patent Examining Procedure (MPEP) states that "a greater than additive [i.e., synergistic] effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." § 716.02(c).

C. Inequitable Conduct

The overall contours of the defense of patent unenforceability due to inequitable conduct have been summarized by Judge (now Chief Judge) Rader as follows:

> Applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty; *see also* 37 C.F.R. § 1.56. A breach of this duty – including affirmative misrepresentations of material facts, failure to disclose material information, or submission of false material information – coupled with an intent to deceive, constitutes inequitable conduct. In determining whether inequitable conduct occurred, a trial court must determine whether the party asserting the inequitable conduct defense has shown by clear and convincing evidence that the alleged nondisclosure or misrepresentation occurred, that the nondisclosure or misrepresentation was material, and that the patent applicant acted with the intent to deceive the United States Patent and Trademark Office. The nondisclosure or misrepresentation must meet threshold levels of both materiality and intent. Once the threshold levels of materiality and intent have been established, the trial court must weigh materiality and intent to determine whether the equities warrant a conclusion that inequitable conduct occurred. *Id.* The more material the information misrepresented or withheld by the applicant, the less

> evidence of intent will be required in order to find inequitable conduct.

Honeywell Int'l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 999 (Fed. Cir. 2007) (internal citations omitted).

Even if a threshold level of both materiality and intent to deceive are proven by clear and convincing evidence, a court may still decline to render the patent unenforceable. *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

The applicable definitions of materiality and intent, however, are less settled.[5] "Materiality" is defined by the Patent Office's current rule as follows:

> (b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> > (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
> >
> > (2) It refutes, or is inconsistent with, a position the applicant takes in:

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[5] The Federal Circuit granted a petition for rehearing en banc in *Therasence, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289 (Fed. Cir. 2010), and requested briefing on all aspects of the current framework for determining and balancing materiality and intent. *See* 374 Fed. Appx. 35 (Fed. Cir. 2010). Oral argument was held on November 9, 2010.

> ([i]) Opposing an argument of unpatentability relied on by the office, or
>
> (ii) Asserting an argument of patentability.
>
> A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

37 C.F.R. § 1.56(b) (2009).

The Federal Circuit has held that this current version, effective since 1992, was not intended to supplant the earlier "reasonable examine" standard or the case law interpreting it. *Digital Control v. Charles Machine Works*, 437 F.3d 1309, 1316 (Fed. Cir. 2006). The court further held that if a misstatement or omission is material under either test, or even under other previously applied tests, such as the "but for" test (the misrepresentation caused the examiner to approve claims he or she would not otherwise have approved) or the "but it may have" test (the misrepresentation may have influenced the examiner), then it is material. *Id.* at 1315-16. "To the extent that one standard requires a higher showing of materiality than another standard, the requisite

finding of intent may be lower." *Id*. In fact, recent Federal Circuit decisions have applied the definition from the earlier version of 37 C.F.R § 1.56, namely, information is material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent."[6]

Some decisions have found it appropriate, when weighing inferences relevant to intent, to consider plausible reasons for the withholding of material information:

> The intent element of the offense is . . . in the main proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred. . . . however, inequitable conduct requires not intent to withhold, but rather intent to deceive. Intent to deceive cannot be inferred simply from the decision to withhold [information] where the reasons given for the withholding are plausible.

McKesson Information Solutions, Inc. v. Bridge Medical, Inc., 487 F.3d 897, 913 (Fed. Cir. 2007) (reasons for withholding prior art patent and information from related applications held insufficient to negate inference of deceptive intent).

> An inference of intent to deceive is generally appropriate, however, when (1) highly mate-

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[6] *E.g., Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 829 (2010); *Symantec Corp. v. Computer Assocs. Int'l*, 522 F.3d 1279, 1297 (2008).

> rial information is withheld; (2) "the applicant knew of the information [and] . . . knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding."

Praxair, Inc. v. ATMI, Inc., 543 F.3d 1306, 1313-14 (Fed. Cir. 2008) (no good faith explanation given for failure to disclose material prior art).

Another 2008 decision of the Federal Circuit raises an additional hurdle for inferring deceptive intent when alternative inferences can be drawn from the evidence.

> We have also held that because direct evidence of deceptive intent is rarely available, such intent can be inferred from indirect and circumstantial evidence. But such evidence must still be clear and convincing, and inferences drawn from lesser evidence cannot satisfy the deceptive intent requirement. Further the inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence to meet the clear and convincing standard.
>
> [internal citations omitted]

Star Scientific, *supra*, 537 F.3d at 1365 (emphasis added) (no deceptive intent found; withheld document found to be cumulative, and therefore not material). *See also, Advanced Magnetic Closures, supra*, 607 F.3d at 829. In *Star Scientific,* the Federal Circuit held that the existence of a reasonable alterna-

tive explanation completely precludes an inference of deceptive intent. A contemporaneous decision, however, gave the district court broad discretion to weigh the patentee's alternative explanations against the inference of deceptive intent, affirming a finding of deceptive intent, without imposing the "single most reasonable inference" standard. *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 525 F.3d 1334, 1344 (Fed. Cir. 2008) (failure to disclose that half life studies were done at different doses).

V. THE PATENT

A. Technical Overview

For ease of reference, in Parts V through VIII the paragraphs are numbered.

1. This overview is essentially based on the Glossary of Terms lodged with the Court on June 20, 2010 by the parties. This overview is a brief tutorial of the underlying technology.

2. One of the byproducts of the body's digestion of food is glucose (sugar), which enters the bloodstream. A persistently too high level of bloodstream glucose is termed hyperglycemia, while a persistently too low glucose level is called hypoglycemia. Insulin is a hormone produced by beta cells in the pancreas, where it is stored until rising blood glucose levels cause it to be released. Insulin instructs the body's cells to take up glucose from the blood for use as an energy source, and also instructs the liver to stop producing glucose and to instead take up glucose from the blood and store it as glycogen until needed by the body.

3. **Diabetes** is a glucose metabolism disorder characterized by hyperglycemia after meals and in the fasting state. About 24 million people in the United States have diabetes. Type I diabetes, represented by five percent of the diabetic population, occurs when the pancreas' beta cells fail to manufacture and secrete insulin in response to elevated blood glucose levels. The only therapy is treatment with exogenous (externally originated) insulin.

4. In **Type II diabetes**, representing the remaining 95 percent of the diabetic population, the beta cells fail to secrete sufficient insulin, and/or the body is resistant to the effects of insulin. Type II diabetes is also known as non-insulin dependent diabetes (NIDDM). It can be treated with orally administered antidiabetic drugs (**OADs**) in the form of monotherapy (a single OAD) or combination therapy (more than one OAD). **Insulin resistance** is a characteristic of Type II diabetes in which the cells and the liver are insensitive to the presence of insulin, and do not respond to the chemical message carried by insulin.

5. There are several groups of OADs. The two groups which are the primary focus of this lawsuit are insulin **secretagogues** and insulin **sensitizers**. The secretagogues stimulate insulin release from the pancreas' beta cells. Sensitizers reduce insulin resistance by acting on the liver to reduce glucose production from glycogen stored there, and improve insulin sensitivity in muscle and fat tissues.

6. Repaglinide,[7] one of the two ingredients specified in Claim 4 of the '358 Patent, is an insulin secretagogue. It is one of five members of the meglitinide class of secretagogues, only one other of which (nateglinide or A-4166) has been approved by the FDA. A second class of secretagogue consists of thirteen sulfonylureas.

7. Metformin, the other claimed ingredient in Claim 4, is an insulin sensitizer. It is the only one of three members of the **biguanide** class that has been approved by the FDA. A second class of sensitizer, the thiazolidinediones ("TZDs"), consists of five drugs.

8. Two measures of glucose control have been referred to in this lawsuit. The first is **HbA_{1c}** or glycosylated hemoglobin, a form of hemoglobin to which glucose in the blood binds. The glucose remains attached for the life of the hemoglobin cell (about four months). This parameter is not influenced by daily fluctuations in blood glucose, and shows the average glucose level in the recent past. It is therefore used to monitor the effect of diet, exercise and drug therapy on blood glucose. The second measure is **FPG** or **fasting plasma (blood) glucose**. This measurement is taken after a patient has not eaten for about

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[7] At the time this case was filed, repaglinide was a patented pharmaceutical, U.S. Patent No. RE37,035E (the '035 Patent). The patent expired on March 14, 2009. It was in anticipation of the expiration of the '035 Patent that Caraco filed the ANDA that precipitated the filing of this case by Novo and the counterclaim by Caraco which is the subject matter of this case and the trial.

eight hours (e.g., overnight). High levels of FPG can be caused by increased glucose production from glycogen stored in the liver, resulting from impaired insulin action in the liver.

9. As will be amplified below, combination therapy – using any two drugs having different mechanisms of action – will generally be more effective than monotherapy – using just one of those drugs. If monotherapy with a drug proves successful, a logical testing progression was to test that drug in combination therapy. Combination therapy using an insulin sensitizer and an insulin secretagogue was a well-known successful technique for treating Type II diabetes long before the invention claimed in the '358 Patent.

10. A combination of drugs is said to have an additive effect when the total effect equals the sum of the effect of each drug taken separately (e.g., Drugs A and B each reduce hypertension by 10% when administered separately, and reduce hypertension by 20% if administered together). If the combined effect exceeds the sum of the separately administered effects, the effect is said to be **greater-than-additive** or synergistic (e.g., Drugs A and B in the above example yield a 25% reduction in hypertension when administered together). If Drug B inhibits or counteracts the effect of Drug A, the drugs are said to be antagonistic (e.g., the combination of the same Drugs A and B reduce hypertension by only 5%).

B. Conception and Development of the Patented Combination

11. Novo is a large producer of drugs used to treat diabetes. In November, 1990, it acquired license rights to repaglinide, a known but still unapproved insulin secretagogue. Development of repaglinide became the exclusive focus of Müller, who joined Novo in Denmark as a clinical researcher in 1989. He is the patentee of the '358 Patent. During 1991-92, he treated Type II patients with repaglinide to determine proper dosages and prove its efficacy and safety. He also compared its performance with sulfonylureas, a well-known class of insulin secretagogues. 6/7/10 Tr. at 186-95 (Müller).[8]

12. As Müller explained, in that time period there were sulfonylureas (secretagogues) and metformin, an insulin sensitizer that had been around for many years. He conceived the repaglinide/metformin combination at an unknown date before June of 1994, and did not study any other repaglinide combinations. *Id*. 192, 198. He thought "it would make more sense" to combine repaglinide with metformin than with sulfonylureas, because of metformin's complementary mechanism of action. "That's why my thought was a good idea to combine those two." *Id*. at 192-93. Relative to patients whose glucose levels were not adequately controlled on metformin alone, he therefore "expected some additional improvements

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[8] References to the transcript will be cited in the following form: "Date, Tr. at __", followed by the witnesses name in parenthesis, where appropriate.

in the glucose control of the patients treated with the combination." 6/8/10 Tr. at 18 (Müller)

13. Damsbo, who worked with Müller, testified that metformin was the first drug they tested in combination with repaglinide because repaglinide "was a natural thing to combine with a sensitizer . . . it's not more complicated than that." 8/5/10 Tr. at 49 (Damsbo). That combination "was the only relevant other angle for treating Type II diabetes . . . apart from the sulfonylureas." *Id*. at 52. The sensitizer metformin was chosen because, by attacking the disease from different angles, "you might get a better effect, a synergistic effect." *Id*. at 54 [].

14. Müller had another reason for studying the effect of the repaglinide/metformin combination on patients that were not adequately controlled on metformin alone. While monotherapy with a new drug is necessary for regulatory review:

> you also try to keep a focus on how you can prove something new and exciting, not least for your marketing colleagues when they have to go out and sell your product after approval . . . [T]his would be an obvious – not obvious, but a good idea of where to expand your market . . . . It would be a scientifically sound thing to do. It would not cannibalize on the markets we were already looking for. So in that respect, I think it made sense.

6/8/10 Tr. at 13-14 (Müller).

15. The protocol for a clinical trial of the repaglinide/metformin combination on patients failing on metformin alone was developed under Müller's direc-

tion. *Id*. at 22. The study was conducted in Australia during 1995-96 by a team of investigators led by Moses. 8/5/10 Tr. at 201 (Miller).

16. On June 13, 1997, Novo filed a patent application on this combination therapy in Denmark, and filed a provisional application in the United States on October 29, 1997. The '358 patent was granted on January 13, 2004. The critical date for prior art under 35 U.S.C. § 102(b) is therefore October 29, 1996. The same critical date applies to prior art under § 102(b)/103. *See* Memorandum of June 9, 2010 (Doc. 417).

17. Claim 4, the only claim in suit, reads as follows:

> 4. A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.

C. Prosecution History

18. The patent examiner issued four successive rejections of Müller's application as obvious over the prior art. The first rejection was based upon a 1996 written by one of Novo's expert witnesses, Melander. (Melander Article).[9] The examiner stated:

> Melander teaches combination therapy as a rational approach to the treatment of NIDDM comprising administering agents that have different mechanisms of action and

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9 *See* Appendix I and n.1, *supra*.

> different side-effect profiles. . . . One skilled in the diabetes art would have been motivated to combine two hypoglycemic agents as one pharmaceutical composition to treat NIDDM based on their onsets and durations of action in view of the teaching of Melander. Such would have been obvious in the absence of evidence to the contrary because it would have been reasonable to expect clinical efficacy to be additive, while dosage and side-effect profiles could be decreased, following the administration of clinically effective agents that demonstrate different modes of action.

JX 2A, Tab 3 at C0172889-90, Office Action dated 10/19/2000.

19. In response, Novo's argument included reliance on Example 3 of the application, which contains the data from the Moses Study, as demonstrating an unexpected "synergistic effect." *Id*. at Tab 4, C0172904-05, Amendment and Response filed 1/15/2002.

20. The examiner then repeated her obviousness rejection based upon the Melander Article and made the rejection [f]inal. *Id*. at Tab 6, C0172930-31, dated 3/15/2001.

21. Novo's next Amendment and Response argued that the Melander Article did not suggest the specific combination of repaglinide and metformin; that "obvious to try" is not a proper basis for rejection (KSR's endorsement of that basis had not yet occurred); and again argued that Example 3 in the application dem-

onstrated an unexpected synergistic effect. *Id*. at Tab 8, C0172937-39, dated 7/6/2001.

22. The examiner withdrew the Final Rejection because she entered an additional ground of rejection, not here relevant. She further stated that the claims failed to recite a synergistic effect in quantitative terms, and repeated her position that Melander's teaching made the claimed combination obvious. *Id*. at Tab 9, C0172944-45, dated 7/23/2001.

23. Novo then repeated its earlier arguments, adding that the law does not require that the improved or unexpected properties relied upon be included in the claims. *Id.* at Tab 11, C0172955-57, dated 1/15/2002.

24. A fourth and final obviousness rejection of all claims followed:

> The prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy [additional prior art publications omitted]. One skilled in the diabetic art would have been motivated to combine metformin for its longer acting effects and its ability to reduce blood glucose levels with a shorter acting, insulin-releasing agent having a rapid onset of action, in view of the teachings of Melander. Repaglinide and A-4166, which are more rapid in their onset of action and are shorter-acting, and are specifically disclosed by Melander, would have reasonably been preferable to the older sulfonylureas.

Id. at Tab 13, C0173001-02, dated 4/16/2002.

25. Novo's next Amendment and Response reiterated its "unexpected and synergistic effect" arguments, and submitted a Declaration of Sturis (Sturis Declaration, PX 233). The Sturis Declaration reported the results of his study of the repaglinide/metformin combination on Zucker obese rats,[10] and concluded that his data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002.

26. Although the Sturis Declaration did not itself conclude that the test results were either unexpected or surprising, the accompanying Remarks of Novo's attorney, Dr. Richard Bork (Bork), asserted that the data contained in the application and in the Declaration "provides clear evidence of synergy . . . in the treatment of type II diabetes," and that any prima facie case of obviousness "is rebutted by the evidence of synergistic and surprising results achieved by the claimed combined therapy in humans." *Id*. at Tab 14, C0173010.

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[10] Zucker obese rats are a breed of rats specifically bred for use in research as models for obesity, diabetes and heart disease. *See* http://www.ratbehavior.org/RatSpecies.htm (last visited Jan. 13, 2011).

27. These submissions caused the examiner to withdraw her rejection of claims to the repaglinide/metformin combination. She unequivocally stated her reason:

> Based solely on the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14, which are limited to the combination of metformin and repaglinide, this rejection of record is withdrawn for claims 25-29 and 31-33. Neither the Declaration nor the showing in the specification is directed to an unexpected synergistic effect resulting from the combination of compound AY4166 [nateglinide] and metformin. For the reasons of record, the rejection of record under 35 U.S.C. 103 is maintained with respect to claim 30.

Id. at Tab 17, C0173146. Although the examiner's first sentence is clear enough, the second sentence confirms that it was the presence or absence of evidence of the "unexpected synergistic effect" that was the sole basis of her decision. Although the examiner's first rejection opined that it was "reasonable to expect clinical efficacy to be additive" when drugs having differing modes of action were combined, the examiner cited no prior art describing or predicting synergistic (i.e., more than additive) results.

28. Additional Patent Office proceedings, not relevant to the issue of validity of Claim 4 in suit, followed the examiner's withdrawal of the rejection, and the '358 Patent issued on January 13, 2004. (JX 1).

Claim 4 corresponds to application claim 29, which was never amended during the prosecution of the application.

VI. ANTICIPATION

A. Discussion

29. Caraco contends that Claim 4 is anticipated by [ ]Rachman's 1995 article (Rachman). The article teaches the benefits of combination therapy for treatment of Type II diabetes, using insulin sensitizers and insulin secretagogues. It specifically identifies metformin as one of the first group and repaglinide as one of the second. Novo's expert, Garber, conceded that Rachman "suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients]" 8/11/10 Tr. at 87 (Garber).

30. However, Rachman does not specifically describe the metformin/repaglinide combination in its listing of many individual drugs and drug types. The article also states that it is "uncertain" whether repaglinide will have clinical advantages, "and initial studies do not indicate a major effect" (Rachman at 471). Also, Rachman is listed in the '358 Patent as a reference that was considered by the examiner.

B. Conclusion

31. In sum, Rachman, though strongly probative on the issue of obviousness, does not fairly or directly teach the claimed metformin/repaglinide combination of Claim 4, and therefore does not anticipate Claim 4; the '358 patent is not invalid on grounds of anticipation.

VII. OBVIOUSNESS

A. Discussion

1. The Level of Skill in the Art

32. A person of ordinary skill in the art is a person having a medical degree with training in endocrinology and three years of clinical experience or laboratory research in the field of diabetes treatment. 6/1/10 Tr. at 100 (Accili). This definition, based on Accili's definition, is similar to Garber's except that the latter's definition would require that the three years of experience be in clinical treatment of diabetes. 8/10/10 Tr. at 109 (Garber). The inclusion of the alternative laboratory research experience is appropriate because excellent diabetes research on OADs has been done by laboratory researchers without clinical experience but having familiarity with OAD uses and combinations. 6/1/10 Tr. at 100 (Accili).

2. The Prior Art

33. The critical date for prior art under 35 U.S.C. § 102(b)/103 is October 29, 1996. *See*, ¶ 16, *supra*.

34. Garber testified that the prior art taught "two drugs are better than one" when they have "different mechanisms of actions" and attack diabetes from different angles. 8/11/10 Tr. at 51 (Garber). In response to the Court's question, Garber also agreed that "in general any two drugs which have different mechanisms of action are better than one." *Id*. at 53. Melander testified that the logical progression in testing new diabetes drugs is to test it in monotherapy, including comparison with other monotherapy drugs; then, if successful in monotherapy, in most

cases the "next logical step" is to test the drug in combination therapy. 8/9/10 Tr. at 183 (Melander).

35. The "most widely used and most extensively studied" OAD combination as of the critical date was metformin (an insulin sensitizer) combined with a sulfonylurea (a class of insulin secretagogues). (Consensus Statement at 1517); *see also* 6/1/10 Tr. at 125-26 (Accili). "[D]octors have been treating diabetes patients with combinations of metformin with secretagogues for about a half of a century." 8/11/10 Tr. at 44 (Garber). This combination had been prescribed both as separate and as co-formulated tablets. 6/1/10 Tr. at 128 (Accili); 8/11/10 Tr. at 44 (Garber).

36. The rationale for the metformin/secretagogue combination therapy is well summarized in the Melander Article[11] and was further explained by Accili at trial. Insulin secretagogues are OADs that act upon the pancreas' beta-cells to stimulate insulin secretion, thereby lowering blood glucose. OADs that reduce insulin resistance are "insulin sensitizers," because they increase receptivity of muscle and fat tissue to insulin's action. Thus, sensitizers improve glucose utilization by the body, and act on the liver to reduce glucose production there. 6/1/10 Tr. at 114-16 (Accili). Melander taught that if monotherapy with either of these types of drugs does not result in near-normal glucose levels:

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[11] The Melander Article was published in September, 1996, before the critical date, and is a survey of pre-1996 literature rather than an original study. 6/7/10 Tr. at 23-25 (Accili).

> [C]ombination treatment seems rational for a number of reasons. These agents have different mechanism of action and different side-effects; hence the clinical efficacy would be additive while dosage and side-effects could be minimized.

(Melander Article at 146).

37. Other prior art reported the beneficial effect of combination therapy using the sensitizer metformin with secretagogues such as the sulfonylureas, because of their different mechanisms of action. A 1965 article stated that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin, and the diguanides [biguanides, such as metformin] to potentiate its effect on the tissues. . . . The *apparent synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clarke at 1251) (emphasis added); 6/1/10 Tr. at 127 (Accili).

38. In 1995, the Consensus Statement reported that "the availability of agents that act by differing mechanisms or may have differing side effects permits the design of individualized regimens that address the heterogeneity of the pathophysiology of NIDDM." (Consensus Statement at 1515). After discussing sulfonylureas and metformin, the Consensus Statement observed that where glycemic goals are not maintained with an initial medication, "in most patients, it is reasonable to consider combination therapy." *Id*. at 1517. Further, "[t]he most widely used and most extensively studied combinations are a sulfonylurea plus metformin or a sulfonylurea plus

insulin." *Id.* *See also*, 6/1/10 Tr. at 125-26 and 148 (Accili).

39. Metformin is a member of the biguanide class, the oldest class of insulin sensitizers. Of the three members of that class known before the critical date, it was the only one currently available for clinical practice in most countries, the other two either having been withdrawn or never approved because of safety issues. 6/1/10 Tr. at 116 (Accili); Melander Article at 145. Metformin was approved by the FDA in 1995, and quickly became popular in the United States, both in monotherapy and combination therapy. 6/1/10 Tr. at 119 (Accili).

40. Two classes of insulin secretagogues were known before the critical date: sulfonylureas (used since the 1950s) and meglitinides (repaglinide and netaglinide). At that time, only the sulfonylureas were approved by a regulatory body for treatment of NIDDM. The Melander Article identified two new non-sulfonylurea "insulin-releasing drugs," then under study: repaglinide and A-4166 (netaglinide, repaglinide's sister meglitinide). He described them as having similar action to sulfonylureas, though absorbed and eliminated more quickly. Although they had not yet been approved, Melander said they "look very promising" because possibly less likely than sulfonylureas to cause dangerously low blood sugar levels. (Melander Article at 145). *See also*, 6/1/10 Tr. at 114-15 (Accili); 8/9/10 Tr. at 145 (Melander). Melander himself admitted at trial that his article would have encouraged a person of ordinary skill in the art to scientifically study the combination of repaglinide with metformin. 8/9/10 Tr. at 197 (Melander).

41. A 1995 article also encouraged combining OADs having different mechanisms of action, because "the limited efficacy of sulphonylureas and metformin on their own . . . make polypharmacy inevitable in many cases." (Rachman at 474). He added that it was "likely" that such therapy "will have additive effect." *Id*. at 467. The article specifically described repaglinide as a "non-sulphonylurea secretagogue." *Id*. at 471. Although Rachman did not specifically describe the repaglinide/metformin combination, Garber conceded that Rachman "suggests that metformin combined with repaglinide will give you additive effects [in diabetes patients]." 8/11/10 Tr. at 87 (Garber).

42. Further evidence of the state of the art as of the October 29, 1996 critical date is found in a November 12, 1996 publication (Kaku). Although published two weeks after the critical date, Garber agreed that the article was "just recapping the prior art" and that it had been written and submitted for publication 2-6 months earlier.[12] 8/11/10 Tr. at 78, 83-84 (Garber). Kaku described repaglinide as a "new insulin secretagogue" that is rapid and short-acting, and stated that "it is expected to be used" to improve postprandial hyperglycemia and to reduce delayed hypoglycemia (Kaku at NOVO-6741638). He also stated that that "combination therapy using these agents will be performed largely, because these

[12] "The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art." *Ecolochem, Inc. v. So. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).

agents have individual unique characteristics." *Id*. at NOVO-6741641. Figure 2 of the article displayed secretagogues as being combined with biguanide sensitizers (such as metformin). *Id*. at NOVO-6741644.

43. Garber acknowledged that, before the critical date, one of ordinary skill in the art "may" have considered repaglinide an appropriate candidate for combination therapy for at least some patient populations (namely, those whose "post-prandial," or after-meal, glucose levels were not under control.) 8/11/10 Tr. at 94 (Garber).

44. As part of the argument that it would not have been obvious to try combining repaglinide with metformin, Novo asserted that in 1996 there were at least 44 known OADs that provide at least 900 possible two-drug OAD combinations. *See* PX 477. This list includes seven insulin sensitizers (one biguanide, i.e., metformin and six TZDs), twenty insulin secretagogues (fifteen sulfonylureas and five meglitinides, including repaglinide), five glucose absorption inhibitors, six gluconeogenesis inhibitors and six weight-loss agents. Appropriately, Novo listed but did not count among the 44 OADs two other biguanides that were widely recognized as unsafe.

45. Accili, however, disagreed that each of these 44 OADs was appropriate for treatment of Type II diabetes. He considered the list "the proverbial kitchen sink," including drugs whose use would be considered malpractice. He named seven of the 44 that he could not in good conscience prescribe to anyone. 6/3/10 Tr. at 21 (Accili). In response to the Court's questions, Accili stated that Novo's expanded list included drugs that had been considered as po-

tential OADs at some time before 1996, but had been "totally discredited" by 1996. *Id*. at 21-22. He gave specific reasons, such as limited efficacy, discontinued availability, toxicity or other concerns for long-term safety. *Id.* at 8-13, 18, 24. Even Garber admitted that there were "no reputable weight-loss agents" due to "either limited efficacy or . . . concerns about their long-term safety." 8/11/10 Tr. at 75 (Garber). Similarly, he admitted that development of gluconeogenesis inhibitors "had been hampered by toxicity," and that none had reached the market even as of today. *Id*.

46. Later, again in response to the Court's questions, Accili stated that Novo's expanded list was the "potential universe" but it would have to be modified to show the "effective universe." 6/7/10 Tr. at 22-23 (Accili). At the Court's request, Accili prepared a chart showing the effective universe of OAD drugs. PX 477A, a copy of which is found in Appendix II. The chart lists (1) five sensitizers, including one biguanide (metformin) and four TZDs; (2) nine insulin secretagogues, including seven sulfonylureas and two meglitinides (repaglinide and nateglinide); and two glucose absorption inhibitors. As of the critical date, the TZDs were still in the testing stage, some having been withdrawn. Only two were considered viable, and none was approved by the FDA until 1997. 6/1/10 Tr. at 119 (Accili). Glucose absorption inhibitors interfere with the conversion of carbohydrates to glucose in the small intestine. As of the critical date it was known that this class of drugs does not directly treat either of the two causes of NIDDM, i.e., decreased insulin secretion or impaired insulin action. One of these, acerbose, was used be-

fore the critical date, but was known to have a modest effect relative to metformin and the sulfonylureas. 6/1/10 Tr. at 119-20 (Accili).

47. According to the Consensus Statement, the metformin/sulfonylurea combinations had already been widely studied and used, and several other potential combinations had been examined and used to a lesser extent. Consensus Statement at 1517. Thus, the untested candidates for combination therapy represented only a fraction of the seventeen OADs comprising the effective universe charted on PX 477A. Melander explained that it would have been "more interesting scientifically and clinically to examine combination therapies with metformin and repaglinide," as well as some others, than the already studied combinations of metformin and sulfonylureas. 8/9/10 Tr. at 195-96 (Melander).

48. Accili's testimony regarding the effective universe of candidates for combination therapy was credible. As of the critical date, this universe of potential or previously combined OADs included a "finite number of identified, predictable solutions." *KSR, supra.* The guidance provided by the prior art's teaching of the benefits of combining insulin secretagogues and insulin sensitizers created a reasonable expectation of success in achieving at least additive results from combination of these candidate OADs. *See Bayer Schering* and *Pfizer, supra*. In other words, the Court is not persuaded by Novo's argument that it was not obvious by the prior art to try combining repaglinide and metformin. Indeed, as explained above and below, quite the opposite was true.

49. Novo also asserts that prima facie obviousness is precluded because the prior art taught away from the claimed combination. Specifically, repaglinide was known to have a small impact on fasting plasma glucose (FPG) due to its short biological activity life.

50. According to Melander[,] because repaglinide was quick-acting and quickly eliminated from the body, it was viewed as a "niche compound" useful for only a "narrow and very specific patient population." 8/9/10 Tr. at 84 (Melander). However, Melander's own article, after citing these properties, stated that repaglinide would lessen certain risks and looked "very promising." (Melander Article at 145). He also admitted that his article taught that a short-acting sulfonylurea (glipizide) could be combined with metformin in some circumstances, without problem; that all sulfonylureas, in principle, achieve the same results; that "sulfonylurea and repaglinide are alternatives if you're looking for an insulin secretagogue;" and that the article encouraged a person of ordinary skill to study the metformin/repaglinide combination. 8/9/10 Tr. at 177-78, 182, 193-94, 197-98 (Melander); *see also* 8/11/10 Tr. at 64-66 (Garber). And Garber admitted that even if repaglinide were not beneficial for high-FPG patients, Rachman still suggested that its combination with metformin could produce additive effects and be useful for patients with elevated post-prandial glucose. *Id*. at 87, 94 (Garber); Rachman.

51. The examiner, as more fully quoted above (¶¶ 18, 24), also cited the Melander Article to support her view that rapid and short-acting repaglinide "would have reasonably been preferable to the older sulfonylureas" for combination with longer-acting

metformin. PX 2A at Tab 13, C0173001-02, dated 4/16/2002.

52. In sum, the prior art as a whole did not teach away from combining repaglinide with metformin, even if beneficial results might not be obtained for all Type II diabetes patients.

3. Prima Facie Obviousness

53. As presented in detail above, the record clearly and convincingly establishes that the prior art supplied the teaching, suggestion and motivation to combine repaglinide with metformin as combination therapy for Type II diabetes. The prior art taught that two drugs having different mechanisms of action in treating Type II diabetes are better than one.

54. The combination of metformin (an insulin sensitizer) and a sulfonylurea (a class of insulin secretagogues) had been widely studied and successfully used because of their differing mechanisms of action. This drug combination was the closest prior art. The prior art described the effect of this combination therapy as additive and synergistic.

55. Repaglinide was a known insulin secretagogue having a similar mechanism of action to sulfonylureas, especially the fast-acting sulfonylureas, and hence was known to have a different mechanism of action than metformin.

56. It was a logical testing progression to try combination therapy once monotherapy with a new drug (here, repaglinide) proved successful. Clinical efficacy would be additive while dosage and side-effects could be minimized.

57. Whether looking for a secretagogue to combine with metformin, or a sensitizer to combine with repaglinide, a finite number of identified predictable solutions existed among the OADs in the effective universe of candidates for combination therapy.

58. Metformin was the most widely used insulin sensitizer, and the only one available in most countries. The effective universe of insulin secretagogues to combine with it comprised a maximum of seven sulfonylureas (several of which had already been successfully so combined), and two new meglitinides (repaglinide and nateglinide).

59. The effective universe of insulin sensitizers to combine with repaglinide comprised a maximum of four TZDs and one biguanide (metformin, the most widely used sensitizer). This universe qualifies as a "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421.

60. Novo's experts admitted that the prior art suggested to persons of ordinary skill in the art that the combination of repaglinide and metformin be studied (Melander), and that such combination would produce additive effects in the control of glucose levels in Type II diabetes patients (Garber). There was a reasonable expectation of successful and beneficial results from the claimed combination, including reduction in HbA_{1c}, FPG and insulin resistance.

61. Market pressure motivated Müller to expand Novo's market for repaglinide by incorporating it in combination therapy as well as in monotherapy.

62. Müller, who was charged with developing repaglinide for the market, considered it a good idea to combine it with metformin because of their comple-

mentary mechanisms of action. He expected such combination therapy to provide additional improvement in glucose control for patients inadequately controlled on metformin alone.

63. Metformin was the first and only sensitizer chosen by Müller for combination therapy testing with repaglinide. His colleague, Damsbo, considered it the "natural" combination, and the only relevant angle for treatment other than a sulfonylurea.

64. These facts are reinforced by the repeated rulings of the examiner, quoted above, regarding the teaching, suggestion and motivation provided by the prior art, based primarily upon the same Melander Article. Significantly, the examiner did not have the benefit of the testimony Müller and Damsbo as to their motivation to make the claimed combination, and their expectations for its results. Those expectations were consistent with those taught by the prior art.

65. In view of these facts, established by clear and convincing evidence, a person of ordinary skill in the art, as of the critical date, would have found it obvious to try the combination of metformin with repaglinide as a potential treatment for Type II diabetes. As such, the Court finds that a prima facie case of obviousness exists.

4. Secondary Considerations

(a) Background and Relevant Precedents—Unexpected Results

66. Before reaching the ultimate conclusion on the issue of obviousness, the evidence and assertions of unexpected and surprising results, as well as syner-

gistic results, must be considered. The case law has sometimes referred to this factor as a "secondary" consideration, placing it in the category with commercial success, copying, failure of others and long-felt but unsolved need. These sources of evidence provide only an indirect bas[i]s for inferring nonobviousness, whereas the Court views evidence of surprising or expected properties as more direct and technological evidence bearing more directly on the statutory inquiry as to "the differences between the subject matter sought to be patented and the prior art."[13] 35 U.S.C. § 103(a). Because in patent law, "a compound and all of its properties are inseparable," evidence of the properties of the claimed compound is directly relevant to show what the claimed invention is. *In re Papesch*, 315 F.2d 381, 391, 50 C.C.P.A. 1084, 1963 Dec. Comm'r Pat. 334 (C.C.P.A 1963).

67. In response to a question by the Court, Novo's counsel provided a useful definition: "a surprising result or surprise in the context of this case would be if there is a result that is inconsistent with what was known in the art, inconsistent with an expectation of a person of skill in the art based on the literature or the accumulated knowledge . . . ." 8/5/10 Tr. at 29.

68. Two contrasting Federal Circuit decisions involving allegedly unexpected results provide a useful perspective and framing for the present issue. First, in *McNeil-PPC, Inc. v. L. Perrigo, Co.*, 337 F.3d 1362

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[13] On this and other points, the thorough and insightful analysis of Professor Rebecca S. Eisenberg in her article, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 418 (2008) should be considered.

(Fed. Cir. 2003), McNeil was faced with the expiration of its patent on loperamide, the active ingredient in its best-selling antidiarrheal product. McNeil sought to patent an improvement to extend its market-leading position. *Id*. at 1364. The patent had composition and method claims drawn to loperamide (or one of a specified group of other antidiarrheal compounds) in combination with the known antiflatulent simethicone for the treatment of diarrhea and flatulence (gas). The prior art described many combinations of various antidiarrheal drugs with simethicone, and the court found it obvious to substitute loperamide in the combination with simethicone, *id.* at 1367). Thus, the Federal Circuit found the patents invalid. The Federal Circuit also found that the district court had properly discounted the secondary indicia of nonobviousness, in that McNeil had commercial motivation to make the combination; the evidence commercial success was obscured by massive advertising; and the proffered clinical studies were too inconsistent and lacking in appropriate comparative tests to demonstrate unexpected or synergistic effects. *Id*. at 1370.[14]

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[14] Caraco strongly relies on *Richardson-Vicks, Inc. v. Upjohn Co.*, et al, 122 F.3d 1476 (Fed. Cir. 1997), where obviousness was found, notwithstanding unexpected and unchallenged synergism. While that case has many factual similarities to the present case, a careful reading reveals that the only difference between the claimed combination and the prior art was that the same two prior art drugs that were claimed in the patent as a "combinatory immixture" (i.e., in a single tablet) had been prescribed together but as separate tablets. *Id.* at 1480, 1483-84. Relevant to the issue of claim scope discussed in Part VI(A)(4)(a)(iv), *infra*, the examiner allowed the claims only

69. In *Ortho-McNeil v. Mylan Laboratories*, 520 F.3d 1358 (Fed. Cir. 2008), the patent was directed to a new chemical compound that has had substantial commercial success as a significant epilepsy drug. The new compound was created as an intermediate byproduct in the course of the inventor's search for a new antidiabetes drug. The record showed that it was unlikely that a person of ordinary skill would have started with the formulation that the inventor started with; there were no clues as to what properties that the claimed intermediate might have; and no reason to interrupt the development process and test this intermediate "for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes)." *Id.* at 1364. The court observed that "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness. *Id.* The record also showed "powerful unexpected results," skepticism of experts, copying and commercial success. *Id*. at 1365. Accordingly, the Federal Circuit affirmed the holding of nonobviousness.[15]

[Footnote continued from previous page]

when a new claim set limited in scope to the specific dosages used in the synergy-proving tests was submitted. *Id*. at 1482. Thus, this case is not particularly illuminating to the issue at hand.

[15] Novo strongly relies upon *Sanofi-Synthelabo v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008), where nonobviousness was found. Unlike Müller's combination of two prior art drugs, following the roadmap of the prior art, the patent in *Sanofi* was on an entirely new compound for preventing blood-thrombotic

70. These cases illustrate that determining whether an unexpected result exists requires a detailed factual analysis of the trial record.

(b) The Trial Record—Unexpected Results

71. The question of unexpected and surprising results was extensively and vigorously contested by the experts at trial. All of them, including Garber, aided in an understanding of this complex subject matter. However, on the particular issue of unexpected results, Garber was frequently required to retreat from opinions expressed in his direct testimony when confronted by his earlier deposition testimony and his own and others' prior contradictory publications.

72. Although the examiner cited the Melander Article as suggesting that combination therapy should be additive, she cited no predictions or reports of synergistic results from the closest prior art. As noted above (¶ 27), the examiner ultimately withdrew her rejection of Claim 4 "solely" on the basis of the evidence of the unexpected synergistic effects of the claimed combination. However, the examiner:

[Footnote continued from previous page]

events such as heart attacks and strokes. It resulted from a very complex, costly and unpredictable process of separating components of a compound that itself had been the result of years of costly trial and error research. The physical properties of the separated components, even if they could be obtained, were not only unpredictable, but were most likely to have an unpredictable blend of beneficial and toxic properties. The component that became the subject of the patent had the "rare" characteristic of possessing only favorable activity and no toxicity. *Id*. at 1080-81, 1087-90. Thus, this case is not analogous.

- did not have the benefit of the testimony of Müller and Damsbo as to the results they expected (¶¶ 12-13, *supra*);
- was unaware that several prior art publications described or predicted synergistic results from combination therapy with metformin and secretagogues of the sulfonylurea type (¶¶ 71-75 *infra*);
- did not have the benefit of expert testimony concerning reasonable expectations for, and explanation of the results of, the claimed combination (¶¶ 34-36, 40-43, 50 *supra*; 83-85, *infra*);
- was unaware of the undisclosed conclusions of the Sturis Declaration (¶ 141, *infra*).

70. Repaglinide was known to have properties and effects similar to those of the sulfonylureas in the context of combination therapy. The teachings of several prior art or contemporaneous publications have been described above. (Melander Article, Rachman and Kaku). Moreover, the examiner herself observed that, because of its properties, repaglinide "would have reasonably been preferable to the older sulfonylureas" in combination with metformin. JX 2A at Tab 13, C0173002.

71. Indeed, a 1995 article discussing the results of clinical trials stated that the differing mechanisms of action of metformin and sulfonylureas "can be used alone or together to produce synergistic, if not complementary, actions in various clinical situations." "When metformin and sulfonylureas are used in dual therapy, there is an apparent synergy of action . . . .

Such synergy should produce adequate glycemic control in all but the most severe or advanced cases of NIDDM." Karlsson/Garber (DX 307 at 78, 81) (emphasis added).

72. Referring to the results of other clinical trials involving the diguanide (or biguanide) metformin and a sulfonylurea, Clarke, in 1965, *see*, ¶ 37, *supra*, states that "[t]he two drugs thus act synergistically, the sulphonylureas to augment release and plasma activity of insulin, and the diguanides to potentiate its effect on the tissues. . . . The apparent *synergistic* effect of the sulphonylureas and diguanides is probably due to their different modes of hypoglycaemic action." (Clark at C0173325[,] emphasis added).

73. A 1995 article by Novo's expert, Garber, states that:

> Combination therapy with both sulfonylureas and metformin is the next logical step to control NIDDM patients not adequately treated with either agent alone. Additive or synergistic action to control hyperglycemia should be anticipated . . . .

(Garber at 84[,] emphasis added).

74. Another 1995 article by Garber refers to the extensive clinical experience with metformin in Europe and Canada in the past 30 years, and states that "[i]t may also be used in combination with a sulfonylurea in patients not responding adequately to sulfonylurea or metformin monotherapy, because these agents work by different mechanisms and appear to have a *synergistic* effect when used concomitantly." (Garber II at 568, emphasis added, *see also* at 578-80).

75. Similarly, a 1995 Bristol-Myers Squibb Company product monograph describing its Glucophage brand metformin drug states that it is "synergistic in combination with a sulfonylurea." (Bristol-Myers at 3, emphasis added).

76. As of the critical date, a person of ordinary skill in the art would have reasonably expected success in the form of beneficial, and even synergistic, results in the control of glucose levels by combination therapy using metformin and repaglinide. This finding is based upon the evidence described above establishing that: (1) the closest prior art was combination therapy using metformin and a sulfonylurea; (2) combination therapy using metformin and one of the sulfonylurea class of secretagogues was well known in the art to produce beneficial and even synergistic results in controlling glucose levels in Type II diabetes patients; (3) repaglinide was known as an insulin secretagogue having a similar mechanism of action to the sulfonylurea class of secretagogues.

77. As part of its counterargument, Novo relies on three studies to support its claim of substantial and unexpected improvements in glucose control and insulin sensitivity resulting from metformin/repaglinide combination therapy: the Moses Study, that was the basis for data found in the '358 Patent, the Sturis Study, and the Pfeiffer Study. Each study is discussed in turn below.

(i) The Moses Study

78. For the Moses Study, patients failing on metformin monotherapy were chosen for the test population. One test parameter was HbA_{1c} or glycosylated hemoglobin, which shows the average glucose level in

the recent past. Combination therapy reduced that level by 1.41%, about twice the drop produced by the two monotherapy treatment results combined. 8/5/10 Tr. at 124 (Miller); Moses Study at table 8-1, Figure 8-1; top half of DX 393, page 2.

79. Novo particularly emphasizes the dramatic reductions in fasting plasma glucose (FPG) levels resulting from metformin/repaglinide combination therapy for the patients in the Moses Study. Novo's witnesses testified that little or no reduction in FPG was expected in patients who were failing on metformin monotherapy because of repaglinide's known short duration of action. 8/10/14 Tr. at 148 (Garber); 6/7/10 Tr. at 91, 97-98 (Moses). Yet the combination therapy test results showed a reduction in FPG of more than eight times the reduction achieved by metformin alone. (Moses Study at Table 8-3, Figure 8-2; top half of DX 393, page 1). This result was asserted to be even more surprising because achieved with lower repaglinide dosages than given to the repaglinide monotherapy patients in the study, i.e. an unexpected "dose-sparing effect."

80. Various Novo witnesses and documents described the Moses Study results as "suggestive" of synergy, or showing synergistic "effects" or "properties" in the metformin/repaglinide combination. These qualifications were appropriate, because it was agreed that the Moses Study was not designed to show, and could not show, statistically significant synergy because ethical reasons precluded removing the sick patients from all therapy in order to perform the required placebo-placebo control group arm of a more comprehensive test. *See[,] e.g.*, 6/7/10 Tr. at 120

(Pagano); 6/10/10 Tr. at 54-55 (Thaler); 6/7/10 Tr. at 89 (Moses).

81. Novo contends that, to this day, there is no explanation for the unexpected improvements in HbA_{1c} and FPG resulting from this combination therapy, and no explanation for the "dose-sparing effects" from such therapy.

82. However, the dispositive fact in this analysis of Novo's various study test results, however, is whether the results were unexpected, not whether they were suggestive of synergism or even statistically synergistic. *See* MPEP § 716.02(c), quoted in footnote 3, *supra*. If synergistic results were expected, they would not negate obviousness. Moreover, a convincing explanation for the Moses Study test results was offered at trial.

83. Accili explained that the patients in the Moses Study, chosen because they were failing on metformin monotherapy, were therefore experiencing the effects of glucose toxicity and insulin resistance, wherein the body resists insulin's action. 6/1/10 Tr. at 110-12 (Accili). In this condition, the pancreas no longer can compensate for this insulin resistance. Both post-prandial and fasting hyperglycemia result, the former because the body is unable to process glucose from the meal, and the latter because of increased glucose production by the liver resulting from impaired insulin action there. The resulting hyperglycemia is self-perpetuating and extremely dangerous. On the other hand, lowering hyperglycemia in such patients "jump-starts a virtuous cycle that tends to improve glucose metabolism." *Id.* at 111-12. *See also*, 8/1/10 Tr. at 141-43 (Garber).

84. The patients in the Moses Study had been suffering from uncontrolled glycemic levels for three years. 6/3/10 Tr. at 61-62 (Accili). The prior art taught that glucose toxicity interferes with any OAD's effectiveness, including metformin's ability to improve insulin sensitivity. And reducing glucose toxicity will increase insulin sensitivity. 8/11/10 Tr. at 142-44 (Garber). Garber admitted that the prior art Clark article taught that patients suffering from glucose toxicity, upon receiving combination therapy with metformin and an insulin secretagogue (a sulfonylurea in Clark's study), saw their glucose toxicity wane, allowing the metformin to work as it should to increase insulin sensitivity. That in turn lowered their fasting plasma glucose levels below what it had been with either drug alone. *Id*. at 139-44 (Garber); Clark.

85. Garber was not surprised by Clark's explanation for the increased insulin sensitivity, as that phenomenon was understood even before that prior art article. *Id*. at 140. Clark's conclusion supplies the explanation for the "unexpected" reductions in the HbA_{1c} and FPG level improvements in the patients in the Moses Study once the secretagogue repaglinide was combined with their formerly insufficient metformin therapy. The repaglinide "jump-started a virtuous cycle" that caused their glucose toxicity to wane so that the metformin could work.

86. Similarly, the result achieved by combination therapy on the patients in the Moses Study, using lower dosages of repaglinide than used in the monotherapy, was the known "dose-sparing" consequence of combination therapy. The examiner cited the Melander Article as support for her view that "[t]he

prior art is replete with examples of combination therapy wherein side-effects are minimized, dosages are reduced and a more clinically beneficial outcome is observed as compared with monotherapy." JX 2A, Tab 13, C0173001-02; Melander Article at 146; Hermann/Melander at 1107.

87. The evidence does not establish that the claimed combination therapy produces clinical results superior to those produced by the closest prior art. The evidence is to the contrary. Two prior art studies reported greater reductions in HbA_{1c} and FPG than those of the Moses Study. The Hermann/Melander study, using metformin and the sulfonylurea glyburide, yielded a 2.3% reduction in HbA_{1c} and 6.1 mmol/l reduction in fasting plasma glucose for patients inadequate controlled on metformin monotherapy; a 2.0% reduction in HbA_{1c} and 4.8 mmol/l reduction in fasting plasma glucose for patients inadequately controlled on glyburide monotherapy; and a 2.2% reduction in HbA_{1c} and 6.1 mmol/l reduction in fasting plasma glucose for naïve patients treated with the metformin/glyburide combination. Hermann/Melander, Table 4.

88. The DeFronzo study of the same metformin/glyburide combination yielded a 1.7% drop in HbA_{1c} and 3.5 mmol/l reduction in FPG. DeFronzo; 6/2/10 Tr. at 25 (Accili). These reductions are all greater than those of the Moses Study (a 1.4% reduction in HbA_{1c} and 2.18 mmol/l reduction in FPG).

89. The probative value of these comparative numerical results is challenged by Novo, because of differences in the patient populations and treatment parameters, and the associated expectations for the

treatments. Both Novo and Caraco have stressed the important role of the particular characteristics of various Type II diabetes patient sub-populations in predicting and explaining the results of OAD therapy. While these numerical comparisons may therefore not establish that clinical results of the claimed combination were inferior to those of the closest prior art, neither does the record contain any comparative test results establishing superiority of the claimed combination.

90. But there is other less challengeable evidence that is persuasive of the fact that the clinical efficacy of the claimed combination therapy is not superior to the efficacy of the closest prior art. First, Garber is a practicing physician who has spent his entire 35-year career focused on the treatment and management of diabetes, both treating patients and conducting clinical studies. 8/10/10 Tr. at 100-01 (Garber). Garber testified that he "rarely prescribe[d]" the claimed combination, and "the situations in which I would normally use repaglinide would not be situations in which I'd normally use metformin." 8/11/10 Tr. at 132, 134 (Garber). He also testified that he was "probably not" offering an opinion that the claimed combination is superior in terms of efficacy to the prior art metformin/sulfonylurea combination. *Id*. at 112-13.

91. Second, and by contrast, Accili has spent 24 years doing research in diabetes in academia, administrative agencies and clinical capacities. He also treats patients and supervises diabetes-related clinical trials. 6/1/10 Tr. at 95-96 (Accili). Accili testified that he prescribes combination therapy with metformin and sulfonylureas about 20 times more often

than with the metformin/repaglinide combination. 6/7/10 Tr. at 37.

92. Third and finally, a Novo-financed literature review published in 2008 discusses the Moses Study and Pfeiffer Study, along with studies of metformin/sulfonylurea combinations. The author concludes that "[c]ollectively, these data indicate that combination therapy with repaglinide plus metformin may provide efficacy *comparable* to other combinations plus a favorable safety profile in the early treatment of type 2 diabetes." Raskin, at 1172 (emphasis added). Thus, twelve years after the Moses Study, Raskin was unable to conclude that the claimed combination produced results superior to those provided by the closest prior art.

93. These specific examples are reinforced by the overall market's reaction to the claimed combination. As presented more fully in Part VII(A)(4)(c) Commercial Success, *infra*, only a small and declining percentage of Type II diabetes patients taking OADs are taking the claimed combination therapy. The record as a whole therefore does not support a conclusion that the claimed combination yields superior results to those of the closest prior art.

94. Notwithstanding that several Novo witnesses testified as to their surprise at the Moses Study results, the weight of published prior art and expert testimony compels the conclusion that one of ordinary skill in the art should have expected successful, and perhaps even synergistic, results from the combination therapy given to the patients in the Moses Study.

95. Further, the trial testimony in 2010 of Novo's witnesses proclaiming their surprise in 19[9]6 concerning the unexpected and "synergistic" results of the Moses Study is unsupported by contemporaneous documents. The 1996 Clinical Trial Report of the Moses Study, signed by Moses, stated that the combination therapy "produced statistically superior glycemic control" compared to monotherapy with the two constituent drugs. There is no mention of synergism or even suggestions of synergistic effects in the Report. Nor does the Moses Study use the words "unexpected" or "surprising" anywhere in its discussion of Efficacy Results, Conclusions, Efficacy Evaluation, Efficacy Conclusions, Discussion, Overall Conclusions or anywhere else. Miller, who supervised all of Novo's clinical studies in Australia, testified in response to the Court's question that he did not know of any contemporaneous Novo document that mentioned synergism. 8/5/10 Tr. at 194-96 (Miller).

96. The only contemporaneous document in the record is a December, 1996, draft abstract prepared by Novo in Denmark for upcoming medical society meetings, and stating that the data from the Moses Study "suggest" that the claimed combination "*may* have synergistic properties in this type of patients." DX 9 (emphasis added); 6/7/10 Tr. at 84-85 (Moses); *see also* DX 12, PX 206, PX 207. Garber, who studied the paper trail, stated in response to a question by the Court that he did not recall anything exclusive of the trial record that described the results of the Moses Study as surprising and unexpected. 8/11/10 Tr. at 189-90 (Garber). As such, the Moses Study does not support Novo's contention that the claimed

combination produces unexpected results in Type II diabetes patients.

(ii) The Sturis Study

97. Novo also relies upon the Sturis Declaration, which was submitted to the examiner to reinforce the results of the Moses Study in demonstrating unexpected and synergistic results from the claimed combination therapy. Sturis stated in his Declaration that his test results showed ". . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." JX 2A at Tab 14, C0173015, 10/16/2002.

98. Sturis used Zucker obese rats for his tests. These rats are an accepted animal model with excellent predictive capabilities for humans with Type II diabetes.[16] Sturis, however, admitted at trial that his test results may not translate to humans, and that was why he relied upon the Moses Study's results as well to support his conclusion of "strongly suggest[ed]" synergy in humans. 6//9/10 Tr. at 22-24, 88-89 (Sturis). Notably, the final draft of his abstract of his study stated that "[t]he presence of greater-than additive effects *may* be of relevance to the clinical efficacy of the claimed combination." PX 242 (emphasis added). Three days after his Declaration, Sturis' PowerPoint presentation to Novo's core group in charge of repaglinide development stated with re-

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16 *See* ¶ 25, n.10, *supra*.

spect to the Moses Study that it was "not possible to assess whether REP/MET combination is additive, synergistic or antagonistic," by which he meant that it was not statistically possible to so assess. DX 56 at 105702; 6/9/10 Tr. at 91-93, 97 (Sturis). These two documents were not provided to the examiner. Sturis was unwilling to testify that the two studies together proved synergism in Type II patients. *Id.* at 99.

99. Caraco attacks several aspects of the Sturis Study, including the statistical analysis and his selection of a data point that departed from his test protocol. These issues are addressed below in Part VIII(A)(1)(a), dealing with the inequitable conduct issues.

100. The Sturis Study, while pertinent to the synergy debate, is not probative on the question of whether the claimed combination produces unexpected results in Type II diabetes patients.

(iii) The Pfeiffer Study

101. Novo also relies upon a 2003 Novo-funded study by Pfeiffer. The study compared the insulin sensitivity of patients taking only metformin with that of the same patients after they had taken the metformin/repaglinide combination. Because repaglinide is an insulin secretagogue and not an insulin sensitizer, Novo contends that one of ordinary skill in the art would not have expected the results observed by Pfeiffer: the insulin sensitivity of the patients taking both drugs was 35% greater than when those same patients were taking metformin alone. Pfeiffer Study, Pfeiffer II Study, 6/8/10 Tr. at 106-10 (Pfeiffer). Pfeiffer testified that the extent of this increase was extraordinary, statistically significant, clearly

synergistic and unexplainable even today. *Id*. at 102, 110, 118.

102. Accili questioned the reliability of conclusions that can be drawn from the Pfeiffer Study, based upon the small number of patients (eleven) and the wide range of their base line characteristics, such as body mass and changes in insulin sensitivity. 6/2/10 Tr. at 38 (Accili). *See also*, 8/11/10 Tr. at 151-52 (Garber). Caraco also asserts that Pfeiffer's results were fully predicted by the prior art Clark article, which taught that even monotherapy with an insulin secretagogue could increase insulin sensitivity. Clark at 9243; 6/8/10 Tr. at 144-49 (Pfeiffer). In response, Pfeiffer pointed out that Clark's study was with a very different type of patient. In contrast to Clark['s] patients, who were suffering from glucose toxicity, the Pfeiffer Study patients were well controlled on metformin. Pfeiffer testified that reduction in glucose toxicity could therefore not fully explain the 35% increase in sensitivity; it would only account for about a 10% increase in sensitivity. *Id*. at 144-46, 179-83 (Pfeiffer).

103. Pfeiffer's trial testimony is inconsistent with the explanation found in his contemporaneous report of his 2004 Study. There, he discussed two possible explanations for the improved insulin sensitivity. He admitted at trial that he copied his first explanation, almost verbatim, from the Clark article. 6/8/10 Tr. at 155-58 (Pfeiffer). The texts of Clark and of Pfeiffer are shown below (and in DX 416):

> The extrapancreatic effects – glucose metabolized per unit of insulin – of glimepiride treatment observed in this study are likely to

> be secondary to the improved glycemic control during the week of therapy. The latter would be associated with an increase in insulin mediated glucose disposal.

Clark at C0209243.

> This extrapancreatic effect may be related to the improved glycemic control during the one week of treatment hence to the reduction of hyperglycemia-induced insulin resistance (Yki-Jarvinen, 1992). The latter would be associated with an increase in insulin mediated glucose disposal.

Pfeiffer at NOVO-0005433.

104. This discussion describes the glucose toxicity issue, for which Pfeiffer cited Yki-Jarvinen but not Clark's article, which he admittedly copied. 6/8/10 Tr. at 155-58 (Pfeiffer); *see also*, 8/11/10 Tr. at 148-49 (Garber). Pfeiffer's report included "an alternative explanation" for which he cited prior art sources (including Clark), but he concluded that it was "*incredibly likely* that the improvement of insulin sensitivity is related to a waning of glucose toxicity." (Pfeiffer Study at NOVO-0005433, emphasis added).

105. Pfeiffer's contemporaneous explanation that he copied from Clark's prior art article (i.e., waning of glucose toxicity) for the increased insulin sensitivity found in his test results is entitled to greater credibility and weight than his trial testimony that those results were unexpected and unexplainable.

106. Aside from the issue of unexpected results, Pfeiffer's testimony concerning his study contradicts Novo's position that the study is evidence supporting

the nonobviousness of the claimed invention. Pfeiffer contended that his study's patient population was not suffering from glucose toxicity because they were well controlled on metformin at the time therapy with the metformin/repaglinide combination began. But Novo asserts that Claim 4 of the '358 Patent is explicitly limited to use for patients "in need of such treatment," i.e., in need of the combination therapy (Post-Trial Brief at 34, emphasis added). If Pfeiffer's patients were already well controlled, and therefore not "in need," then his test results cannot be probative of a "dramatic and unexpected effect of the [claimed] combination therapy" on those in need. *Id.* at 25. Thus, the Pfeiffer Study does not support a finding that the results of the combination was unexpected.

(iv) Scope of Claim 4

110. Also relevant to obviousness in terms of expected results is a determination as to the scope of Claim 4 of the '358 Patent, which specifies a method "for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need" [of] the claimed combination[.] As previously stated, the examiner ultimately granted Claim 4 "solely" on the basis of the Sturis Declaration concerning his rat study and "reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14." JX 2A, Tab 17 at C0173146.

111. During discovery, Novo admitted that Claim 4 covers "all instances in which repaglinide is administered in combination with metformin to treat NIDDM." 6/8/10 Tr. at 84-85 (Novo Response to Request for Admission No. 203)[.] Now, Novo contends

that Claim 4 is limited to use for patients "*in need of such treatment*." Novo Post-Trial Br. at 34 (emphasis by Novo). Other than stating that it does not assert that the claimed combination therapy is needed by all Type II diabetes patients, Novo does not specify who is "in need of such treatment" or how to determine whether such need exists.

112. To the extent that there is a difference in scope between "all instances" of administration and administration only to those "in need," Novo should be bound by its earlier admission. Further, Novo would presumably assert that all administrations of the claimed combination would be an infringement, without inquiring into whether the patient really was "in need" of that particular treatment.

113. By Novo's admission, Claim 4 necessarily covers administration of the combination to, e.g., patients who are drug-naïve who start on the metformin/repaglinide combination without previously having taken any OADs. Drug-naïve patients are a known and quantifiable sub-population of NIDDM patients who have received the claimed combination therapy. *See* PX 175 at NOVO-6900704, 6900707 (showing monthly totals of drug-naïve patients starting on such combination therapy).[17]

114. Novo presented no evidence that the claimed combination therapy produced unexpected or syner-

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[17] PX 175 is a compilation of historical prescription data (including, e.g., prescriptions for repaglinide, metformin and the combination thereof) published by IMS, the industry standard source for pharmaceutical market data. 8/10/10 Tr. at 22 (Reisetter).

gistic results in drug-naïve patients. In fact, the evidence is to the contrary. In one Novo Integrated Clinical Trial Report where 56% of the tested patients were drug-naïve ("OHA-naïve" or oral antiglycemic agent-naïve, in that Report), "the synergistic effect of combination therapy observed by Moses et al was not consistently seen in this trial." (AGEE-3010, dated 12/2/02[,] at NOVO-0029328-29). In another, where all of the tested patients were drug-naïve, the conclusion was that "the combined therapy has not shown statistically better results than the drugs used in monotherapy." (AGEE-1411, dated 2/20/06, at NOVO-1008845 and 1008897).

115. The '358 Patent Abstract and the Field of the Invention both identify just one group: "NIDDM patients poorly controlled on metformin alone." The Moses Study was designed to compare the results of metformin/repaglinide combination therapy with monotherapy with either drug "in NIDDM patients inadequately controlled on MET alone." JX 1, at col. 7:66 to 8:3. The specification summarized the results by saying that: "the data also suggest that the combination of REP and MET may have synergistic properties in this type of patient." *Id*. at col. 8:30-31[.] Novo's other unexpected-result evidence was confined to Zucker obese rats (the Sturis Study) and patients whose glucose levels were adequately controlled on metformin (the Pfeiffer Study).[18]

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[18] It would appear that the latter group, being adequately controlled, were not "in need" of combination therapy. If, as Novo belatedly asserts, the scope of Claim 4 is confined to patients "in need," then the Pfeiffer Study cannot be evidence of

116. The type of NIDDM patient involved in the Moses Study (those failing on metformin alone) represents less than 25% of Type 2 diabetes patients. 8/11/10 Tr. at 127 (Garber). Müller admitted that the Moses Study results could not be extrapolated to other patient populations. 6/8/10 Tr. at 77. *See also*, 6/2/10 Tr. at 29 (Accili). Other Novo studies conducted on other patient sub-populations yielded results that were "inconsistent" with, and even "contrary to," those of the Moses Study. AGEE-3018 at 57; AGEE-3011 at 62, AGEE-1411 at 54. When Damsbo was asked how important the characteristics of a tested patient population is, he answered:

> You have to remember that Type II diabetes is a disease where you have different categories. People have different levels of the disease. So *it's very important* that the population you pick out for a starting is the same, meaning that they have the same weight, the same body mass index, the same glucose levels and the same – that the match each other. *That's critical*.

8/5/10 Tr. at 90-91 (emphasis added).

117. Consistent with Damsbo's testimony, Novo has argued that the Moses test results cannot properly be directly compared with those of the prior art DeFronzo and Hermann/Melander studies because of differences in the tested patient populations.

[Footnote continued from previous page]

unexpected results achieved by the claimed invention. Novo cannot have it both ways.

118. The Moses Study, and the evidence submitted to the Patent Office was limited to one type of patient (not counting the Zucker obese rats). Solely on the basis of that evidence, the examiner allowed Claim 4. Other patients might well have different results from the same treatment. 8/5/10 Tr. at 108 (Damsbo).

119. Thus, even if the Moses Study results in one narrow NIDDM patient sub-population were found to be unexpected, the record does not support a conclusion that the claimed combination would generate unexpected results in "all instances" of administration of that combination to NIDDM patients. In fact, the record is to the contrary, as exemplified by the evidence described above. Therefore, this is not a case where "one having ordinary skill in the art could ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." *In re Clemens*, 622 F.2d 1029, 1036 (C.C.P.A. 1980). Novo could have, but did not seek a patent claim restricted in scope to patients failing on metformin alone, or even to those failing on insulin sensitizers generally.

120. Just as a broad independent claim cannot be unobvious when a narrower dependent claim is invalid as obvious, *see Comaper Corp. v. Antec. Inc*., 596 F.3d 1343, 1350 (Fed. Cir. 2010), so here, when the evidence concerning a subset of Claim 4 (drug-naïve patients) showed no improvement over monotherapy, then prima facie obviousness of Claim 4 has not been overcome by Novo's evidence of alleged unexpected results confined to one narrow subset of patients.

(c) Commercial Success

121. Novo's claim of commercial success of the claimed invention is "a short horse soon curried."[19]

122. Only about 0.5% of NIDDM patient prescriptions for oral anti-diabetes drugs are for the claimed repaglinide/metformin combination. PX 262; 8/10/10 Tr. at 33, 35 (Reisetter). Further, from 2003 to 2007, the number of prescriptions for the claimed combination dropped from 1.24% to 0.71% of the total NIDDM patients taking OADs. PX 175; 8/10/10 Tr. at 41 (Reisetter). Reisetter, Novo's commercial success expert, agreed that use of the claimed combination dropped by 25% from 2003 to 2007. PX 366A; 8/10/10 Tr. at 44-45, 92-93.

123. As cited above, both Garber and Accili stated [a] preference for other combination therapies in their practice.

124. As evidence of commercial success or copying, Novo cites the fact that six major generic drug manufacturers have filed ANDAs for repaglinide. That argument has been rejected by the Federal Circuit. *See Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed. Appx. 978, 2010 WL 2203101, at *4 (Fed. Cir. 2009) ("we do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval"). Here, the record shows that to the extent that Caraco and other generic manufacturers are seeking to market

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[19] According to the Oxford Dictionary of Proverbs, this centuries-old saying means "A slight task is soon completed. Curried here means 'groomed with a curry-comb.'"

the combination, they are doing so only under duress because of a belief that Novo had manipulated the FDA Orange Book. This conduct has prevented them from carving out the combination from their proposed labels for repaglinide, the patent on which has expired. Novo's expert on commercial success conceded that these activities of the generic manufacturers should not be characterized as evidence of commercial success of the claimed combination. 8/10/10 Tr. at 69 (Reisetter).

125. The record falls far short of establishing commercial success of the combination therapy of Claim 4.

B. Conclusion

126. Claim 4 of the '358 Patent is invalid because the claimed combination was obvious to a person of ordinary skill in the art at the time the invention was made. Whether measured against the teaching/suggestion/motivation test or the obvious-to-try test, the record contains an abundance of clear and convincing evidence establishing a strong prima facie case of obviousness.

127. That strong prima facie case of obviousness has not been overcome by Novo's attempt to prove unexpected results and commercial success. Clear and convincing evidence establishes that the results of the claimed combination therapy said by Novo to be unexpected and unexplainable were, to the contrary, expected and explainable in light of the state of the art as of the critical date. Further, the scope of Claim 4 substantially exceeds the scope of the evidence of allegedly unexpected results, and the record clearly and convincingly precludes extending the pro-

bative value of those results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the record fails to establish that the claimed invention has been commercially successful.

VIII. INEQUITABLE CONDUCT

A. Discussion

1. Materiality

128. Caraco contends that material information concerning the Moses Study and Sturis Study was, with an intent to deceive the patent examiner, omitted and misrepresented by Sturis and Bork, the attorney who prosecuted the '358 Patent. Attention is primarily directed to their communications to the examiner on October 16, 2002. JX 2A at Tab 14.

129. As more fully quoted above (¶ 27, *supra*), the examiner's decision to allow Claim 4 of the '358 Patent was "[b]ased solely on the Sturis Declaration and reconsideration of the synergistic effects demonstrated in Example 3, pages 11-12 of the specification, and Table I, page 14." *Id*. at Tab 17, C0173146. In light of the examiner's previous four rejections based on obviousness, it is clear that the examiner considered the representations of Sturis and Bork concerning synergy (along with Example 3 of the specification) to be highly material to her decision on patentability.

130. The question of unexpectedness of results, rather than the fact or degree of synergism of those results, is the relevant inquiry as to whether prima facie obviousness has been overcome (*see* n[.]4, *supra*). It is not necessary to delve any deeper into the thicket of disputed evidence and arguments relating

to whether mathematical proof of synergism was established by either the Moses Study or Sturis Study. Nevertheless, representations to the Patent Office by Sturis and Bork about alleged synergism are relevant to the issue of inequitable conduct, in view of the examiner's focus on synergism as the sole basis for the allowance of Claim 4.

(a) The Sturis Declaration

131. Caraco asserts that the Sturis Declaration: (1) highlighted a statistically significant[20] test data point (the two-hour point) that, unknown to the examiner, was not part of his original test protocol; (2) failed to tell the examiner that the area under the glucose vs. time curve, which proved to be statistically insignificant, was the test protocol's primary endpoint; (3) failed to tell the examiner that the rat study alone did not establish that the claimed combination is synergistic in humans; (4) failed to tell the examiner that, as he reported to a Novo team responsible for repaglinide development, it was "*not possible* to assess whether rep/met combination additive, synergistic or antagonistic" based on the Moses Study, and that the Moses Study was not designed to show synergy. 6/9/10 Tr. at 74, 82-84, 130 (Sturis); DX 56 at NOVO-1015702 (emphasis added).

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[20] Statistical analyses that result in "p" values of 0.05 or less are, by accepted standards, considered statistically "significant," while values greater than 0.05 are not. 6/7/10 Tr. at 173-74 (Pagano). The p-value is a value that statisticians use to show the uncertainty in the results of a study. Values of 0.05 or less mean that there is 5 percent or less likelihood that the outcome is the result of pure chance. *Id*. at 126-27.

132. At the time of his Declaration, Sturis was a non-physician Principal Scientist at Novo Nordisk. Responding to the Court's questions, he testified that he knew that mathematical proof of synergy is helpful in getting a patent, and that the Patent Office is interested in knowing whether there is mathematical proof of synergy. 6/9/10 Tr. at 47 (Sturis). For him to be satisfied that there is synergy, he "needed statistical evidence." *Id.* at 49. Sturis knew that the Moses Study did not demonstrate synergy from a statistical point of view. *Id*. Before the filing of his Declaration, Sturis told Bork that the Moses Study did not demonstrate synergy with statistical proof, and that "you needed mathematical proof" to argue synergy to the Patent Office. *Id*. at 52; *see also*, *id*. at 42-43, 47, 53.

133. At trial, Sturis further acknowledged that viewing the Moses Study and his rat study together, he would not say that they "prove[d]" that the claimed combination has synergistic properties in human Type II diabetic patients. *Id*. at 99. Nevertheless, Sturis declared to the Patent Office that his rat study data showed:

> . . . synergistic effects on glucose tolerance in Zucker obese rats and that this data, taken together with the data presented in Example 3 of the present application, strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients.

Id. at Tab 14, C0173015, 10/16/2002[.]

134. Accili testified that Sturis' use of the qualifier "suggests" was appropriate, and that he had no disagreement with this qualified statement. Pagano, a

biostatistics expert, acknowledged that the Sturis Declaration informed the examiner of the p-values for both the area-under-the-curve and the two-hour test results, and that the tests were performed on rats rather than humans. 6/7/10 Tr. at 150-51.

135. However, Pagano criticized the fact that the two-hour data point, though statistically significant, was post hoc and "cherry-picked," in that it was not part of the original test protocol. Pagano explained that biostatisticians base their analyses on an established protocol, to avoid result-oriented conclusions. Calculation of p-values based upon a single data point that was not part of the original protocol should include a correction factor. However, Sturis did not do so with regard to the 0.02 p-value that he obtained for the two-hour test point. *Id*. at 128-32, 172-73 (Pagano).[21] Nor did Sturis inform the examiner that such data point was post hoc, or in the alternative submit the protocol so that the examiner could determine that on her own. *Id*. at 177 (Pagano); 6/9/10 Tr. at 83-84 (Sturis). Therefore, Pagano considered it "statistically unsound" for Sturis to conclude, as he expressly did with respect to that test point, that the p-value of 0.02 "shows that significant synergy exists" at that data point for the combination therapy.

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[21] Thaler testified that there is a "strict set of well-accepted guidelines for correcting or adjusting analysis obtained from the 'post hoc' analysis." 6/10/10 Tr. at 49-50 (Thaler). The Bonferroni correction is a method used in statistics to address the problems of multiple comparisons performed simultaneously. http://wikipedia.org/wiki/Bonferroni_correction (last visited Jan. 18, 2011).

JX 2A at Tab 14 at C0173015, ¶ 6B; 6/7/10 Tr. at 130-32.

136. Second, Pagano considered as incorrect Sturis' statement that the p-value of 0.061 for the protocol's original end-point of the area-under-the-curve "indicates a synergistic effect," because that p-value is greater than the 0.05 standard. *Id.* at 176-77. JX 2A, Tab 14 at C0173014, ¶ 6A. That assertion of "synergistic effect" is also contrary to Sturis' own standards requiring statistical proof. Sturis admitted that he did not disclose to the examiner that this data point was not statistically significant or that it was the protocol's primary endpoint. 6/9/10 Tr. at 63-65, 82 (Sturis).

137. Because Sturis himself admitted that the Moses Study did not prove synergism, and his rat study did not prove synergism in rats, Pagano found "no statistical support" for Sturis' stated conclusion that the combined rat and Moses Study "strongly suggests that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic patients." 6/7/10 Tr. at 130-31.

138. Thaler's testimony that the Moses Study "support[s] the finding that a synergism exists between repaglinide and metformin," and that the Sturis Study "demonstrates that repaglinide and metformin have a synergistic effect," 6/10/10 Tr. at 36, is weakened by his acknowledgment that what he was saying was "[no]thing more than that the effect of the combination of the drugs that were used was greater than the sum of the effects of the individual drugs when given alone." *Id*. at 97.

139. Sturis did not represent to the examiner that synergism in humans was mathematically proven. He also knew that his "strongly suggests" statement could make the difference between Novo getting or not getting the patent. 6/9/10 Tr. at 85-86 (Sturis). His "strongly suggests" qualified conclusion concerning the combined effect of the two studies was aggressive advocacy. However, it must be said that it has not been shown by clear and convincing evidence to be false. Nonetheless, to the extent that the examiner drew further conclusions from the Sturis Declaration per se, they were not warranted.

140. Rather, it was the material omissions from the Sturis Declaration that violated his duty to disclose material information, not the representations. Undisclosed to the examiner were the facts that the two-hour data point was not part of the test protocol, and that a correction factor had not been applied to that p-value. That data point was the only one in his rat test that appeared to produce a statistically significant p-value of less than 0.05. Also undisclosed were Sturis' opinions (listed below) that, by his own standards requiring mathematical proof, neither his rat study nor the Moses Study alone proved synergy in humans.

141. Clearly, the examiner, focused as she was on the Sturis Declaration and the "synergistic effects" described in the patent specification, would have wanted to consider Sturis' expressed negative views on synergism, inconsistent as they were with the conclusions expressed or "strongly suggest[ed]" in his Declaration, and with Bork's exaggerated arguments

based on Sturis' view. Undisclosed to the examiner were Sturis' conclusions that:

> (1) the Moses Study "*did not demonstrate synergy*" with statistical proof. 6/9/10 Tr. at 42-43, 53, 129-30 (Sturis) (emphasis added). He expressed this opinion to Bork a few months before his Declaration to the Patent Office;
>
> (2) it is "*not possible* [based on Moses' Study] to assess whether rep/met combination is additive, synergistic or antagonistic." DX 56 at NOVO-0105702 (emphasis added); 6/9/10 Tr. at 130 (Sturis). He expressed this conclusion to the Novo core repaglinide development group just a few days after his Declaration;
>
> (3) his rat study was not designed to test for synergy in humans, and the results "do not necessarily translate into humans;" 6/9/10 Tr. at 74. Indeed, in the abstract of his rat study report he was only willing to state that "[t]he presence of greater-than-additive effects may be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242[;] *id*. at 77.
>
> (4) his rat study alone does not prove that the claimed combination is actually synergistic in humans. *Id.*
>
> (5) even viewing the Moses Study and Sturis study together, Sturis would not say that they "prove[d]" that the claimed combination

> has synergistic properties in human Type II diabetic patients. *Id*. at 99.

142. Clear and convincing evidence is present that the opinions of Sturis were highly material to the patentability of Claim 4, because they refuted or were inconsistent with the opinions expressed in his Declaration in support of patentability. 37 C.F.R. § 1.56(b)(2). A reasonable examiner, focused on the issue of synergism as was the examiner here, would have wanted to consider any qualifications or reservations held by Sturis concerning the conclusions he expressed in his Declaration.

> The fact that the conduct here consists of an omission rather than a *misrepresentation* does not compel a different result, as either may mislead an examiner. An examiner must be able to evaluate information in an affidavit in context, giving it proper weight . . . Affidavits are inherently material, even if only cumulative. The affirmative act of submitting an affidavit must be construed as being intended to be relied upon.

Refac Intern., Ltd. v. Lotus Development Corp., 81 F.3d 1576, 1582-83 (Fed. Cir. 1996) (emphasis in original). Indeed, the examiner's explicit reliance on the Sturis Declaration warrants the conclusion that the Declaration satisfied the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(b) The Bork Representations

143. In support of the Sturis Declaration, Bork asserted in response to the Final Rejection:

> Applicant therefore submits that the data presented in the application, in combination with the data presented in the Declaration of Dr. Sturis, provides *clear evidence of synergy* for the use of the claimed combination of repaglinide and metformin in the treatment of type II diabetes.
>
> . . . a prima facie case [of obviousness] is rebutted by the evidence of *synergistic and surprising results* achieved by the claimed combination therapy in humans (Example application) and in Zucker obese rats (Sturis' Declaration).

JX 2A, Tab 14 at C0173010 (emphasis added).[22]

144. In light of what Bork then knew, his representations to the examiner go beyond aggressive advocacy; the representations were known by him to be unsupported by the Sturis Declaration, and known to be untrue. With respect to synergistic results in humans, the Sturis Declaration never went beyond "strongly suggests." More importantly, Sturis had previously told Bork directly that the Moses Study

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[22] The patent specification states that, with respect to NIDDM patients, "[I]t has been found that there is a synergism between repaglinide and metformin." JX-1 at col. 3, lines 11-12[.] Sturis testified that such statement was talking about humans, not rats, and that he has seen no evidence proving synergism with the combination in humans. 6/9/10 Tr. at 128 (Sturis).

did not mathematically or statistically demonstrate synergy in humans. 6/9/10 Tr. at 53-54 (Sturis). Bork's representations, however, asserted "clear evidence of synergy" and "synergistic and surprising results" in humans[.] There is no evidence that Bork's exaggerations were based on any sources other than the Sturis Study and the Moses Study.

145. In addition to the contrary information possessed by Bork at the time of his representations to the examiner, he later received explicit contrary information from Sturis. On January 1, 2003 (the '358 Patent issued a year later, on January 13, 2004), Sturis sent an e-mail to Bork, enclosing a final draft of the repaglinide/metformin abstract. The abstract sent to Bork stated: "The presence of greater-than-additive effects *may* be of relevance to the clinical efficacy of the REP-MET combination." DX 74; PX 242; 6/9/10 Tr. at 77 (Sturis) (emphasis added). Bork's duty to disclose this highly qualified statement, inconsistent with his own earlier representations to the examiner, continued until the issuance of the patent, over one year later:

> The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.

37 C.F.R. § 1.56(a).

146. The evidence is clear and convincing that Bork's representations of October 16, 2002, as well as his failure to correct them in light of the later-received information described above, went beyond acceptable advocacy because they did not contain the limitations and qualifications communicated to him

by Sturis. Further, they were highly material to patentability, because their absolute and unqualified character "refutes, or is inconsistent with, a position the applicant takes in . . . asserting an argument of patentability." *Id*. at § 1.56(b)(2). As in the case of the Sturis Declaration, they also satisfy the alternative "but for" materiality test. *Digital Control*, 437 F.3d at 1315-16.

(c) Novo's Post-Clinical Trials

147. Caraco also relies upon Novo's failure to disclose to the Patent Office the unfavorable results of several clinical trials of the repaglinide/metformin combination Novo conducted while the application for the '358 Patent was pending. In two of the trials that had been completed before the patent issued, "the synergistic effect of combination therapy observed by Moses et al was not consistently seen" (AGEE-3018 at 57; AGEE-3018 at 62). The former study concluded that "[t]he results observed in this study were *contrary* to the study by Moses et al." AGEE-3018 at 57 (emphasis added).

148. Although Müller was Novo's lead scientist in connection with repaglinide's development, and these studies were conducted out of Novo's New Jersey facility during his tenure there, he was "surprised" that he knew nothing of them until this litigation. 6/8/10 Tr. at 53 (Müller). There is no contradictory evidence concerning his unawareness of these test results in the record. And there is no evidence that Novo informed Bork of the existence or content of these test results.

149. These two Novo post-clinical trials were highly material to patentability because they refuted

or were inconsistent with Novo's representations to the Patent Office concerning the synergistic results of the Moses Study. 37 C.F.R. § 1.56(b)(2).

150. Admittedly, there is no evidence that Müller, Sturis or Bork were aware of these test results, or that Novo deliberately concealed that information from them. Under the applicable Patent Office Rules, those were the only three Novo individuals to whom the duty of candor and disclosure applied, there being no record of any other inventors, attorneys or other persons substantively involved in the preparation or prosecution of the patent application. *Id*. at § 1.56(c). *Compare, Synthon IP, Inc. v. Pfizer, Inc.*, 472 F. Supp. 2d 760, 779-80 (E.D. Va. 2007), *aff'd per curiam on inequitable conduct*[,] [281 Fed. Appx. 995] (Fed. Cir. 2008) (non-precedential):

> [T]he duty of candor cannot be avoided by willful ignorance or compartmentalization of knowledge within a company in an effort to insulate the patent applicants and their attorneys from information unfavorable to patentability.

See also, Ranbaxy Laboratories Ltd. v. Abbott laboratories, 2005 U.S. Dist. LEXIS 27753, 2005 WL 30503608, at *8 (N.D. Ill. Nov. 10, 2005). Further, the bare fact that undisclosed material information existed within a patent assignee company is insufficient to impose an obligation of disclosure. *Nordberg, Inc. v. Telsmith, Inc.*, 82 F.3d 394, 397 (Fed. Cir. 1996).

151. Overall, it must be said that Caraco did not establish by clear and convincing evidence that there was any inequitable conduct relating to Novo's fail-

ure to disclose these post-clinical trials to the Patent Office.

2. Intent

152. Sturis, as discussed above, withheld from the Patent Office the opinions he expressed to Bork and to Novo's core repaglinide development group concerning the individual significance of each of the Moses Study and his own study. Sturis also withheld his opinion, expressed at trial, that synergistic properties in humans were not proven even when these two study results are viewed together. Before the filing of his Declaration, Sturis was already aware that a showing of synergy was helpful in securing a patent, and that the examiner would be interested in knowing if there were mathematical proof of synergy. DX 79; 6/9/10 Tr. at 43-47, 85-86 (Sturis).

153. There is clear and convincing evidence in the record justifying the inference that Sturis had the intent to deceive the Patent Office by withholding his opinions and conclusions respecting the significance of the results of the Moses Study and the Sturis Study. He knew of the importance of synergism to the examiner's consideration of the patentability of the claimed invention. The close relationship of his withheld opinions and conclusions to those in his Declaration was inescapable. No plausible reason for his omissions, other than an intent to deceive, has been offered. Under the circumstances, no other reason would be credible. *McKesson, supra*, 487 F.3d at 913; *Praxair*, *supra*, 543 F.3d at 1313-14. An intent to deceive is the "single most reasonable inference able to be drawn from the evidence." *Star Scientific, supra*, 537 F.3d at 1365.

154. As previously stated, Bork was fully informed by Sturis himself of the qualified and contrary opinions he held. Bork's exaggerated arguments to the examiner in support of the Sturis Declaration went beyond aggressive advocacy; they misstated key conclusions. As a patent attorney, he had to have known of the materiality of his representations and the significance attached to them by the examiner. As in the case of Sturis, no plausible explanation, other than an intent to deceive, was offered, and none would be reasonable or credible under the circumstances. It is important to note that although Novo brought to trial witnesses from across this country and several from Europe and Australia, it did not bring Bork (presumably still in New Jersey) to testify concerning his role in the prosecution of the patent application.

155. Additional evidence of Novo's less than rigorous attitude toward its duty of candor arises from its untimely filing of the Ajinomoto Opposition papers that were filed against Novo's corresponding European application. That opposition, filed in February, 2002, presented prior art based arguments against the patentability of the European application. Novo filed its response in the European Patent Office in February, 200[2]. JX 2A at Tab 22, C0173163, item 4. It did not disclose the papers to the examiner until May 6, 2003. *Id.* at C0173162, items 1 and 4 and attached Form PTO-1449 at C0173167. Novo's submission to the Patent Office did not occur until 15 months after the filing of the European Opposition, and four months after the Patent Office had allowed Claim 4 (application claim 29).

156. Applicable Patent Office rules require that an information disclosure statement (IDS), if not filed

within three months of the application's filing date or before the mailing of a first Office action, will still be considered if accompanied by a statement that the disclosed item "was first cited in a communication from a foreign patent office in a counterpart application not more than three months prior to the filing of the [IDS]," or that "to the knowledge of the person signing the certification after making reasonable inquiry," no person subject to the duty of disclosure was aware of such item more than three months prior to the filing of the IDS. 37 C.F.R. §§ (d) and (e). Bork failed to file the required statement, and Novo failed to provide the Court with any explanation for its long delay in filing the opposition evidence until after the examiner had allowed Claim 4.

157. The MPEP makes several references to the importance of timely filing of material information. Section 609 states that the relevant rules "are designed to encourage individuals to submit information to the Office *promptly*" (emphasis added). Section 2001.06(a) focuses on the duty to disclose material information from "related foreign applications." Suggestion No. 12 of Section 2004's list of "Aids to Compliance with Duty of Disclosure" advises that "potentially material information discovered late in the prosecution should be *immediately* submitted." (emphasis added).

158. Based upon Sturis' omissions of clearly material information, the similar omissions and misrepresentations by Bork, and the unexplained and therefore apparently calculated delay in filing the Ajinomoto opposition papers, an inference of intent to deceive the examiner is appropriately inferred. *Praxair, supra*, 543 F.3d 1306, 1313-14.

159. It is clear, however, that the finding of materiality is not the basis for finding intent. Indeed, the Federal Circuit has recently emphasized that

> . . . materiality and intent are separate requirements, and intent to deceive cannot be found based on materiality alone. *Larson Mfg. Co. of S.D., Inc. v. Aluminart Prods. Ltd.*, 559 F.3d 1317, 1340 (Fed. Cir. 2009). A court cannot simply infer that an applicant "should have known" the materiality of withheld information and thus intended to deceive the PTO because the applicant knew of the information and the information is material. A district court must find some other evidence that indicates that the applicant appreciated the information's materiality.

Cancer Research Technology Ltd. v. Barr Laboratories, Inc., 625 F.3d 724, 733-34 (Fed. Cir. 2010). As explained above, there is more than just the fact that the materials withheld from the Patent Office were material which establishes intent.

B. Conclusion

159. Under prevailing law, the evidence compels the conclusion that the '358 Patent is unenforceable due to inequitable conduct in the prosecution of the patent application before the Patent Office. Sturis withheld from his Declaration highly material information with intent to deceive the patent examiner. Bork both misrepresented and withheld highly material information with intent to deceive the examiner. The violations of the duties of disclosure by both men exceeds the necessary threshold levels of materiality

and intent, and the equities warrant the conclusion that inequitable conduct occurred, and therefore the '358 patent is unenforceable.

IX. CONCLUSION

A.

Based on the findings of fact and the governing law as above, Claim 4 of the '358 patent is invalid. The claimed combination of metformin with repaglinide was obvious to a person of ordinary skill in the art at the time of the invention. Whether measured against the teaching/suggestion/motivation test or the obvious to try test, the record of the trial contains clear and convincing evidence establishing a prima facie case of obviousness. The prima facie case of obviousness was not overcome by proof of unexpected results and commercial success. The results of the combination claimed to be unexpected and unexplainable were, to the contrary, to be expected and were explainable in light of the state of the art as of the critical date. The scope of Claim 4 substantially exceeds the scope of the evidence of the asserted unexpected results, and the record clearly and convincingly precludes extending the probative value of the results beyond the small Type II diabetes patient sub-population that experienced them. Finally, the evidence in the record did not establish that the claimed invention has been commercially successful.

B.

Also, based on the findings of fact and the governing law above, Claim 4 of the '358 patent is unenforceable because of inequitable conduct in its prosecution. Sturis withheld from his Declaration highly material evidence which misled the patent examiner.

Bork misrepresented and withheld highly material information from the patent examiner. The conclusion to be drawn from what Sturis and Bork did and did not do is that, with deceptive intent, they were successful in misleading the patent examiner to approve the application, which resulted in the issuance of the '358 patent.

C.

The Court is mindful of the attendant consequences of this decision. While Novo argued vigorously to sustain the '358 patent, at the end of the day the record simply does not support its arguments. Rather, the record shows, quite clearly, that the patent should never have issued. The idea to combine repaglinide with metformin was natural. Moreover, the results of the combination were not at all unexpected.

Novo knew the obstacles to obtaining a patent, as seen by the several rejections. Knowing what was needed to be shown to establish patentability, in what would be Novo's final attempt before the Patent Office, Novo omitted material information. The only inference which can be drawn from its conduct was that it was done with the intent to deceive the examiner and obtain a patent.

Perhaps market forces drove Novo to do what it did; the Court can only speculate. In the end, however, the patent cannot be sustained. An appropriate judgment will enter.

Dated: January 19, 2011

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

JUDGMENT

For the reasons stated in the Decision entered this date,

IT IS ORDERED AND ADJUDGED that judgment be entered in favor of CARACO PHARMACEUTICAL LABORATORIES, LTD. and against NOVO NORDISK A/S and NOVO NORDISK, INC. as the Court finds that *U.S. Patent No. 6,677,358*B1, NIDDM REGIMEN is (1) not invalid because of anticipation, (2) invalid because of obviousness, and (3) not enforceable because of inequitable conduct.

Dated: January 19, 2011

/s/ Avern Cohn

AVERN COHN

UNITED STATES DISTRICT JUDGE

Appendix I
Reports and Articles Referenced in Decision

DX 52 – AGEE-3018 Integrated Clinical Trial Report, "Repaglinide A 3-month, open-label, randomized multi-center study of repaglinide in combination with metformin as compared to metformin or repaglinide given as monotherapy for the treatment of type 2-diabetes" (9/29/2003) ("AGEE-3018").

DX 53 – AGEE-3010 Integrated Clinical Trial Report, "NovoNorm A 16-week, multi-centre, open-labeled study on type 2 diabetic patients treated with repaglinide and repaglinide in combination with metformin" (12/2/2003) ("AGEE-3010").

DX 54 – AGEE-1411 Integrated Clinical Trial Report, "Multicentre, randomized, comparative, open, three armed parallel group study on the use of metformin, repaglinide or the combination of both in type 2 diabetic patients after failure of dietary measures" (2/20/06) ("AGEE-1411").

DX 61 – DeFronzo et al, "Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus," N. Engl. J. Med. (1995) ("DeFronzo").

DX 200 – Rachman et al, "Drugs on the Horizon for Treatment of Type 2 Diabetes," Diabetic Medicine (1995) ("Rachman").

DX 202 – The American Diabetes Association, "Consensus Statement: The Pharmacological Treatment of Hyperglycemia in NIDDM," Diabetes Care (1995) ("Consensus Statement").

DX 203 – Melander, "Oral Antidiabetic Drugs: an Overview," Diabetic Medicine (1996) ("Melander").

DX 212 – Kaku et al, "Possibility of the Appearance of New Antidiabetic Agents (1): Oral Antidiabetic Agents," Practice (1996) ("Kaku").

DX 246 – Hermann and Melander, "Therapeutic Comparison of Metformin and Sulfonylurea, Alone and in Various Combinations, A Double-Blind Controlled Study," Diabetes Care (1994) ("Hermann/Melander")

DX 307 – Karlsson and Garber, "Metformin Comes to America: What to Do Now," Clinical Diabetes (1995) ("Karlsson/Garber").

DX 311 – Clarke et al, "Combined Metformin-Chlorpropamide Therapy in 108 Diabetic Sulphonylurea Failures," The Lancet (1965) ("Clarke").

DX 319 – Rudovich, Pfeiffer et al, "Enhancement of Early- and Late-Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400 (2004) ("Pfeiffer Study").

DX 350 – Garber, "Incremental Therapy for NIDDM," Clinical Diabetes (1995) ("Garber I").

DX 351 – Garber, "Metformin Therapy for Type II Diabetes Mellitus," P&T (1995) ("Garber II").

DX 361 – Bristol-Myers Squibb Product Monograph, "Glucophage, Metformin Hydrochloride Tablets" (1995) ("Bristol-Myers").

DX 369 – Raskin, "Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes," Diabetes, Obesity and Metabolism, 10:1167-77 (2008) ("Raskin").

DX 383 – Clark et al, "The Effect of Glimepiride on Pancreatic-Cell Function Under Hyperglycaemic Clamp and Hyperinsulinaemic, Euglycaemic Clamp Conditions in Non-Insulin-Dependent Diabetes Mellitus," Horm. Metab. Res. (1996) ("Clark").

PX 138 – Rudovich, Pfeiffer et al, "Enhancement of Early and Late Phase Insulin Secretion and Insulin Sensitivity by the Combination of Repaglinide and Metformin in Type 2 Diabetes Mellitus," Exp. Clin. Endocrinal Diabetes, Vol. 112, No. 7, pp. 395-400 (2004) ("Pfeiffer Study").

PX 201 – AGEE-053 Integrated Clinical Trial ("Moses Study" or "Australian Study").

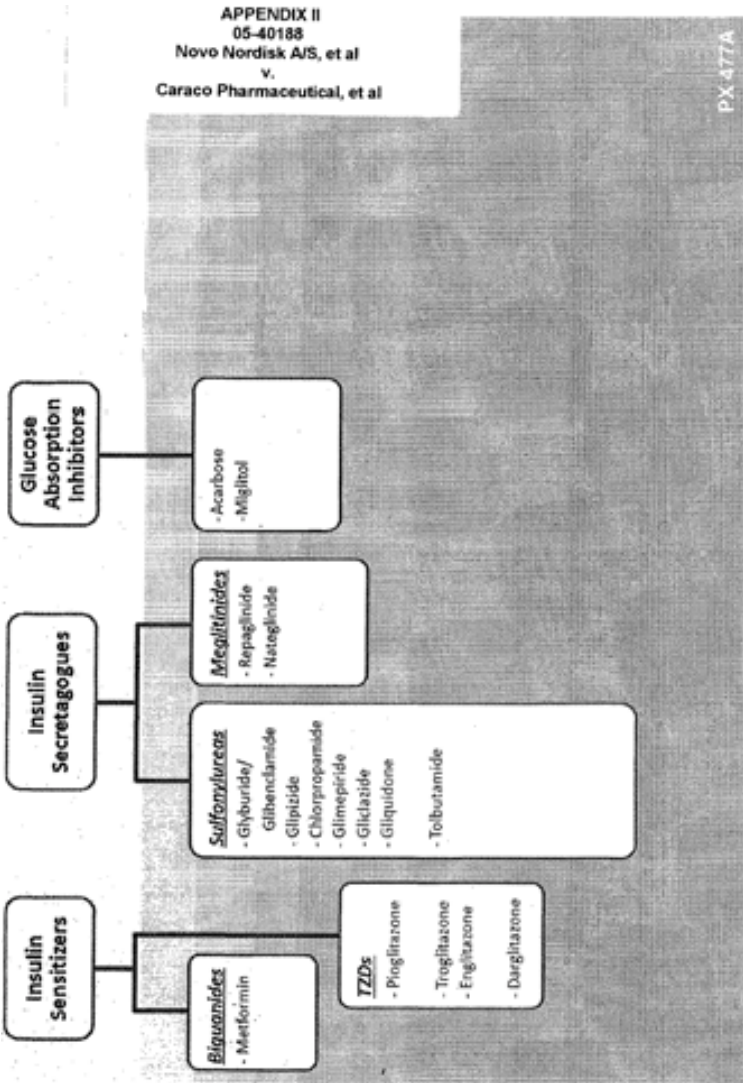
PX 401 – Sturis et al, "Combination of repaglinide and metformin results in greater than additive (synergistic) effects on glucose tolerance in obese Zucker (fa/fa) rats" ("Sturis Study").

PX 438 – Roudavitch et al, "Repaglinide plus Metformin: effects on insulin secretion and sensitivity in type 2 diabetes" ("Pfeiffer II Study").

APPENDIX II

05-40188

Novo Nordisk A/S, et al
v.
Caraco Pharmaceutical, et al



APPENDIX C

35 U.S.C. § 271 provides:

§ 271. Infringement of patent

(a) Except as otherwise provided in this title [35 U.S.C. §§ 1 et seq.], whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

(b) Whoever actively induces infringement of a patent shall be liable as an infringer.

(c) Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

(d) No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: (1) derived revenue from acts which if performed by another without his consent would constitute contributory infringement of the patent; (2) licensed or authorized another to perform acts which if performed

without his consent would constitute contributory infringement of the patent; (3) sought to enforce his patent rights against infringement or contributory infringement; (4) refused to license or use any rights to the patent; or (5) conditioned the license of any rights to the patent or the sale of the patented product on the acquisition of a license to rights in another patent or purchase of a separate product, unless, in view of the circumstances, the patent owner has market power in the relevant market for the patent or patented product on which the license or sale is conditioned.

(e) (1) It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

(2) It shall be an act of infringement to submit–

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 355(j)] or described in section 505(b)(2) of such Act [21 U.S.C. § 355(b)(2)] for a drug claimed in a patent or the use of which is claimed in a patent,

(B) an application under section 512 of such Act [21 U.S.C. § 360b] or under the Act of March 4, 1913 (21 U.S.C. [§§] 151-158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA,

hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent, or

(C) (i) with respect to a patent that is identified in the list of patents described in section 351(l)(3) of the Public Health Service Act [42 U.S.C. § 262(l)(3)] (including as provided under section 351(l)(7) of such Act [42 U.S.C. § 262(l)(7)]), an application seeking approval of a biological product, or

(ii) if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act [42 U.S.C. § 262(l)(2)(A)], an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act [42 U.S.C. § 262(l)(3)(A)(i)], if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, offering to sell, or selling within the United States or importing into the United States of a patented invention under paragraph (1).

(4) For an act of infringement described in paragraph (2)–

(A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product,

(C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product, and

(D) the court shall order a permanent injunction prohibiting any infringement of the patent by the biological product involved in the infringement until a date which is not earlier than the date of the expiration of the patent that has been infringed under paragraph (2)(C), provided the patent is the subject of a final court decision, as defined in section 351(k)(6) of the Public Health Service Act [42 U.S.C. § 262(k)(6)], in an action for infringement of the patent under section 351(l)(6) of such Act [42 U.S.C. § 262(l)(6)], and the biological product has not yet been approved because of section 351(k)(7) of such Act [42 U.S.C. § 262(k)(7)].

The remedies prescribed by subparagraphs (A), (B), (C), and (D) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285 [35 U.S.C. § 285].

(5) Where a person has filed an application described in paragraph (2) that includes a certification under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. [§] 355), and neither the owner of the patent that is the subject of the certification nor the

holder of the approved application under subsection (b) of such section for the drug that is claimed by the patent or a use of which is claimed by the patent brought an action for infringement of such patent before the expiration of 45 days after the date on which the notice given under subsection (b)(3) or (j)(2)(B) of such section was received, the courts of the United States shall, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under section 2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed.

(6) (A) Subparagraph (B) applies, in lieu of paragraph (4), in the case of a patent–

(i) that is identified, as applicable, in the list of patents described in section 351(l)(4) of the Public Health Service Act [42 U.S.C. § 262(l)(4)] or the lists of patents described in section 351(l)(5)(B) of such Act [42 U.S.C. § 262(l)(5)(B)] with respect to a biological product; and

(ii) for which an action for infringement of the patent with respect to the biological product–

(I) was brought after the expiration of the 30-day period described in subparagraph (A) or (B), as applicable, of section 351(l)(6) of such Act [42 U.S.C. § 262(l)(6)]; or

(II) was brought before the expiration of the 30-day period described in subclause (I), but which was dismissed without prejudice or was not prosecuted to judgment in good faith.

(B) In an action for infringement of a patent described in subparagraph (A), the sole and exclusive remedy that may be granted by a court, upon a finding that the making, using, offering to sell, selling, or importation into the United States of the biological

product that is the subject of the action infringed the patent, shall be a reasonable royalty.

(C) The owner of a patent that should have been included in the list described in section 351(l)(3)(A) of the Public Health Service Act [42 U.S.C. § 262(l)(3)(A)], including as provided under section 351(l)(7) of such Act [42 U.S.C. § 262(l)(7)] for a biological product, but was not timely included in such list, may not bring an action under this section for infringement of the patent with respect to the biological product.

(f) (1) Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(2) Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

(g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a proc-

ess patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after–

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product.

(h) As used in this section, the term "whoever" includes any State, any instrumentality of a State, and any officer or employee of a State or instrumentality of a State acting in his official capacity. Any State, and any such instrumentality, officer, or employee, shall be subject to the provisions of this title in the same manner and to the same extent as any nongovernmental entity.

(i) As used in this section, an "offer for sale" or an "offer to sell" by a person other than the patentee, or any designee of the patentee, is that in which the sale will occur before the expiration of the term of the patent.