United States Court of Appeals for the Federal Circuit

SANTARUS, INC.,
Plaintiff-Appellant,

AND

THE CURATORS OF THE UNIVERSITY OF MISSOURI,
Plaintiff-Appellant,

v.

PAR PHARMACEUTICAL, INC.,
Defendant-Cross Appellant.

2010-1360, -1380

Appeals from the United States District Court for the District of Delaware in consolidated Case Nos. 07-CV-0551 and 07-CV-0827, Chief Judge Gregory M. Sleet.

Decided: September 4, 2012

MORGAN CHU, Irell & Manella LLP, of Los Angeles, California, argued for both plaintiffs-appellants. With him on the brief for The Curators of the University of Missouri were JAMISON E. LYNCH, Mayer Brown LLP, of Chicago, Illinois. Of counsel for Santarus, Inc. were GARY N. FRISCHLING and

JOSEPH M. LIPNER, Irell & Manella LLP, of Los Angeles, California; and ANDREA C. HUTCHINSON, Mayer Brown LLP, of Chicago, Illinois, for The Curators of the University of Missouri.

Janine A. Carlan, Arent Fox, LLP, of Washington, DC, argued for defendant-cross-appellant. On the brief was Richard J. Berman. Of counsel were Timothy W. Bucknell, Aziz Burgy, Janine A. Carlan, Joshua T. Morris, Amy E.L. Schoenhard, and Anthony W. Shaw.

Before RADER, C*hief Judge*, NEWMAN, AND MOORE, *Circuit Judges*.

Opinion for the court filed PER CURIAM. Opinion concurring in part and dissenting in part filed by *Circuit Judge* NEWMAN.

PER CURIAM.

Appeal and cross-appeal are taken from the judgment of the United States District Court for the District of Delaware.[1] Plaintiff Santarus, Inc. is the exclusive licensee of patents on specified formulations of benzimidazole proton pump inhibitors (PPI) – a class of chemical compounds that inhibit gastric acid secretion and help prevent and treat stomach acid-related diseases and disorders. The patents are for the inventions of Dr. Jeffrey Phillips, and are assigned to the University of Missouri. Santarus provides the PPI product omeprazole in the formulations covered by the Phillips patents, with the brand name Zegerid®.

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[1] *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427 (D. Del. 2010).

Defendant Par Pharmaceutical, Inc. filed an Abbreviated New Drug Application (ANDA) for FDA approval to sell a generic counterpart of the Santarus Zegerid® products, invoking the Hatch-Waxman Act (the Drug Price Competition and Patent Term Restoration Act of 1984), which established a procedure called a "Paragraph IV certification," 21 U.S.C. § 355(j)(2)(A)(vii)(IV), whereby an entity that seeks to market a generic counterpart of a patented drug product or method of use, before the patent has expired, may challenge the patent before actually marketing the drug. Thus the parties are here litigating the issues of infringement, validity, and enforceability of the Phillips patents.

The district court found that Par's ANDA products infringe the Phillips patents, but held all of the asserted claims invalid on the ground of obviousness, 35 U.S.C § 103. The court also held certain claims invalid on the ground of inadequate written description, 35 U.S.C. § 112. On the defense of unenforceability, the district court held that there was not inequitable conduct by Dr. Phillips, the University of Missouri, or their counsel in procuring the patents. Each side appeals the rulings adverse to it, except that Par does not appeal the finding of infringement. We conclude that the district court erred by holding that some of the thirty-six asserted claims would have been obvious over the prior art; these rulings are reversed. The court's other rulings are affirmed.

I. THE PHILLIPS PATENTS

Proton pump inhibitors affect the action of an enzyme within the stomach's parietal cells, the cells within the membrane of the stomach that secrete hydrochloric acid. It was known that chemicals of the class of benzimidazoles have the property of inhibiting or inactivating this proton pump enzyme. The benzimidazoles operate by a mechanism

whereby the benzimidazole PPI, upon ingestion or intravenous infusion, circulates in the bloodstream, from which it reaches and accumulates in the parietal cells and affects the proton pump enzyme. Hydrochloric acid secretion does not recover until the body produces a new quantity of the proton-producing enzyme. Several benzimidazoles have been approved by the FDA for PPI use, including products having the common names omeprazole (brand name Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), rabeprazole (Aciphex®), and pantoprazole (Protonix®).

Although these PPIs are effective at blocking stomach acid production, they are extremely acid-sensitive. It was known that unprotected PPIs in the stomach's acidic environment do not survive long enough to be absorbed into the bloodstream, and thus do not reach the parietal cells. To avoid this destruction, PPI products for oral ingestion were provided with an acid-resistant enteric coating, whereby the coated PPI passes safely through the stomach to the intestine, where the coating dissolves and the PPI is absorbed.

Before Dr. Phillips's invention, all PPI products that were FDA-approved for oral administration had an enteric coating. In contrast, the Phillips products do not have an enteric coating. The products can be administered as liquid suspensions of the solid uncoated PPI together with a buffering agent, whereby the PPI is absorbed directly from the stomach into the bloodstream. This formulation has the advantages of rapid and consistent bioavailability and increased effectiveness, as well as ease of administration to patients unwilling or unable to swallow capsules or tablets. The Phillips patents explain:

> in their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to

> administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia.

U.S. Patent No. 7,399,772, col.7 l.65 - col.8 l.4. The Phillips products "can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets and granules." *Id.* col.11 ll.50-53. The Phillips patents claim specific combinations of the uncoated benzimidazole PPI and buffering agents.

Par Pharmaceutical filed ANDA documents with the FDA, requesting permission to market the same formulations as the Zegerid® PPI, and describing the Par products as bioequivalent to the Zegerid® products marketed by Santarus. Par asserted unenforceability of all of the claims of the Phillips patents, and invalidity of the claims for which Santarus charged Par with infringement: U.S. Patent No. 6,489,346 (the '346 patent) claims 26, 37, 38, 49, 50, 58, 59, 60, 66, 68, 80, 81, 82; U.S. Patent No. 7,399,772 (the '772 patent) claims 1, 4, 5, 8, 10, 12, 14, 15, 20, 21; U.S. Patent No. 6,780,882 (the '882 patent) claims 11, 12, 15, 27; U.S. Patent No. 6,699,885 (the '885 patent) claims 2, 9, 11, 15, 16, 17, 18, 41; and U.S. Patent No. 6,645,988 (the '988 patent) claim 29.

Each of the Phillips patents is a continuation or continuation-in-part in a chain that originated with Patent No. 5,840,737 (the '737 patent) based on a provisional application filed on January 4, 1996. The '737 patent describes the combination of the PPI and sodium bicarbonate, and states the broadest claim as follows:

> 1. A method for treating gastric acid disorders by administering to a patient a single dose of a pharmaceutical composition of omeprazole or lansoprazole in a pharmaceutically acceptable carrier consisting essentially of a bicarbonate salt of a Group IA metal wherein said administering step consists of providing to the patient orally a single dose of an aqueous solution or, suspension of the pharmaceutical composition without requiring further administration of the bicarbonate salt of the Group IA metal.

'737 patent claim 1.

The '346 patent is a continuation-in-part of the '737 patent, with an intervening abandoned application. Similar to the '737 patent, the '346 patent generally claims a method for treating an acid-caused gastrointestinal disorder comprising administering a solid pharmaceutical composition in a dosage form that is not enteric coated. *See, e.g.*, '346 patent claim 24. The dosage consists of PPI and a buffering agent, and the claims specify certain ranges of PPI and buffer.

The '988 patent is a continuation-in-part of its predecessors. It includes a new Figure 5 showing the pH of gastroesophageal reflux disease and discusses the scientific mechanism of operation of the PPI. Only claim 29 is asserted. It recites a non-enteric coated solid oral pharmaceutical dosage form comprising approximately 5-300 mg of PPI and a buffer in an amount of 0.1-2.5 mEq per mg of PPI. '988 patent claim 29. The dosage form also includes a pharmaceutically-acceptable excipient, indicating that it is a conventional dosage form such as a tablet, capsule, or granule. *Id.*

The other patents include additional limitations. For example, the '885 patent claims recite the serum concentration or blood level of PPI that is obtained within 30 minutes after administration. *See, e.g.*, '885 patent claim 2. The '882 patent claims a stable powder for suspension, having a specified ratio of buffering agent to PPI, and a thickening agent. The composition recited in the '772 patent contains no sucralfate. '772 patent claim 1.

Par argues that every asserted claim would have been obvious over any one of several pieces of prior art. Par also argues that Dr. Phillips's own '737 patent renders obvious those claims to which it is prior art. Finally, Par argues that all of the patents are unenforceable for inequitable conduct in the Patent and Trademark Office. We start with the issue of inequitable conduct, for this defense is asserted against all claims of all of the patents in suit.

II. INEQUITABLE CONDUCT

Par argues that all of the Phillips patents are unenforceable due to inequitable conduct by Dr. Phillips, the University of Missouri, and their attorneys, on the ground that they were tardy in informing the PTO that Dr. Phillips had made the uncoated PPI formulation and administered it to some hospital patients, and had informed medical colleagues and recorded the medication and its test results in hospital records, before the filing date of his first patent application. Par cites a "Critical Care Abstract" written by Dr. Phillips at St. Vincent's Hospital, entitled "The Effect of Omeprazole/Sodium Bicarbonate Solution Administration on the Accuracy of subsequent pH Measurements Through the Nasogastric Tube." This document reports his measurements of stomach acidity for these formulations.

Par charged that this test information and report should have been provided to the PTO during the prosecution of the

first Phillips application, instead of during the prosecution of the second, continuing application. Par did not and does not argue that this information invalidates any patent, but argues that the disclosure to the PTO should have occurred during prosecution of the first-filed application, and that failure to do so renders unenforceable all of the patents.

Dr. Phillips testified that he was unaware that his experimental administration to patients and his measurement of the effect on stomach acidity required disclosure to the PTO. He testified that he had believed that only sale and public use were required to be disclosed, not experimental development, and that he had not intentionally withheld information or delayed its disclosure to the PTO. The University's patent counsel testified that when he became aware of this test information he provided it to the PTO by Information Disclosure Statement during prosecution of the '346 application, which was the first continuing application, for the first application had already issued as a patent.

Par also stated that Dr. Phillips submitted a misleading declaration to the PTO regarding a "Carroll Abstract," where, in response to an examiner's rejection, Dr. Phillips submitted a declaration describing a test in which he crushed enteric-coated PPI and mixed the crushed pellets with a sodium bicarbonate solution; he declared that a suspension did not form, and provided a photograph of the test tube containing the crushed pellets. Par argued that Dr. Phillips distorted the study because he did not shake or swirl the crushed pellets with the sodium bicarbonate solution. Par's expert testified that in his opinion it would take no more than five to ten minutes for the shaken suspension to become homogeneous; this opinion was not supported with evidence.

The district court found that Par had shown materiality of some of this information, and that the explanation by Dr. Phillips of why his test information was not initially provided to the PTO "strained credibility." However, the court also found that "the evidence presented is not sufficient to establish by clear and convincing evidence that Dr. Phillips acted with an affirmative intent to deceive." *Santarus*, 720 F. Supp. 2d at 461. This finding is in accord with *Therasense, Inc. v. Becton, Dickinson & Co.*, where this court explained that "[t]o prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO." 649 F.3d 1276, 1290 (Fed. Cir. 2011) (en banc).

On this appeal Par stresses the district court's remark of "strained credibility" and argues that this court should disbelieve Dr. Phillips, and that the only reasonable inference is that he and his legal representatives acted in bad faith and with intent to deceive. Santarus responds that the district court did not find any testimony false, and that intent to deceive was not established. We agree with the district court that intent to deceive was not shown by clear and convincing evidence. The district court's ruling that inequitable conduct was not established is affirmed.

III. VALIDITY

The district court invalidated the asserted claims of the '772 patent on the ground of inadequate written description and determined that the '772 claims are not entitled to claim priority to the application that issued as the '737 patent. The court also invalidated all of the asserted claims on the ground of obviousness over any of several prior art references. The court held that the '737 patent rendered obvious every claim to which it is prior art.

A. WRITTEN DESCRIPTION

The written description issue relates to the inclusion of the clause "wherein the composition contains no sucralfate" in the claims of the '772 patent. This limitation is present in the sole independent claim of the '772 patent, claim 1, which recites:

> A method for treating an acid-caused gastrointestinal disorder comprising the step of administering to a subject suffering from said disorder a solid pharmaceutical composition comprising:
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> (a) about 10mg to about 40mg of non-enteric coated omeprazole; and
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> (b) sodium bicarbonate in an amount of 0.2 mEq to 5 mEq per 2mg omeprazole;
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> *wherein the composition contains no sucralfate*, the acid-caused gastrointestinal disorder is selected from the group consisting of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and erosive esophagitis, and the sodium bicarbonate is present in the composition in an amount sufficient to substantially prevent or inhibit acid degradation of at least some of the omeprazole by gastric acid upon administration to the subject.

'772 patent claim 1 (emphasis added).

The district court held that it is necessary for the '772 specification to include evidence demonstrating that sucralfate is "contraindicated," in order to meet the written description requirement of § 112 ¶1. The court held that it is inadequate that the specification states that Phillips's claimed composition is "advantageous" as compared with

sucralfate, a product then commonly used to treat gastric ulcers and acid reflux. As a result, the court found that neither the priority applications, such as the application that issued as the '737 patent, nor the '772 specification support the "no sucralfate" limitation. *Santarus*, 720 F. Supp. 2d at 444. For the same reasons, the court concluded that the asserted claims of the '772 patent are not entitled to claim priority to the '737 patent's filing date. *Id.*

The '772 specification states that "H_2 antagonists, antacids, and sucralfate . . . have certain disadvantages associated with their use . . . . Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2 antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage." '772 patent, col.7 II.62-65. The district court held that this statement is insufficient to meet the written description requirement, stating: "While this indicates that omeprazole is preferable to sucralfate, the same statements indicate with no less force that omeprazole is preferable to antacids such as sodium bicarbonate. Nonetheless, sodium bicarbonate, an antacid, is listed as the preferred carrier or buffer in the disclosed invention. Thus it cannot be true that the priority applications' disclosure of the disadvantages of sucralfate, by itself, implies that its use is contraindicated." *Santarus*, 720 F. Supp. 2d at 443-44. The district court held that "consequently, the court finds that neither the priority applications nor the specification of the '772 patent support the no sucralfate limitation, for they do not show why a person of ordinary skill in the art reading the application would believe that sucralfate was 'contraindicated' in the claimed composition." *Id.* at 444.

The '737 patent specification states that sucralfate, "possibly the ideal agent for stress ulcer prophylaxis, [citing references]," was known to have occasional adverse effects.

'737 patent, col.3 ll.14-15, ll.25-27 ("[T]he only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm . . . ."). Santarus argues that it is not necessary to include in the specification evidence of "contraindication" of sucralfate, and cites the testimony of Dr. Gilbert Banker, an expert witness for Santarus, who testified that a person of ordinary skill in this field would have known the properties and effects of sucralfate, and would have understood from the specification that disadvantages of sucralfate may be avoided by the Phillips formulation.

We agree. The claim limitation specifying that sucralfate is not administered in conjunction with the Phillips formulation restricted the claims to this preferred use of the Phillips formulations. This exclusion narrowed the claims, as the patentee is entitled to do. The Manual of Patent Examining Procedure explains that claims may state the exclusion of alternatives. *See* MPEP § 2173.05(i) ("If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims."). For example, in *In re Johnson*, 558 F.2d 1008, 1019 (CCPA 1977), the applicant narrowed the claims to exclude the content of a lost interference count, and the court observed that: "It is for the inventor to decide what bounds of protection he will seek."

Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation. Such written description support need not rise to the level of disclaimer. In fact, it is possible for the patentee to support both the inclusion and exclusion of the same material. The claim limitation that the Phillips formulations contain no sucralfate is adequately supported by statements in the specification expressly listing the disadvantages of using sucralfate. The district court's

holding that the '772 patent claims are invalid on written description grounds is thus reversed. Because the lack of written description for the "no sucralfate" limitation was the district court's only reason for concluding that the '772 patent claims cannot claim priority to the application that issued as the'737 patent, we also reverse this holding. As a result, the '772 patent claims are entitled to claim priority to the '737 patent, which thus cannot be used as prior art against them.

B. OBVIOUSNESS – 35 U.S.C. § 103

The primary issue on appeal is whether a solid dosage form of non-enteric coated PPI such as omeprazole would have been obvious to one of ordinary skill in the art. A patent is invalid for obviousness "if 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). "Obviousness is a question of law, which we review *de novo*, with underlying factual questions, which we review for clear error following a bench trial." *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). These underlying factual inquires are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the field of the invention; and (4) objective considerations such as commercial success, long felt need, and the failure of others. *KSR Int'l Co., v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). Patent invalidity must be established by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

The district court held that the asserted claims would have been obvious over several pieces of prior art. The

scope and content of the prior art applicable to each asserted claim, however, differs depending on the claim's effective filing date. Due to breaks in the chain of priority, Santarus is unable to claim an early enough priority date to preclude use of Dr. Phillips's own '737 patent as prior art for some of the asserted claims. In a thorough analysis of priority, the district court determined that the '737 patent is prior art to claims 26, 37, 38, 49, 50, 66, 68, and 80-82 of the '346 patent and the asserted claims of the '885 patent, '988 patent, and '772 patent. *Santarus*, 720 F. Supp. 2d at 436-37. Santarus appeals the court's priority determination *only* as to the '772 patent (and as described above, we reverse), and does not contend that the district court erred by finding that the '737 patent was prior art to the other claims. Accordingly, Santarus waived any argument that the '737 patent is not prior art to the other claims. *See Advanced Magnetic Closures, Inc. v. Rome Fastener Corp.*, 607 F.3d 817, 833 (Fed. Cir. 2010). The asserted claims thus fall into one of two categories depending on whether the '737 patent is prior art, and our validity analysis must proceed on this basis.

1. Claims to Which the '737 Patent is Prior Art

The district court correctly held that the '737 patent would have rendered obvious all claims to which it is prior art. *Santarus*, 720 F. Supp. 2d at 452. The '737 patent is prior art to: claims 26, 37, 38, 49, 50, 66, 68, and 80-82 of the '346 patent; claims 2, 9, 11, 15-18, and 41 of the '885 patent; and claim 29 of the '988 patent.

The '737 patent discloses formulating omeprazole both in conventional dosage forms (e.g., tablets, capsules, and granules) and also as an aqueous suspension of omeprazole with a buffering agent. For example, the '737 patent discloses treating gastrointestinal conditions by administering:

> A pharmaceutical composition for making a solution/suspension of omeprazole . . . includes omeprazole . . . and a bicarbonate salt of a Group 1A metal in a form for convenient storage whereby when the composition is dissolved in aqueous solution, the resulting solution is suitable for enteral administration.

'737 patent at [57].

The '737 patent discloses an example of such a suspension, which is formed by mixing enteric coated omeprazole particles with a solution of water and sodium bicarbonate. *Id.* col.8 ll.6-41. Importantly, however, the '737 patent teaches that the omeprazole does *not* need to be enterically coated. '737 patent col.8 ll.18-22 ("In a preferred embodiment of the present invention, enterically-coated omeprazole particles are obtained from delayed release capsules (Astra Merck) *additionally omeprazole powder can be used*." (emphasis added)). Even when examples use enteric coated omeprazole, the '737 patent teaches that the sodium bicarbonate suspension "dissolves the enteric coating" and emphasizes that "[i]t is important . . . that the enteric coated pellets of omeprazole must be allowed to completely breakdown in the suspension vehicle or carrier prior to administration." *Id.* col.8 ll.21-28. The '737 patent also teaches that "[t]he omeprazole or other substituted benzimidazoles and derivatives thereof and bicarbonate can be formed into a tablet, capsules, or granules, by methods well known to those skilled in the art." *Id.* col.10 ll.29-33. While the prior art before the '737 patent taught away from tablets, capsules, and granules with non-enteric coated PPI, the '737 patent expressly teaches these formulations. The '737 patent thus discloses a solid dosage form within the meaning of the asserted claims.

Santarus designates claims 2 and 17 as exemplary of the asserted claims of the '885 patent. These claims depend from independent claim 1, which recites:

> A method of treating a gastric acid related disorder in a subject in need thereof, comprising:
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> providing a solid pharmaceutical composition for oral administration to the subject, the composition consisting essentially of: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H^+, K^+-ATPase proton pump inhibitor; (b) *at least one buffering agent in an amount of about 0.1 mEq to about 2.5 mEq per mg proton pump inhibitor*; and (c) one or more optional pharmaceutically acceptable excipients, wherein at least some of the proton pump inhibitor is not enteric coated and the solid pharmaceutical composition has a *total buffering agent to total proton pump inhibitor weight ratio of greater than 20:1*; and
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> orally administering the pharmaceutical composition to the subject,
>
> wherein upon oral administration of the pharmaceutical composition to the subject, *an initial serum concentration of the proton pump inhibitor greater than about 0.1 μg/ml is obtained at any time within about 30 minutes after administration* of the composition.

'885 patent claim 1 (emphases added). Claim 2 additionally requires an initial serum concentration "greater than about 0.15 μg/ml at any time within about 30 minutes after administration of the composition." *Id.* claim 2. Claim 17 also requires that the buffering agent be sodium bicarbonate "in

an amount from about 1000 mg to about 2000 mg." *Id.* claim 17.

Santarus makes three arguments with regard to the '885 patent claims: (1) they require an uncoated PPI and buffer in specific amounts and ratios not disclosed in the prior art; (2) they achieve the desired results using only 1000 mg to 2000 mg of sodium bicarbonate; and (3) they achieve specific blood serum concentration levels not disclosed in the prior art.

Santarus is incorrect that the '737 patent fails to disclose non-enteric coated PPIs and buffer within the claimed ratios. The '737 patent discloses broad ranges for the amounts of omeprazole and sodium bicarbonate that can be used, which overlap with the range of ratios of buffering agent to PPI claimed in the '885 patent. For example, the '737 patent teaches that the amount of sodium bicarbonate can vary between 0.75 mEq to 1.5 mEq per 2 mg of omeprazole (0.375 to 0.75 mEq per mg of omeprazole). '737 patent col.10 ll.15-19. This falls within the range of about 0.1 mEq to about 2.5 mEq of buffering agent per mg of PPI claimed in the '885 patent. Sodium bicarbonate weighs roughly 84 mg/mEq, *see Santarus*, 720 F. Supp. 2d at 441, and thus the range of buffering agent taught in the '737 patent equates to a weight ratio of buffering agent to PPI of greater than 20:1 (i.e., 31.5-63 mg of sodium bicarbonate per mg of PPI), as required by the claims.

The '737 patent also discloses claim 17's limitation that the buffering agent be sodium bicarbonate "in an amount from about 1000 mg to about 2000 mg." The '737 patent teaches that the dosage range of non-enteric coated omeprazole can vary from approximately 2 mg/day to 100 mg/day. '737 patent col.9 ll.9-13. Because the ratio of sodium bicarbonate to PPI disclosed in the '737 patent ranges from 0.75

mEq to 1.5 mEq per 2 mg of omeprazole, the '737 patent teaches a range of 0.75-75 mEq of sodium bicarbonate. This range equates to about 63-6300 mg of sodium bicarbonate, which overlaps with the claimed range of 1000-2000 mg.

Santarus is also incorrect that the claims reciting specific blood serum concentrations of PPI would have been nonobvious. The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. *See, e.g.*, *In re Kao*, 693 F.3d 1057, 1070 (Fed. Cir. 2011) ("[The prior art's] express teachings render the claimed . . . formulation obvious, and the claimed [blood concentration] adds nothing of patentable consequence."). To hold otherwise would allow any formulation – no matter how obvious – to become patentable merely by testing and claiming an inherent property. There is no dispute that the blood serum concentrations claimed in the '885 patent are expected in light of the dosages. In fact, a publication by Pilbrant and Cederberg entitled "Development of an oral formulation of omeprazole" (Pilbrant) includes a blood serum chart that indicates that the claimed levels are easily achieved within the first thirty minutes after administration of a suspension of non-enteric coated omeprazole buffered with sodium bicarbonate. J.A. 1315-16.

Santarus does not designate any of the other claims to which the '737 patent is prior art as being exemplary, nor does Santarus identify any other specific limitations that are not disclosed in the prior art. We thus hold that the district court correctly determined that claims 26, 37, 38, 49, 50, 66, 68, and 80-82 of the '346 patent, claims 2, 9, 11,

15-18, and 41 of the '885 patent, and claim 29 of the '988 patent would have been obvious.[2]

2. Claims to Which the '737 Patent is Not Prior Art

The '737 patent is not prior art to claims 58-60 of the '346 patent or to the asserted claims of the '882 and '772 patents. For these claims, the two most relevant pieces of prior art are the Pilbrant reference and an article by Lamers et al. entitled "Absorption of omeprazole in Zollinger-Ellison syndrome is accelerated by alkali" (Lamers), J.A. 1464-65. The district court held that Pilbrant and Lamers each individually render obvious every asserted claim. *Santarus*, 720 F. Supp. 2d at 449.

The parties raise several issues relating to these prior art references. They dispute whether, at the time of the Phillips invention, the prior art taught away from the use of non-enteric coated oral dosage forms of PPIs. The parties also disagree as to whether Pilbrant and Lamers teach certain limitations of the asserted claims and whether objective evidence justifies a finding of nonobviousness.

a. Teaching Away – The Solid Oral Dosage Limitation

A reference "teaches away" when it "suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Whether a prior art reference teaches away from the claimed invention is a question of fact. *Para-Ordnance Mfg., Inc. v. SGS Imps. Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995).

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[2] For the same reasons discussed in section 2.c., *infra*, the district court's fact findings regarding objective considerations are not clearly erroneous.

Santarus argues that the prior art, particularly Pilbrant, taught away from the claimed invention. Specifically, Santarus contends that the dosing regimen Pilbrant discloses for suspensions of buffered non-enteric coated omeprazole was so complex that it would discourage a person of ordinary skill in the art from pursuing such formulations. Santarus argues that this, coupled with the fact that Pilbrant expressly "ruled out" non-enteric coated tablets, capsules, and granules, would discourage a skilled artisan from using *any* non-enteric coated oral dosage forms of PPIs.

Santarus is partly correct. Pilbrant teaches that the options for formulating omeprazole are limited because it is minimally soluble in water but degrades rapidly in the acidic environment of the stomach. J.A. 1313. Pilbrant discusses four options: 1) solutions; 2) suspensions of buffered non-enteric coated omeprazole; 3) conventional oral dosage forms – tablets, capsules or granules – with non-enteric coated PPIs; and 4) conventional oral dosage forms with enteric-coated PPIs. J.A. 1313-14. Pilbrant states that the fourth option, conventional dosage forms with enteric-coated PPIs, "offers the best possibilities." J.A. 1314. Pilbrant explicitly "ruled out" the third option – non-enteric coated conventional oral dosage forms such as tablets, capsules, or granules – because they degrade too quickly in the stomach to be absorbed in sufficient amounts to be effective. J.A. 1313. This disclosure would discourage a person of ordinary skill in the art from pursuing *conventional oral dosage forms* such as tablets, capsules, or granules with non-enteric coated PPIs, and thus teaches away from such formulations. As a result, we hold that the district court erred by concluding that claims directed to such conventional dosage forms would have been obvious over Pilbrant or Lamers. We thus reverse the court's obviousness holding with respect to claims 4, 5, 8, 10, 12, 14,

and 15 of the '772 patent, which all are directed to conventional dosage forms, such as tablet or capsules, containing non-enteric coated PPIs.[3]

Santarus is incorrect, however, that the prior art taught away from *all* non-enteric coated omeprazole formulations. The district court broadly construed the claim terms "solid pharmaceutical composition in a dosage form" and "solid oral pharmaceutical dosage form" as "including a powder that can be combined with an aqueous medium then orally administered." J.A. 300. As a result of these undisputed constructions, many of the asserted claims cover powder formulations for use in aqueous suspensions. The prior art does not teach away from such powder formulations.

As the district court found, "[t]he Lamers and Pilbrant references teach that *uncoated omeprazole formulations* containing a sodium bicarbonate buffer could be used as an alternative to enteric coating in order to protect omeprazole from degrading in the stomach." *Santarus*, 720 F. Supp. 2d at 448-49 (emphasis added). Although Pilbrant "ruled out" conventional dosage forms such as tablets, capsules, or granules with non-enteric coated PPIs, it states that a "rapidly dissolving suspension of micronized omeprazole is the *second best choice* as the reference formulation." J.A. 1315 (emphasis added). As Par's expert testified, Pilbrant also teaches that such buffered suspensions using non-enteric coated omeprazole have a similar effect on gastric acid secretion as enteric coated omeprazole without bicarbonate. J.A. 1316; J.A. 1130-31.

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[3] Claims 4 and 5 of the '772 patent are not expressly limited to a tablet or capsule dosage form, but require specific pharmaceutical excipients (disintegrants and lubricants) that are commonly used in conventional dosage forms such as tablets, not in powder formulations.

Pilbrant thus teaches that, although suspensions of buffered non-enteric coated omeprazole may be the "second best choice," they are a viable alternative to enteric coating. "A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). Describing a formulation as "second best" is not a "clear discouragement," as is required by our precedent.

Nor do we see any merit to Santarus's contention that the dosing regimen Pilbrant discloses for suspensions of buffered non-enteric coated omeprazole was so complex that it taught away from such formulations. Pilbrant teaches that a total of 40 mmoles of sodium bicarbonate should be given with 250 mL of water in five divided doses after a ten-hour overnight fast. J.A. 1315. The district court did not clearly err by declining to find that this regimen, which basically requires dissolving less than half a teaspoon of sodium bicarbonate in just over a cup of water, is such a strain on patient compliance as to teach away from using a buffered suspension of non-enteric coated omeprazole. *Santarus*, 720 F. Supp. 2d at 447-48.

Thus, Pilbrant discloses, and does not teach away from, "a powder that can be combined with an aqueous medium then orally administered." For the claims that are broad enough to include this powder (i.e., those not limited to tablets, capsules, or granules), the solid pharmaceutical dosage limitation is taught by Pilbrant.

b. Other Claim Limitations

The thrust of this appeal is whether the prior art discloses the claimed non-enteric coated solid pharmaceutical dosage forms. In cursory form, Santarus argues a limited number of additional limitations that it alleges are not

present in the prior art, such as the claimed amounts and ratios of PPI and buffer. We conclude that the district court was correct that claims 58-60 of the '346 patent and claims 12 and 27 of the '882 patent would have been obvious over Pilbrant.

Santarus contends that Pilbrant and Lamers fail to teach a dosage with PPI and buffer in the amounts and ratios recited in claim 60 of the '346 patent, which Santarus designated as an exemplary claim. Claim 60 of the '346 patent depends from claim 57, which recites:

> A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:
>
> > (a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and
> >
> > (b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

'346 patent claim 57. Claim 60 further requires that the buffering agent be sodium bicarbonate in an amount of at least 800 mg. *Id.* claim 60.

As the district court found, Pilbrant discloses administering approximately 3360 mg of sodium bicarbonate with 60 mg of omeprazole, a ratio of 56:1 on a weight to weight

basis. *See Santarus*, 720 F. Supp. 2d at 447. Pilbrant thus teaches the limitation of using an amount of buffer "more than about 40 times the amount of proton pump inhibitor on a weight to weight basis." Pilbrant's use of 3360 mg of sodium bicarbonate also meets claim 60's limitation of using "at least about 800 mg" of sodium bicarbonate. Pilbrant similarly teaches using PPI and buffering agent in the amounts and ratios recited in claims 58-59 of the '346 patent and claims 12 and 27 of the '882 patent. Thus we find no merit in the arguments related to these claims.

Exemplary claims 20 and 21 of the '772 patent, however, require amounts of buffering agent not disclosed in the prior art. Claim 20 requires 2-25 mEq of sodium bicarbonate buffer while claim 21 requires 4-25 mEq of sodium bicarbonate. '772 patent claims 20, 21. Pilbrant discloses using 40 mEq (3360 mg) of sodium bicarbonate, which is significantly more than the amount claimed in the '772 patent. J.A. 1315. Par appears to contend that, because Pilbrant and Lamers both teach the claimed ratio of sodium bicarbonate to PPI, it would have been obvious to a person of ordinary skill in the art to reduce the total amount of sodium bicarbonate buffer disclosed in those references. *See, e.g.*, Cross-Appellant's Br. 19-20. Par, however, failed to establish this by clear and convincing evidence. Pilbrant states that the purpose of consuming sodium bicarbonate with the omeprazole solution was to "buffer the pH of the gastric content to neutral values." J.A. 1315. Par points to nothing in the prior art that indicates it was the ratio of buffering agent to PPI, as opposed to the total amount of buffer consumed, that was the key to preventing the stomach from being too acidic. Given the prior art's teachings regarding protecting omeprazole from stomach acid, we hold that it would not have been obvious to a person of ordinary skill in the art to decrease the amount of sodium bicarbonate disclosed in Lamers or Pilbrant.

Likewise, the required amount of buffering agent in claims 11 and 15 of the '882 patent are not disclosed by Pilbrant or Lamers. Claim 11 requires an amount of buffering agent of about 15-30 mEq. '882 patent claim 11. Claim 15 requires about 12.5-30 mEq of sodium bicarbonate buffer. *Id.* claim 15. As a result, we reverse this portion of the district court judgment and hold that Par did not establish by clear and convincing evidence that these claims would have been obvious over Pilbrant or Lamers.

c. Objective Considerations

Santarus argues that the district court's fact findings regarding objective evidence were clearly erroneous. Santarus cites the testimony of its expert Dr. Fennerty that skepticism in the industry, unexpected results, long-felt need, industry recognition, and commercial success support a holding of nonobviousness. Appellant's Br. 50-53. Santarus also cites a statement by researcher Dr. George Sachs expressing his skepticism that Zegerid® would work. *Id.* at 11-12. The district court, however, reviewed all of the secondary consideration evidence and concluded that:

> The evidence in the record on several relevant secondary considerations does not undermine the court's finding that the patent is obvious in light of the prior art. On the contrary, the weight of the evidence as to the relevant secondary considerations confirms the court's finding in this regard.

Santarus, 720 F. Supp. 2d at 453. The court expressly found that there was no commercial success. *Id.* at 453-55. For example, the court found that sales of Zegerid® were dwarfed by those of other PPIs and "fell far short of Santarus' own expectations." *Id.* at 453-54. The court also rejected Santarus's arguments with respect to the other objective factors. *Id.* at 455-59. For example, the district

court found the statement by Dr. Sachs unpersuasive for several reasons, including that Dr. Sachs was not a witness at trial and thus was not subject to cross examination. *Id.* at 456. The district court's findings of fact are entitled to deference, and Santarus failed to show that they are clearly erroneous. *See, e.g.*, *Para-Ordnance Mfg., Inc.*, 73 F.3d at 1091. We thus hold that Santarus's objective evidence is insufficient to overcome the obviousness of the claims over Pilbrant. We thus affirm the district court's conclusion that claims 12 and 27 of the '882 patent and claims 58-60 of the '346 patent would have been obvious over Pilbrant and reverse the court's holding that claims 11 and 15 of the '882 patent claims 20 and 21 of the '772 patent would have been obvious.

IV. SUMMARY

In view of the foregoing, we affirm the district court's ruling that Par failed to establish inequitable conduct. We also affirm the court's determination that the following claims would have been obvious over the prior art: claims 12 and 27 of the '882 patent; claims 26, 37, 38, 49, 50, 58-60, 66, 68, and 80-82 of the '346 patent; claims 2, 9, 11, 15-18, and 41 of the '885 patent; and claim 29 of the '988 patent. We reverse the district court's ruling that the asserted claims of the '772 patent and claims 11 and 15 of the '882 patent would have been obvious. We also reverse the district court's holding that the claims of the '772 patent are invalid for lack of written description. We remand for further proceedings consistent with this opinion.

AFFIRMED-IN-PART, REVERSED-IN-PART, and REMANDED

United States Court of Appeals for the Federal Circuit

SANTARUS, INC.,
Plaintiff-Appellant,

AND

THE CURATORS OF THE UNIVERSITY OF MISSOURI,
Plaintiff-Appellant,

v.

PAR PHARMACEUTICAL, INC.,
Defendant-Cross Appellant.

2010-1360,-1380

Appeal from the United States District Court for the District of Delaware in consolidated Case Nos. 07-CV-0551 and 07-CV-0827, Chief Judge Gregory M. Sleet.

NEWMAN, *Circuit Judge*, concurring in part, dissenting in part.

I agree that inequitable conduct has not been shown. However, the court errs in three major areas, misconstruing established law. First, the court creates a new "written description" requirement for limitations in claims, a requirement with important consequences for patent content and prosecution, and that will taint large numbers of issued patents.

The panel majority also holds that the disclosure in a parent patent is a reference against the common disclosure in a continuation-in-part patent, again tainting many properly granted patents.

The panel majority also holds that most of the claims in suit are invalid on the ground of obviousness over references that explicitly teach away from the inventions in the Phillips patents. In the district court, the experts for both sides agreed that for oral dosage of PPIs the protective enteric coating was understood to be essential. Only the panel majority finds that the extreme conditions that the prior art deemed necessary for oral dosage of uncoated PPIs, would be acceptable for patient treatment.

The court's new rulings are contrary to statute, precedent, and common sense. They simply add to the unreliability of duly granted patents, in new and unacceptable ways.

I

WRITTEN DESCRIPTION

The claims of the '772 patent (U.S. Patent No. 7,399,772) contain the limitation that these uncoated PPI formulations do not contain the known therapy sucralfate. I agree that the district court clearly erred in finding that since the specification did not contain evidence of "contraindication" of sucralfate, the patent failed the written description requirement. On appellate review, correction of this erroneous finding is all that is needed.

However, my colleagues add a gratuitous fillip, and devise the new rule that the specification must "describe a reason" for the claim limitation, or the claims are invalid on written description grounds. Maj. op. at 12 ("Negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant

limitation."). That is not correct. Negative claim limitations may often be appropriately stated in claims although the reason for the limitation is not set forth in the specification.

Negative limitations to claims may arise in a variety of circumstances. For example, a negative limitation may be prudently placed in a claim in response to an examiner's rejection, perhaps to distinguish a reference that was given its "broadest reasonable interpretation" for purposes of examination. *See, e.g.*, *In re Skvorecz*, 580 F.3d 1262, 1268 (Fed. Cir. 2009) ("Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified." (quoting Manual of Patent Examining Procedure (MPEP) §2111)).

A claim limitation may distinguish the prior art although the reason is not in the specification. Claims are routinely adjusted during prosecution in the Patent and Trademark Office. As stated in *In re Johnson*, 558 F.2d 1008, 1018 (CCPA 1977), "applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable." This adjustment may include limitations that respond to the prior art developed by the examiner and traversed by the applicant. The specification need not foresee and describe the reason for every possible examination response.

As another example of routine patent procedures, there may be situations in which comparative data are provided during prosecution in order to respond to an examiner's rejection, *see* MPEP §716, and the distinction from the prior art may lead to a claim limitation. The need for the limitation may not have been apparent when writing the specification. For example, in *In re Johnson*,

supra, the court held that the claims could be limited during prosecution in order to avoid subject matter lost in an interference; the court explained that: "It is for the inventor to decide what bounds of protection he will seek." 588 F.2d at 1018.

The applicant's obligation is to describe and claim the invention in accordance with 35 U.S.C. §112. Thereafter, patent examination may lead to amendments to the claims. The MPEP §2173.05(i) advises that: "If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." The MPEP does not require that the reason for such exclusion must be stated in the specification. The panel majority creates a new and far-reaching ground of invalidity, a ground that received no deliberation and advice from the concerned communities.

Further, this new requirement for patent specifications is not an issue in this case, for the '772 specification states that sucralfate, "possibly the ideal agent for stress ulcer prophylaxis, [citing references]," is known to have occasional adverse effects, and that "the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm." '772 patent, col.4 ll.1-29. Thus the reason for excluding sucralfate was indeed stated in the specification. Nonetheless, the district court held that evidence of "contraindication" of sucralfate was required.

I agree with the panel majority that the Phillips invention was adequately described, and that the district court erred in its requirement. "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem v. Gen-Probe, Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002) (citation

omitted). The panel majority is incorrect in its new general requirement that the reason for any negative limitation must be included in the specification, on pain of invalidity under §112. This new ground of invalidity ignores the factual nature of the written description requirement, and impugns the presumption of validity of a duly granted patent. The court's new rule simply adds to the uncertainty of the patent grant, to the detriment of invention and commerce.

II

THE PARENT PATENT AS PRIOR ART

The panel majority creates another new ground of invalidity, in holding that the common disclosure in a parent patent is prior art to the chain of continuing patents. The court incorrectly holds that the parent '737 patent (U.S. Patent No. 5,840,737) that issued to Dr. Phillips is an invalidating reference based on the common subject matter that has priority to the parent patent's filing date.

The claims at issue all include subject matter disclosed in the '737 patent, subject matter for which priority was properly claimed, with no breaks in the chain of filings. It is beyond debate that the common subject matter in a chain of copending applications is entitled to priority from the earliest application disclosing the common subject matter. *See, e.g.*, Herbert F. Schwartz & Robert J. Goldman, *Patent Law & Practice* §2.III.D.7.c (6th ed. 2008) ("A continuation-in-part is entitled to the parent's filing date as to any subject matter in common, but only to its own filing date as to the new matter."); James E. Hawes, *Patent Application Practice* §18:5.50 (Rel. 27, 2011) ("The parent's filing date will apply to all the material in the child [CIP] that was in the parent, but the new material will not be accorded the benefit of the

parent's filing date."); Irah H. Donner, *Patent Prosecution: Law, Practice, and Procedure* 156 (7th ed. 2011) ("The CIP application priority date is the same as that of the earlier-filed application for subject matter common to the two applications.").

Ignoring this basic tenet of patent law, the panel majority uses the common subject matter from the '737 patent to invalidate many of the claims-in-suit. The panel majority describes this common subject matter at length, but instead of understanding that the common subject matter supports the claims that are entitled to the priority of that subject matter, the panel majority holds that the common subject matter invalidates the claims to that subject matter.

For example, the panel majority goes into detail for the '885 patent (U.S. Patent No. 6,699,885), ruling that because the claims in the '885 patent are supported by the common subject matter in the parent '737 patent, the claims in the '885 are rendered obvious by the parent '737 patent.

Priority for the '885 patent was properly claimed, in accordance with 35 U.S.C. §120, as follows:

> This application is a continuation-in-part of U.S. patent application Ser. No. 09/901,942, filed on Jul. 9, 2001, which is a continuation-in-part of U.S. patent application Ser. No. 09/481,207, filed on Jan. 11, 2000, now U.S. Pat. No. 6,489,346, which is a continuation-in-part of U.S. patent application Ser. No. 09/183,422, filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376, filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Ser. No. 60/009,608 filed on

> Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference.

'885 patent, col.1 ll.4-16. There is no break in the chain of priority. The panel majority correctly observes that the '737 patent describes the subject matter claimed in the '885 patent. The '737 patent describes the combination of the PPI and a Group IA metal salt, as follows:

> The present invention further includes a pharmaceutical composition for making a solution/suspension of omeprazole or other substituted benzimidazoles and derivatives thereof, which consists essentially of omeprazole or other substituted benzimidazoles and derivatives thereof and a bicarbonate salt of a Group IA metal in a form convenient for storage, whereby when the composition is placed into a aqueous solution, the composition dissolves yielding a solution/suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution in the aqueous solution. The omeprazole or other substituted benzimidazoles and derivatives thereof and bicarbonate can be formed into a tablet, capsule, or granules, by methods well known to those skilled in the art.

'737 patent, col.10, ll.20-33. The panel majority explains that the '885 subject matter is disclosed in the '737 patent, stating: "The '737 patent discloses broad ranges for the amounts of omeprazole and sodium bicarbonate that can be used, which overlap with the range of ratios of buffering agent to PPI claimed in the '885 patent." Maj. op. at 17. The panel majority states that the "'737 patent discloses formulating omeprazole both in conventional dosage forms (e.g., tablets, capsules, and granules) and

also as an aqueous suspension of omeprazole with a buffering agent," as claimed in the '885 patent. Maj. op. at 14. The panel majority states that "the '737 patent teaches that the amount of sodium bicarbonate can vary between 0.75 mEq to 1.5 mEq per 2 mg of omeprazole (0.375 to 0.75 mEq per mg of omeprazole)," and observes that "this falls within the range of about 0.1 mEq to about 2.5 mEq of buffering agent per mg of PPI claimed in the '885 patent." Maj. op. at 17.

Focusing on claim 17 of the '885 patent, the panel majority states that: "The '737 patent also discloses claim 17's limitation that the buffering agent be sodium bicarbonate 'in an amount from about 1000 mg to about 2000 mg'." The panel majority points to where the '737 disclosure shows the claim 17 dosage range of uncoated omeprazole, and where "the '737 patent teaches a range of 0.75-75 mEq of sodium bicarbonate, which overlaps with the claimed range [in the '885 patent]." Maj. op. at 17-18. The panel majority illustrates and stresses that the subject matter of claim 17 is within the '737 patent's disclosure.

The panel majority forgets that "matter disclosed in the parent application is entitled to the benefit of the filing date of the parent application." *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558 (Fed. Cir. 1994); *see Litton Sys., Inc. v. Whirlpool Corp.*, 728 F.2d 1423, 1438 (Fed. Cir. 1984) ("The earlier filing date of the parent application pertains to material in the C-I-P application also disclosed in the prior application. 35 U.S.C. §120."). Instead, the panel majority relies upon the common subject matter from the '737 patent disclosure to invalidate the '885 claims supported by that subject matter. This is incorrect, for the common subject matter in the '885 patent is entitled to the '737 filing date. That entitlement is not lost by issuance of the '737 patent.

The common subject matter, properly carried forward in copending continuing patents, cannot be prior art against itself, as the majority holds.

Similarly, the '988 patent (U.S. Patent No. 6,645,988) states the chain of copendency, and incorporation by reference, as follows:

> This application is a continuation-in-part of U.S. patent application Ser. No. 09/481,207 filed Jan. 11, 2000, now U.S. Pat. No. 6,489,346 which is a continuation-in-part of U.S. patent application Ser. No. 09/183,422 filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376 filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Ser. No. 60/009,608 filed on Jan. 4, 1996. This application claims priority to all such previous applications, and such applications are hereby incorporated herein by reference to the extent permitted by law.

'988 patent, col.1 II.4-15. There is no break in the chain, no flaw in the entitlement to priority for the common subject matter in the prior copending filings.

Similarly, the '346 patent correctly recites the chain of co-pendency. There are no breaks in the chain:

> This application is a continuation-in-part of U.S. patent application Ser. No. 09/183,422 filed on Oct. 30, 1998, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/680,376 filed on Jul. 15, 1996, now U.S. Pat. No. 5,840,737, which claims priority to U.S. Provisional Application Serial No. 60/009,608 filed on Jan. 4, 1996. This application claims priority

> to all such previous applications, and such applications are hereby incorporated by reference.

'346 patent, col.1 ll.4-12.

The novel ground of invalidity here adopted was not accepted by the PTO. During examination, the patent examiner reviews the priority claims, as instructed by the Manual of Patent Examining Procedure §§201.08, 201.11. The examiner did not cite the '737 patent against the later applications in the chain, during either the initial examination of the continuing applications, or on the reexamination of the '885 patent during this litigation.

From the court's incorrect ruling that the '737 patent is a reference against its common subject matter in the later applications in the chain of filings, I respectfully dissent.

III

PATENTABILITY - OBVIOUSNESS

Again ignoring the presumptions and burdens of proof for duly granted patents, the panel majority holds many of the remaining claims in the Phillips patents invalid for obviousness over the prior art. Although the expert witnesses for both sides agreed that it was uniformly understood that a protective enteric coating is essential for oral dosage, my colleagues find it obvious to omit the protective enteric coating.

Many scientists studying PPI degradation by stomach acid consistently confirmed that for practical administration the PPI must be coated with a gastric acid-resistant coating. Nonetheless, the panel majority cites these same scientific studies of PPI degradation in the stomach, and concludes that they render obvious the omission of the enteric coating. My colleagues do not mention the testi-

mony of experts in PPI science, that the Phillips uncoated formulation was "weird," "different," "pretty surprising," and "got people's attention," in the words of Dr. Brian Fennerty. Nor do my colleagues mention the plethora of patents and publications that uniformly stated that the PPI must be enteric coated. *E.g.*, U.S. Patent No. 4,786,505 to Lovgren and Pilbrant, col.1 ll.48-51 ("In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores *must* be enteric coated.").

The panel majority cites a study of stomach acid degradation of PPI led by Dr. Pilbrant, and ignores their conclusion that for oral administration the PPI *must* be enteric coated. This study by Pilbrant and Cederberg, "Development of an oral formulation of omeprazole," 20 *Scand. J. Gastroenterology* 113 (1985) (herein *Pilbrant*), explains the scientists' studies of the rate and conditions of PPI degradation by stomach acid. Drs. Pilbrant and Cederberg reported that the only way they obtained adequate absorption of uncoated PPI from the stomach was to require an initial ten hours of fasting in order to deplete the amount of acid in the stomach, then to drink a sodium bicarbonate solution to neutralize any remaining acid, then to drink buffered omeprazole rinsed down with sodium bicarbonate solution, followed by drinking three more doses of sodium bicarbonate solution over the next thirty minutes.

Dr. Pilbrant described various procedures whereby he attempted to avert or slow PPI degradation by stomach acid, and his conclusion that the rapid acid degradation "ruled out" an uncoated "conventional oral dosage form." *Id.* at 114. Dr. Pilbrant concluded that an "enteric-coated dosage form, which does not release the active ingredient for dissolution and absorption until it has been transported down to the neutral reacting part of the small

intestine, offers the best possibilities." *Id.* Dr. Pilbrant recognized that the complex system whereby uncoated PPI required lengthy fasting and successive consumption of several liquid doses, was not a practical regimen for administration to patients, and his "efforts were, therefore, concentrated on developing an enteric-coated granule formulation." *Id.* at 115.

Despite these teachings, the panel majority holds that this Pilbrant article renders obvious Dr. Phillips' elimination of the enteric coating. My colleagues state that Dr. Pilbrant recommended an oral uncoated suspension as the "second best choice." Maj. op. at 21. That is a mischaracterization, for Dr. Pilbrant made no such recommendation; he was discussing a "reference formulation" for studies of omeprazole in animals and human subjects:

> The solubility and stability properties of omeprazole *prevent the use of water solutions as the reference formulation* in animal and human studies. A rapidly dissolving suspension of micronized omeprazole is the second best choice *as the reference formulation*.

Pilbrant at 116 (emphases added). Dr. Pilbrant explained why water could not be used as the reference formulation:

> In animal experiments and in initial studies in man it is highly preferable to use water solutions of the drug in order to avoid influences of the dosage form on the pharmacokinetics and pharmacodynamics of the drug. Omeprazole is, however, only soluble in alkaline water solutions with physiologically unacceptable, high-pH values.

Pilbrant at 114. The Pilbrant publication stated that a liquid suspension of micronized omeprazole is second best to a water solution as an experimental reference formula-

tion, not, as the majority incorrectly contends, that a non-enteric suspension is a usable "second best" to enteric coated forms for administration to patients. Maj. op. at 21-22.

In determining obviousness, "a court must determine whether, at the time of the invention, a person having ordinary skill in the art would have had reason to attempt to make the composition" and "a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 995 (Fed. Cir. 2009). The presumption of validity under "§ 282 requires an invalidity defense to be proved by clear and convincing evidence." *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011). *See id.* at 2245 ("[T]here is a presumption of validity, a presumption not to be overthrown except by clear and cogent evidence." (quoting *Radio Corp. v. Radio Eng'g Labs., Inc.*, 293 U.S. 1, 3 (1934))); *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("The presumption of validity found in § 282 is reflected in the standard of proof required to prove invalidity, clear and convincing evidence.").

The prior art and the expert witnesses were explicit and uniform, that benzimidazole PPIs require an enteric coating for practical oral administration to patients. Proceeding contrary to the accepted scientific knowledge is "strong evidence of nonobviousness." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983). There was no evidence contrary to the position that an enteric coating was believed to be necessary.

This is a classical example of "teaching away," when persons in the field of the invention "would be led in a direction divergent from the path that was taken by the applicant." *Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008). The principal reference

relied on by the panel majority concluded that an "enteric-coated dosage form, which releases omeprazole for absorption in the small intestine . . . offers the best possibilities." *Pilbrant*, at 114-15. This conclusion was repeated in a patent of which Dr. Pilbrant is an inventor, entitled "Pharmaceutical Preparation for Oral Use." This patent refers to the studies in the *Pilbrant* article, and states:

> From what is said about the stability properties of omeprazole [in the article], it is obvious that an oral dosage form of omeprazole *must* be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

U.S. Patent No. 4,786,505, col.1 ll.35-39 (emphasis added). Undaunted by Dr. Pilbrant's unequivocal statements, my colleagues creatively find that *Pilbrant* teaches that "suspensions of buffered non-enteric coated omeprazole . . . are a viable alternative to enteric coating." Maj. op. at 22. Rather, Dr. Pilbrant reinforced the prevailing belief that the omeprazole *must* be enteric coated to prevent contact with acidic gastric juice.

The panel majority also cites an article by Lamers *et al.* entitled "Absorption of omeprazole in Zollinger-Ellison syndrome is accelerated by alkali," published in 26 *Gut* 1134-35 (1985). Lamers studied the absorption into the blood of coated and uncoated omeprazole in bicarbonate and saline solutions, based on experiments involving uncoated omeprazole taken with large volumes of sodium bicarbonate solution (as did Pilbrant). Lamers stated: "We therefore conclude that addition of alkali accelerates absorption of omeprazole in patients with Zollinger-Ellison syndrome." Lamers, like Pilbrant, did not propose that uncoated omeprazole was a viable alternative for oral administration to patients.

For years after the discovery of the benzimidazole PPI products, an enteric coating was believed to be essential for oral administration to patients. Pilbrant and Lamers and others did not change that belief; they reinforced it. The Court has cautioned against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness. *KSR Int'l Co., v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007).

The word "must" appears throughout the literature on enteric coating for benzimidazole PPIs, all ignored by the panel majority. In earlier litigation concerning omeprazole, this court observed that "an omeprazole formulation needs a protective enteric coating." *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1367 (Fed. Cir. 2007). Although sodium bicarbonate was known to stabilize PPI's, it was the accepted understanding that an enteric coating was needed to avoid rapid degradation by stomach acid. For example, U.S. Patent No. 6,136,344 to Depui, issued in 2000, states:

> It is well known that proton pump inhibitors are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that one of the active substances being a proton pump inhibitor *must* be protected from contact with acidic gastric juice by an enteric coating layer.

'344 patent, col.1 ll.62-67.

The teachings are uniform and uncontradicted, that the PPI must be coated. These teachings surely teach away from elimination of the enteric coating in oral dosing to patients. The panel majority ignores this general knowledge and general acceptance, although it is reiterated and uncontradicted throughout the litigation record.

The references on which the panel majority relies are studies of the rate and mechanism of gastric acid destruction of the uncoated PPI. Before Dr. Phillips' invention, no uncoated PPI formulation was achieved for patient use. The Phillips formulation eluded the experts, despite the extensive study of PPI degradation, despite the value and importance of PPI medications. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360-61 (Fed. Cir. 2011) ("The statutory criterion is whether the invention would have been obvious to persons of ordinary skill at the time of the invention, not whether it is sufficiently simple to appear obvious to judges after the discovery is finally made.").

My colleagues' hindsight pronouncements of obviousness are based on their knowledge of Dr. Phillips' achievement, an achievement that was deemed "weird" and met with incredulity. Determination of obviousness includes whether the prior art suggested, to a person of ordinary skill in the field of the invention, that the method "should be carried out and would have a reasonable likelihood of success." *Rockwell Int'l Corp. v United States*, 147 F.3d 1358, 1366 (1998) (quoting *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)). The prior art shows the uniform belief that oral administration of uncoated PPI is not an effective therapeutic alternative. Dr. George Sachs[1] publicly criticized the Santarus approach:

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[1] The record states that Dr. Sachs was awarded the Beaumont Prize, one of the highest honors of the American Gastrological Association, and was described at the trial as "the dean of PPIs." *See Altana Pharma AG v. Teva Pharms. USA Inc.*, 566 F.3d 999, 1009 (Fed. Cir. 2009) (stating that Dr. Sachs "is one of the leading researchers in the PPI development field").

> The principle of Santarus is to give essentially, if you like, a bicarbonate or carbonate buffer to the omeprazole solution. And so you don't have enteric coating and it comes in a gelcoat or gelcap. We thought about that a long time ago at Astra . . . . Man is a continuous acid secretor; the amount of acid man makes is not really predictable and so you're not really able to particularly buffer the omeprazole solution in the stomach. So as soon as the solution starts to fall below pH 5, which would happen with a high degree of frequency, you simply destroy the omeprazole and it will no longer work. So I think the Santarus principle, though well-founded – you know, in terms of the idea of stabilizing, simply doesn't work in man.

Trial Tr. 23:1-20; J.A. 3672; *Santarus*, 720 F. Supp. 2d at 456.

Dr. Phillips "proceeded contrary to the accepted wisdom. . . . That fact is strong evidence of nonobviousness." *W.L. Gore*, 721 F.2d at 1552 (citing *United States v. Adams*, 383 U.S. 39 (1966)). *See also Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art."); *Arkie Lures, Inc. v. Gene Laren Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997) ("conventional wisdom that a combination should not be made is evidence of unobviousness").

Skepticism within the industry supports unobviousness of the invention. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1304 (Fed. Cir. 2010) (objective evidence of nonobviousness included "evidence of industry skepticism."). This skepticism, reinforced in scientific commentary and

conceded by the experts, leaves no doubt that an enteric coating was believed necessary for oral PPI administration. *See Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (for an obvious combination, skilled artisans must have expected that the combination would work for its intended purpose).

The record states that the Phillips formulation provides effective absorption of the PPI directly from the stomach into the bloodstream, that it achieves faster control of stomach acid, improved nocturnal acid control, dosing independent of meals, and stabilized pharmacodynamics. The direct absorption from the stomach has the advantages of rapid and consistent bioavailability and increased effectiveness, as well as ease of administration to patients unwilling or unable to swallow capsules or tablets, as the Phillips patents explain:

> [I]n their current form (capsules containing enteric-coated granules or enteric-coated tablets), proton pump inhibitors can be difficult or impossible to administer to patients who are either unwilling or unable to swallow tablets or capsules, such as critically ill patients, children, the elderly, and patients suffering from dysphagia.

'772 Patent, col.7 l.65 - col.8 l.4.

These advantages are reflected in the Santarus sales growth of Zegerid® from $46 million in 2006 to over $100 million in 2008. The record states that numerous companies took a license to the Phillips patents. Evidence of "how the patented device is viewed by the interested public: not the inventor, but persons concerned with the product in the objective arena of the marketplace" is "highly probative of the issue of nonobviousness." *Arkie Lures*, 119 F.3d at 957. In *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir.

1985), this court observed that: "Secondary considerations may be the most pertinent, probative, and revealing evidence available to the decision maker in reaching a conclusion on the obviousness/nonobviousness issue."

The uniform belief was that an enteric coating is necessary for oral administration of PPIs to patients. Despite this universal skepticism, my colleagues on this panel find Dr. Phillips' invention obvious to them. I respectfully dissent.