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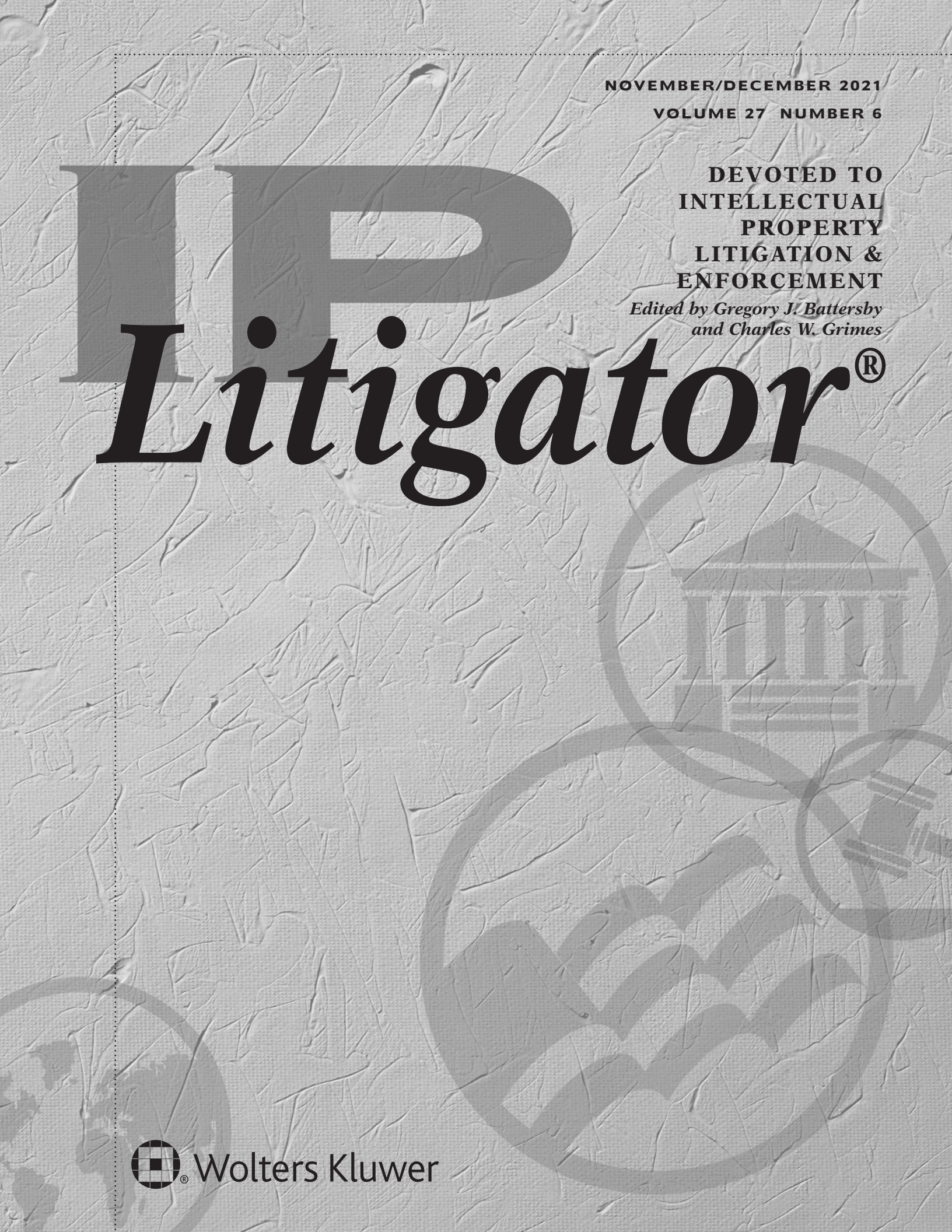

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When Inequitable Conduct is Patent: *Belcher Pharmaceuticals, LLC v. Hospira, Inc.*

Imposition of liability under the equitable doctrine of inequitable conduct (as it has been variously defined) can result in a patent being held unenforceable (even if only one claim is affected). For this reason, former Chief Judge Rader called the doctrine the "atomic bomb of patent law" (*see Aventis Pharma S.A. v. Amphastar Pharms., Inc*., 525 F.3d 1334, 1349 (Fed. Cir. 2008) (Rader, J., dissenting)). The history of the Federal Circuit's approach to the doctrine has been decisions limiting its scope (*Kingsdown Medical Consultants, Ltd. v. Hollister Inc*., 863 F.2d 867 (Fed. Cir. 1988)) followed by slow expansion (*Ferring v. Barr Labs*, 437 F.3d 1181 (Fed. Cor. 2006)). The Federal Circuit's most recent attempt to cabin the application of the doctrine arose in *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (*en banc*), and has generally led to narrowing the application of the doctrine by requiring a showing of both materiality and intent to deceive, each under a clear and convincing evidentiary standard (but imperfectly; *see Regeneron Pharma., Inc. v. Merus N.V.*, 864 F.3d 1343, 1350 (Fed. Cir. 2017)). But sometimes even under this more exacting standard the patency of the violation is evident, as was the case in *Belcher Pharmaceuticals, LLC v. Hospira, Inc.* (Fed. Cir. 2021). As the Christian Bible says, "no one can serve two masters," at least not well. Matthew 6:24. But the attempt to satisfy the statutory requirements for patenting, particularly non-obviousness, can invite contradictory attempts to satisfy regulatory requirements before the FDA. And that can (and did) lead to the outcome in this case.

Background of the Case

The case arose in ANDA litigation involving Belcher Pharmaceuticals' 1 mg/mL injectable L-epinephrine formulation, for which Hospira filed an ANDA and certified under 21 U.S.C. § 355(b)(2)(A)(iv) (a Paragraph IV certification) that Belcher's U.S. Patent No. 9,283,197 was invalid, not infringed, or unenforceable. The '197 patent addressed compositions of L-epinephrine formulated using methods to avoid oxidation of L-epinephrine to adrenalone (which reduced its potency), and to avoid racemization, a separate basis for loss of potency. Both these chemical reactions are related to the pH of the formulation solution, with oxidation increasing with higher pH conditions and racemization increasing at lower pH levels. As stated in the opinion, "[i]n other words, when an epinephrine solution becomes more acidic (*i.e*., pH decreases), racemization increases and oxidation decreases, and when the solution becomes more basic (*i.e*., pH increases), oxidation increases and racemization decreases." This led to the prior art understanding that the optimum pH to minimize the effects of racemization and oxidation was between pH 3.0–3.8.

Belcher's NDA specified that its formulation differed from prior art formulations that included sodium metabisulfite as an antioxidant and an amount of L-epinephrine in 10% excess (to account for losses of potency for whatever reason). Belcher's NDA specified that its product did not contain sulfite antioxidants or other preservatives but rather contained an increased amount of sodium chloride and 15% overage of L-epinephrine at a pH of between 2.8 and 3.3. Importantly for the inequitable conduct question in this litigation, Belcher responded to FDA inquiries as follows:

> Addressing the FDA's question on racemization, Belcher explained that "[r]acemization of the enantiomerically pure L-Epinephrine isomer in injectable formulations of epinephrine is a well-known process," citing literature authored by Fylligen and Stepensky. Responding to the FDA's inquiry on manufacturing process for the stability validation batches, Belcher stated that the only difference between the relied-upon Sintetica batches and Belcher's proposed formulation "is related to the in[-]process pH" and that it "consider[ed] the in[-] process pH change to be a very minor change not requiring additional stability studies." Belcher also explained that the release specification

of 2.2 to 5.0 "complies with [the] USP specification and stays unchanged between all the batches." Id.

In addition, Belcher's consultants advised that the pH maintained during formulation be kept at the art-recognized pH of 2.8–3.3; "Belcher followed that advice," according to the opinion.

Belcher asserted claims 6 and 7 of the '197 patent in the ensuing ANDA litigation:

> 6. An injectable liquid pharmaceutical formulation of l-epinephrine sterile solution; said liquid pharmaceutical formulation having a pH between 2.8 and 3.3; said injectable liquid pharmaceutical formulation compounded in an aqueous solution as 1.0 to 1.06 mg/mL l-epinephrine, and further including a tonicity agent; said liquid pharmaceutical formulation including no more than about 6% d-epinephrine and no more than about 0.5% adrenalone at release, and no more than about 12% d-epinephrine and no more than about 0.5% adrenalone over a shelf-life of at least 12 months.
>
> 7. The said injectable liquid pharmaceutical formulation of claim 6 further having a concentration of 1 mg per mL l-epinephrine.

In the single Office Action, Belcher argued that their claims were non-obvious over a prior art reference that disclosed "a 1 mg/mL epinephrine injection that was free of preservatives and antioxidants, was made in an oxygen free (*i.e.*, nitrogen) environment, and had a pH range of 2.2 to 5.0" because the pH range of 2.8–3.3 "was unexpectedly found to be critical by the Applicant to reduce the racemization of l-epinephrine" and produced unexpected results. These arguments were noted in the resulting Notice of Allowance as the basis upon which the Examiner allowed the claims (making subsequent establishment at trial of the materiality of Applicant's arguments in this regard rather easy).

Hospira's Inequitable Conduct Argument

Hospira's inequitable conduct allegations centered on the knowledge and actions (including failing to disclose to the Examiner) of three pieces of information by Belcher's Chief Science Officer who, by his own admission, was "involved in the development of Belcher's NDA product and participated in drafting the NDA," and "involved in the prosecution of the '197 patent" including helping in application drafting and responding to the Examiner's Office Action (despite being neither a patent agent nor patent attorney). The three pieces of information undisclosed to the patent Examiner were: 1) a label by third party (JHP) for a 1mg/mL epinephrine product; 2) Sintetica's prior art product (0.1 mg/mL L-epinephrine formulation); and 3) the 2004 Stepinsky reference, "Long-term stability study of L-adrenaline injections: kinetics of sulfonation and racemization pathways of drug degradation," 93(4) *J. PHARM. SCI.* 969–80. Hospira's expert testified persuasively that this information was but-for material on the issues of the pH range and level of impurities. As for intent to deceive, the District Court cited Belcher's CSO's behavior (it being evident that he was under the duty of candor set forth in 37 C.F.R. § 1.56) before the FDA that "[Belcher's CSO] knew that Belcher described the claimed pH range of 2.8 to 3.3 as 'old'; that Belcher disclosed Stepensky, which teaches an overlapping pH range of 3.25 to 3.70; that Belcher had submitted data on Sintetica's and JHP's products showing a pH within the claimed range; and that Belcher switched from a lower pH range to the claimed 2.8 to 3.3 pH range at least in part to expedite FDA approval because that range matched the pH range of Sintetica's products," none of which he disclosed to the patent Examiner. In contrast, the District Court found that "[Belcher's CSO] did not merely withhold this information but also used emphatic language to argue that the claimed pH range of 2.8 to 3.3 was a 'critical' innovation that 'unexpectedly' reduced racemization." With regard to intent, the District Court found it "implausible" that Belcher's CSO considered this information to be irrelevant and also asserted that his "repeated efforts to evade questioning and inject attacks of the prior art into his answers [while testifying] raised serious questions as to his credibility." On this basis, the District Court held the '197 patent to be unenforceable for inequitable conduct.

Federal Circuit Ruling

Belcher appealed, and the Federal Circuit affirmed, in an opinion by Judge Reyna, joined by Judges Taranto and Stoll. The panel opinion made short work of the materiality prong of inequitable conduct, *inter alia* because the District Court held claims 6 and 7 to be invalid for obviousness over cited references that included one of the withheld pieces of information (JHP's epinephrine product), citing *Aventis Pharma S.A. v. Hospira, Inc*., 675 F.3d 1324, 1334 (Fed. Cir. 2012). Regarding the intent-to-deceive prong of the *Therasense* test, the Court noted

that Belcher's CSO was aware that the pH 2.8–3.3 range was known in the art and that Belcher had reverted to that range (after originally pursuing formulations having a pH range of 2.4–2.6) as a means to obtain FDA approval more expeditiously because in part that range had been used in the Sintetica prior art product. Nevertheless, Belcher's CSO affirmatively asserted (in the '197 specification and in argument before the Examiner) that the pH 2.8–3.3 range was "a 'critical' innovation contrary to the knowledge of a person of ordinary skill in the art that yielded 'unexpected results,' namely reducing racemization of l-epinephrine." These representations were "false" and "a fiction" according to the District Court and the Federal Circuit saw no reason to disagree. Belcher maintained before the District Court and before the Federal Circuit on appeal that Belcher's CSO's representations were based on a genuine belief that the withheld information was irrelevant due to the high overage amounts used in their product. The Federal Circuit, like the District Court, rejected what it called these "*post hoc* rationales," citing *Aventis* for similar circumstances and crediting the District Court for its firsthand assessment of Belcher's CSO's lack of credibility, stating that this conclusion was also supported by other evidence of record such as the substance of his representations to the FDA and patent Examiner and differences if not outright contradictions between them.

Having found no clear error in the District Court's assessment and factual findings on either materiality or intent, the Federal Circuit affirmed the District Court's finding of inequitable conduct and resulting unenforceability of the '197 patent.

The decision is in no way momentous, but it does illustrate the difficulties that can arise even for individuals fully aware of the arguments made in different fora or to address different issues. The case provides a cautionary tale regarding the prudence in making sure that the arguments made to one decision maker (regulatory agency, the U.S. Patent and Trademark Office, investors, or the courts) are consistent if not identical to arguments and representations made to any of these other actors. Failure to do so can easily *ex post facto* be the basis for inferring the necessary intent to deceive under *Therasense*, as it was in this case.

Kevin E. Noonan, Ph.D. is a partner at McDonnell Boehnen Hulbert & Berghoff LLP in Chicago. Kevin is experienced in all aspects of patenting and in biotechnology and chemistry, representing pharmaceutical and biotechnology companies, as well as universities. He is a founder of the biotechnology and pharma patent law and news weblog, Patent Docs (www.patentdocs.org). In addition to his blog, Dr. Noonan writes and lectures extensively on biotechnology patent law.