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Belcher Pharm. v. Hospira (September 1) provides an example of how a patent can be rendered unenforceable by unethical behavior stemming, in part, from a failure to place patent prosecution under the control of an ethical, knowledgeable, and experienced patent agent or attorney.

Background: Facts & The Issue

Epinephrine degrades over time through racemization (conversion of potent ℓ isomer to less potent ɑ isomer) and oxidation (conversion of ℓ-epinephrine to an impurity). It was known that lower pH promotes racemization and higher pH promotes oxidation, such that pH between about 3.0 to 3.8 "is an optimum pH at which racemization and oxidation can be balanced to minimize loss of intact drug by these two routes."[1]

Belcher's NDA

In 2012, Belcher filed a New Drug Application ("NDA") for an injectable epinephrine solution. Belcher's NDA cited an earlier injectable epinephrine formulation from another company, Sintetica, as the reference drug.[2] Belcher represented to the FDA that:

1. Testing showed the Sintetica reference product had a pH of 3.1 to 3.3; and
2. Regarding a proposal in the NDA to use a lower pH for its product, Belcher described a higher range of 2.8 to 3.3 as "old" and its proposed lower range of 2.4 to 2.6 as "new."

Because it would be expected to increase racemization, the FDA asked for more information about the proposed lower pH range. In response, Belcher represented that:

3. The reduction in the pH range was "a very minor change not requiring additional stability studies."

The FDA then asked Belcher to perform studies on the effect of the reduced pH on racemization. Belcher decided it would be more expedient to instead rely on the "old" pH range and the tests it had already done on the Sintetica formulation, and told the FDA it would request approval based on a reversion of the manufacturing pH . . .

4. ". . . from 2.4 to 2.6 back to the initial pH of 2.8 to 3.3."

While the NDA was pending, Belcher became aware of another injectable epinephrine solution from a company called JHP and obtained relevant information about it:

5. The label of the JHP product stated its pH as between 2.2 and 5.0; and
6. Tests performed on three batches of the JHP product showed a pH range of 2.9 to 3.1.

Belcher's Patent Application

In 2014, Belcher filed a patent application. Belcher placed the prosecution under the control of its Chief Science Officer ("CSO"), who was known (informally, at least) as Belcher's "head of IP" but who was neither a patent agent nor a patent attorney.[3] Despite the CSO having been deeply involved with the NDA, he failed to disclose to the PTO any information about the Sintetica or JHP products. In fact, Belcher disclosed no references or other information during prosecution.

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[1] Connors et al., CHEMICAL STABILITY OF PHARMACEUTICALS: A HANDBOOK FOR PHARMACISTS 438–47 (John Wiley & Sons 2d. ed. 1986).

[2] A "reference drug" is a closely-related previously-approved drug that serves as a predicate for approval of the new drug formulation – *i.e.,* in appropriate cases, data regarding the safety and efficacy of the reference drug can be used for approval of the new drug, allowing for a faster and less costly approval process.

[3] March 31, 2020 Opinion, United States District Court for the District of Delaware in Case No. 17-775, ¶24.

In the specification and an office action response, Belcher made the following representations, which were questionable in light of the content of its NDA, its representations to the FDA, and its knowledge of the JHP product:

- "[T]he idea of raising the in-process pH above the range of 2.2 to 2.6 'was contradictory to one skilled in the art' before the claimed invention." *[Belcher knew that a higher pH range was in the prior art (see representations 1, 2, 4, 5, 6)]*
- "Inadvertently, increasing the in-process pH to 2.8-3.3 unexpectedly reduced the racemization of *l*-epinephrine to *d*-epinephrine at release by approximately two-thirds, from 14% to 5%, respectively." *[Belcher very likely knew the pH dependence of racemization, and Belcher definitely knew that the pH range of 2.9 to 3.3 was in the prior art (see representations 1, 2, 4, 5, 6); Use of the higher pH range also hardly appears "inadvertent" since it was essentially the same range as the reference product and Belcher used it purposely to expedite FDA approval]*
- An overlapping pH range in a prior art reference was, per Belcher, insufficient for obviousness because the claimed pH range of 2.8 to 3.3 "was unexpectedly found to be critical by the Applicant to reduce the racemization of *l*-epinephrine." *[But Belcher knew the range of 2.9 to 3.3 was in the prior art (see representations 1, 2, 4, 5, 6), Belcher deliberately switched to that range to expedite FDA approval, and Belcher described its initial, proposed lower pH range as a "very minor change," suggesting that raising it back to the prior art level would also be "very minor" (see representation 3)]*

The patent issued based on Belcher's representation to the PTO regarding criticality of the pH range.

The Lawsuit

The case began when Hospira sought FDA approval to market an injectable epinephrine solution and submitted a Paragraph IV certification[4] that Belcher's patent claims were invalid, unenforceable, and/or not infringed by Hospira's NDA product.

After bench trial, the district court found the two asserted claims of Belcher's patent obvious over the prior art JHP product and, based on the evidence of what Belcher knew and "serious questions about the credibility" of Belcher's star witness, also found the entire patent unenforceable for inequitable conduct.

Belcher appealed the inequitable conduct decision, but not the obviousness decision.

Background: Relevant Black Letter Law

1. Inequitable Conduct – In General
   a. To prove inequitable conduct . . .
      i. An accused infringer must prove by clear and convincing evidence that the patent applicant:[5]
         1) Misrepresented or omitted *material* information;
         2) *Knew* that the misrepresented or omitted information was material; and
         3) Misrepresented or omitted that material information with *specific intent to deceive* the PTO.
      ii. And, the court must "balance the equities to determine whether the applicant's conduct before the PTO was egregious enough to warrant holding the entire patent unenforceable."[6]
   b. Materiality and intent are separate requirements; no degree of materiality can offset a lack of intent and no degree of intent can offset a lack of materiality.[7]

[4] A Paragraph IV certification is the mechanism by which patents relating to closely-related previously-approved drug products can be asserted by their owner prior to approval of the new drug product.

[5] Elements restated from *Therasense v. Becton, Dickinson & Co.,* 649 F.3d. 1276, 1290 (Fed. Cir. 2011), *Transweb v. 3M Innovative Properties,* 812 F.3d 1295, 1303-04 (Fed. Cir. 2016), and *GS Cleantech Corp. v. Adkins Energy LLC,* 951 F.3d 1310, 1324 (Fed. Cir. 2020).

[6] *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.,* 537 F.3d 1357, 1365 (Fed. Cir. 2008); *see also Therasense*, 649 F.3d at 1292 ("Because inequitable conduct renders an entire patent (or even a patent family) unenforceable, as a general rule, this doctrine should only be applied in instances where the patentee's misconduct resulted in the unfair benefit of receiving an unwarranted claim.").

[7] *Therasense,* 649 F.3d. at 1290 ("Intent and materiality are separate requirements," "a district court may not infer intent solely from materiality," and a "district court should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa").

c. *All* claims of patent become unenforceable (not merely claims directly at issue regarding the inequitable conduct or claims actually asserted in a litigation).[8]

2. Materiality

a. Standard = "but for" materiality – *i.e.,* if the PTO had been aware of the information, it would not have allowed a claim.[9]

b. Use PTO claim interpretation and evidentiary standards for materiality – *i.e.,* broadest reasonable interpretation and preponderance of evidence.[10]

i. Information is necessarily material for inequitable conduct purposes if it forms the basis for proper invalidation of a claim in district court proceedings (*i.e.,* because the standard of proof in district court is higher than in prosecution before the PTO, success in district court necessarily meets the lower PTO standard of proof).[11]

ii. A determination that misrepresented/omitted information is *not* sufficient for invalidity in district court is *not* relevant to the materiality analysis for inequitable conduct (*i.e.,* failure to invalidate under the higher level of proof required in district court says nothing about whether the lower PTO standard of proof is met).[12]

c. Information is not material if it is cumulative to, or less pertinent than, information that was before the examiner.[13]

3. Intent

a. Direct evidence of deceptive intent (*e.g.,* admission of intent to deceive the PTO from a witness or in an email) is rare. Thus, the development of legal rules regarding intent focus on drawing inferences from indirect and circumstantial evidence.[14]

b. Standards:

i. An inference of deceptive intent based on indirect and circumstantial evidence "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."[15]

ii. "In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference."[16]

c. Need *intent to deceive*, not merely intent to withhold (which can be explained, for example, on grounds of good faith but mistaken analysis of cumulativeness or relevance).[17]

What *Belcher Pharm.* Adds or Changes:

[8] *E.g., Therasense,* 649 F.3d. at 1298 ("the remedy for inequitable conduct is the 'atomic bomb' of patent law" because "[u]nlike validity defenses, which are claim specific . . . inequitable conduct regarding any single claim renders the entire patent unenforceable.").

[9] *Therasense,* 649 F.3d. at 1291.

[10] *Therasense,* 649 F.3d. at 1291-92; *see also American CalCar v. American Honda,* 768 F.3d 1185, 1189 (Fed. Cir. 2014).

[11] *Therasense,* 649 F.3d at 1292. It is important to parse the evidentiary standards. Although underlying facts regarding whether the PTO would have allowed a claim are subject to a *preponderance of the evidence* standard, the fact elements of inequitable conduct (*e.g.,* whether the material information was misrepresented or withheld by the applicant, whether the applicant knew the misrepresented/omitted information was material) are subject to the higher *clear and convincing evidence* standard.

[12] *E.g., American CalCar v. American Honda,* 651 F.3d 1318, 1335 (Fed. Cir. 2011) ("Even though the jury rejected Honda's invalidity arguments, both on anticipation and obviousness [based on the withheld information], the withheld information may be material if it would have blocked patent issuance under the PTO's preponderance of the evidence standard, giving those patents' claims their broadest reasonable construction.").

[13] *E.g., Larson Mfg. v. Aluminart,* 559 F.3d 1317, 1327 (Fed. Cir. 2009); *see also* 37 C.F.R. § 1.56(b) ("[I]nformation is material to patentability when it is not cumulative to information already of record or being made of record in the application . . .").

[14] *E.g., Therasense,* 649 F.3d. at 1290 ("Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence"); *Star Scientific,* 537 F.3d at 1366.

[15] *Star Scientific,* 537 F.3d at 1366; *see also Therasense 649* F.3d. at 1290 ("to meet the clear and convincing evidence standard, the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'"), and *GS Cleantech,* 951 F.3d at 1324 (quoting *Therasense*).

[16] *Therasense* 649 F.3d. at 1290 (quoting *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.,* 863 F.2d 867, 876 (Fed. Cir. 1988)).

[17] *E.g., Larson Mfg., 559* F.3d at 1327, 1331-32 (collecting cases).

The Federal Circuit affirmed the inequitable conduct determination by the district court, finding that the district court "did not clearly err in making its factual findings regarding materiality and intent, nor did it abuse its discretion in ultimately deciding that the '197 patent is unenforceable for inequitable conduct."

Materiality

The Federal Circuit found no clear error in the district court's materiality determination:

- Belcher effectively *admitted* materiality of information it withheld regarding the prior art JHP product by not appealing the obviousness determination – since the asserted claims were found invalid over that product, information about that product and its pH is *per se* material.
- Belcher asserted that the information it withheld was merely cumulative of a Canadian patent that the Examiner discovered in their search. The Federal Circuit found this argument unpersuasive because it was "directly at odds with [Belcher's] argument during prosecution that the claimed range was 'critical'" (an argument Belcher made to circumvent obviousness where the Canadian patent disclosed a pH range that overlapped the claimed range).
- "The trial record later established that the JHP product had a pH within the alleged critical range of 2.8 to 3.3. Belcher's alleged critical improvement over the prior art was therefore already within the public domain, just not before the examiner."

Intent

The Federal Circuit similarly found no clear error in the district court's intent determination:

- Belcher's CSO . . .
  - "was an active participant in the FDA approval process and understood that Belcher had stated to the FDA that the 2.8 to 3.3 pH range was an 'old' range"; and
  - knew "that Belcher had reverted from its original pH range (2.4 to 2.6) to the 2.8 to 3.3 range because the latter range corresponded to the reference product, and therefore using that range would expedite FDA approval."
- But in drafting the patent application and communicating with the PTO, Belcher's CSO . . .
  - "performed an about-face and emphatically and repeatedly advanced the position that the 2.8 to 3.3 pH 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."
- At trial, Belcher's CSO . . .
  - claimed "that he withheld the references because he believed that they were irrelevant—even though they directly undercut the most important patentability argument—because they were different from the asserted claims in certain respects, including their high overages."
- Finding Belcher's arguments to be "post hoc rationales for withholding material prior art," and looking at the evidence of the CSO's "prior knowledge of the JHP product, his central role in both FDA approval and patent prosecution, and his arguments to the examiner about the 'criticality' of the 2.8 to 3.3 pH range despite knowing that Sintetica's batches used the same range" and the district courts determination that the CSO's testimony was "implausible and not credible," the Federal Circuit agreed with the district court that "the single most reasonable inference is that [Belcher's CSO] possessed the specific intent to deceive the PTO when withholding the JHP product."

Ultimate Decision – Balancing the Equities

Based on the above reasoning, the Federal Circuit similarly found "no abuse of discretion in the district court's decision that the patent was unenforceable for inequitable conduct.

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The *Belcher Pharm.* case does not change or materially add to the law; rather it provides a cautionary tale about ensuring that patent prosecution is "owned" by an experienced, knowledgeable, and ethical legal professional (*e.g.,* patent attorney or patent agent, be they in-house or outside counsel). This is a real issue. I have seen companies thin-out their patent groups and rely on interested/biased, non-legally-trained technologists and scientists to manage, guide, and control patent prosecution – some more than others, in one case to a frightening extent).