

Biopharma Patentees Must Navigate Inherent Obviousness

By **Pauline Pelletier, Marsha Rose Gillentine and Eric Steffe**

(June 23, 2020, 2:00 PM EDT)

This year, the U.S. Court of Appeals for the Federal Circuit denied rehearing en banc in two appeals involving inherent obviousness — Persion Pharmaceuticals LLC v. Alvogen Malta Operations Ltd.[1] and Hospira Inc. v. Fresenius Kabi USA LLC[2] — perhaps missing an opportunity to clarify a doctrine that both the U.S. Patent and Trademark Office and courts have struggled to apply consistently and coherently.

The difficulty decision-makers face when applying inherency in the context of obviousness can be a stumbling block for patentees and patent challengers alike. Here, we discuss the impact of inherent obviousness on biopharmaceutical patenting and litigation and some strategic implications.

What is inherent obviousness, and how is it applied?

In patent law, inherency typically refers to a characteristic, property or feature that would necessarily have been present when practicing the prior art but that is not expressly disclosed.[3] Inherency does not require recognition at the time of invention that the inherent feature was present, only that the feature necessarily would have been present.[4]

Inherency often arises in biopharmaceutical patenting and litigation, particularly where the defendant is seeking approval to market a generic drug that must be deemed bioequivalent to a previously approved drug.[5]

In recent years, inherency has played an increasingly prominent role in determinations of obviousness. Inherent obviousness is the principle that a claim limitation need not be expressly disclosed in the prior art if the missing limitation is the natural result of the combination or modification of prior art elements.[6]

A classic application of this principle is *In re: Kao*, in which the Federal Circuit held that even though the claimed controlled-release formulation and its associated food effect were not disclosed in the prior art, the formulation would have been obvious and the claimed food effect was an inherent property of the obvious formulation.[7]



Pauline Pelletier



Marsha Rose
Gillentine



Eric Steffe

Another often-cited example is *Santarus Inc. v. Par Pharmaceutical Cos. Inc.*, in which the Federal Circuit held that a specified formulation would have been obvious and that the specific serum concentrations recited in the claims were the natural or inherent result of administering the obvious formulation. The court stated: "[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations."^[8]

The Federal Circuit's recent decision in *Persion* is reminiscent of *Santarus*. In *Persion*, the patentee's claims were directed to a hydrocodone-only formulation that elicited a particular pharmacokinetic profile when administered to a patient subpopulation with mild or moderate hepatic impairment.

The trial court found that the formulation was known and that there was a teaching in the prior art that the subpopulation should be treated the same way as the general population.

Deferring to the trial court's fact findings, the Federal Circuit affirmed, holding that "the pharmacokinetic limitations ... were inherent and added no patentable weight."^[9]

In general, inherent obviousness has been applied in situations where some claimed effect or property is merely the predictable result of administering a known or obvious formulation.^[10] By the same token, it has often proven difficult, historically, for patent challengers to establish inherent obviousness where the art is unpredictable or there is evidence of unexpected results.^[11]

What is the problem with inherent obviousness?

Inherency, a concept that first arose in the context of anticipation, is a question of fact that can be proven at any time, regardless of whether it was recognized at the time of invention. The importation of inherency into obviousness, which must be based on the state of the art at the time of invention, has proven paradoxical and unwieldy.

The Federal Circuit recognized this doctrinal tension in *PAR Pharmaceutical Cos. Inc. v. TWI Pharmaceuticals Inc.*, noting that "the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness."^[12]

Despite the Federal Circuit's warning, patent challengers have often asserted inherent obviousness in a multitude of situations— including in the context of contesting the patentability of new compounds and results associated with the use of new compounds.

In *Millennium Pharmaceuticals Inc. v. Sandoz Inc.*, the Federal Circuit overturned the district court's finding that claims directed to a new compound resulting from the lyophilization of a known drug, the proteasome inhibitor bortezomib, would have been obvious.^[13]

Although bortezomib was known, the D-mannitol ester that Millennium claimed was not. The district court nonetheless held that the claims were obvious because the D-mannitol bortezomib ester was "the inherent result of an allegedly obvious process."^[14]

The Federal Circuit reversed, holding that the district court "clearly erred in its consideration of inherency" by applying inherent obviousness, not to a property of a known compound, but to a new compound with distinctive properties.^[15]

In *Millennium*, the Federal Circuit focused on the fact that the process used to make the D-mannitol

bortezomib ester was not known to solve bortezomib's stability problem and further considered what solutions a skilled artisan would have used to modify the lead compound. The court also analyzed secondary considerations supporting the nonobviousness of the claimed compound.

While not a case relating to biopharmaceutical patents, in *Honeywell International Inc. v. Mexichem Amanco Holding SA*, the Federal Circuit reversed the Patent Trial and Appeal Board's determination that claims directed to a specific mixture of HFO-1234yf and PAG would have been obvious, despite evidence that the mixture had unexpected stability and miscibility, which were properties recited in the claims.[16]

The board reasoned that a person of ordinary skill would have engaged in routine testing of all possibilities to arrive at the specific mixture and that the claimed properties would have been inherent. The Federal Circuit reversed, holding that the board had improperly dismissed or discounted the claimed properties as inherent without adequately taking into account unpredictability in the art and evidence of unexpected results.

In *Honeywell*, the Federal Circuit reiterated that:

the use of inherency in the context of obviousness must be carefully circumscribed because "[t]hat which may be inherent is not necessarily known" and that which is unknown cannot be obvious.[17]

The court emphasized that:

What is important regarding properties that may be inherent, but unknown, is whether they are unexpected. All properties of a composition are inherent in that composition, but unexpected properties may cause what may appear to be an obvious composition to be nonobvious.[18]

A question posed by *Hospira* in its petition for rehearing that was denied by the Federal Circuit is whether it is ever appropriate for a patent challenger to rely on no-prior art examples to establish inherency in the context of an obviousness determination.[19]

The question can arise in situations where the patent challenger must show that an undisclosed property is inherent, not in a particular prior art disclosure, but in a hypothetical combination of prior art elements. What kind of proof is necessary to establish inherency within the hypothetical combination? Does it violate the reasoning in *Honeywell* to prove inherency based on something that was unknown?

Another ambiguity is whether the doctrine of inherent obviousness is strictly limited to properties or features that would have been predictable and expected to a person of ordinary skill in the art at the time of invention.

Persion's petition for rehearing argued that the Federal Circuit has three lines of conflicting precedent:

- One that rejects reliance on inherency in the context of obviousness altogether;[20]
- One that limits inherency to properties or features that would have been predictable at the time;[21] and

- One where the expectations of a person of ordinary skill in the art do not matter and are unnecessary to consider because "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it." [22]

With the denial of these two petitions for rehearing, inherent obviousness remains, as one Federal Circuit judge put it, "tricky," and the task of articulating the standard "maddening." [23]

As a result of this difficulty, parties face significant uncertainty when making and defending against assertions of inherent obviousness. And while the inquiry is largely fact-driven, its many twists and turns make it one where decision-makers are susceptible to making analytical errors. [24]

What are the strategic implications for biopharmaceutical patents?

A reasonable explanation for the growing role of inherent obviousness is the trend over the past decade to procure and enforce patents directed to pharmaceutical reformulations and modified dosage forms in conjunction with pharmacokinetic parameters — e.g., C_{max}, T_{max} and AUC — and other effects of administering the product — e.g., metabolic effects, side effects, toxicities and mechanisms of action.

These types of claims can have significant commercial value because generic drug manufacturers often seek to establish bioequivalence and this type of information is usually included on the drug label, supporting claims of induced infringement. It is also often the case that there is little or no prior art disclosing such parameters for a given formulation. [25]

Inherent obviousness is also arising more frequently during *ex parte* prosecution. It is not uncommon for an examiner to assert that it would have been obvious to modify the prior art to arrive at a claimed formulation and that any claimed properties are inherent. In many cases, the examiner's assertions will be unsubstantiated, but the applicant must rebut them.

As a practical matter, what can applicants do to overcome such rejections? First, consider whether the examiner understands the case law. Inherent obviousness is frequently misunderstood by examiners who may equate it with inherent anticipation and refuse to consider the unpredictability of the art and unexpected results. Taking the time to explain inherency in the context of obviousness can help, including by highlighting the limited role inherency should play in obviousness determinations.

Second, consider whether the examiner has provided a reasoned basis with evidentiary support to establish that a property would be inherent in a given combination. Because inherency is a question of fact, there should be some evidence offered to support a finding of inherency.

A third strategy is to build a record supporting no inherency — e.g., the claimed effect does not necessarily arise from the prior art combination — unpredictability, and/or unexpected results. This record can be established using affidavits or documentary evidence. It can also be beneficial to develop a record on other objective indicia of nonobviousness.

In *Millennium*, for example, the Federal Circuit held that long-felt need, unexpected results and commercial success weighed in favor of nonobviousness. While objective indicia do not play a role in inherent anticipation, this type of evidence can be helpful in countering rejections based on inherent obviousness.

In district court litigation and post-grant proceedings, the patent challenger bears the burden of proof, so the analysis plays out somewhat differently than in ex parte prosecution.[26] In litigation and post-grant proceedings, the patent challenger bears the burden of demonstrating that any missing elements are necessarily and invariably present in the prior art combination.

This can be challenging in practice. Historically, admissions in the specification or by the patentee, e.g., in press releases, regulatory filings, publications, have proven useful. As shown by the case law, an important fact to establish is that the claimed results would have been predictable and necessarily flowed from the prior art, keeping in mind that mere probability is not sufficient.

The interplay with infringement may also eliminate factual disputes about inherency. For example, a plaintiff may be arguing that an accused pharmaceutical product satisfies the claimed pharmacokinetic parameters because it is the same composition as the claimed invention and will therefore necessarily produce the claimed effects.

In making that argument, the plaintiff may become unable to dispute that the claimed effects are anything but a predictable and inevitable result of administering the claimed composition. To the extent a defendant is able to obtain an admission to that effect, the admission can be leveraged for purposes of proving inherency.

Ultimately, inherent obviousness is a twisty and evolving legal doctrine. Patentees and patent challengers alike should keep abreast of developments in the law and carefully evaluate inherency-based obviousness contentions.

For the same reasons, parties should be mindful to preserve these types of arguments for appeal, whether in the context of prosecution or litigation. More appeals on inherent obviousness will hopefully offer clarifications in the years to come.

Pauline M. Pelletier, Marsha Rose Gillentine, Ph.D., and Eric K. Steffe are directors at Sterne Kessler Goldstein & Fox PLLC.

The opinions expressed are those of the author(s) and do not necessarily reflect the views of the firm, its clients, or Portfolio Media Inc., or any of its or their respective affiliates. This article is for general information purposes and is not intended to be and should not be taken as legal advice.

[1] Persion Pharmaceuticals LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1186 (Fed. Cir. 2019), rehearing denied (Feb. 28, 2020).

[2] Hospira, Inc. v. Fresenius Kabi USA, LLC, 946 F.3d 1322, 1330 (Fed. Cir. 2020), rehearing denied (Mar. 13, 2020).

[3] Continental Can v. Monsanto, 948 F.2d. 1264, 1268 (Fed. Cir. 1991).

[4] Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003).

[5] Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) ("it is axiomatic that that which would literally infringe if later anticipates if earlier").

[6] PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc., 773 F.3d 1186 (Fed. Cir. 2014) ("the concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the 'natural result' of the combination of prior art elements").

[7] In re Kao, 639 F.3d 1057 (Fed. Cir. 2011).

[8] Santarus, Inc. v. Par Pharms., Inc., 694 F.3d 1344 (Fed. Cir. 2012).

[9] Persion Pharm. LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1191 (Fed. Cir. 2019).

[10] See, e.g., GeneriCo, LLC v. Dr. Falk Pharma GmbH, IPR2016-00297, Paper 55 at 12-14 (P.T.A.B. May 19, 2017) (finding a claimed release profile obvious based on press releases discussing the administration of the formulation and evidence that measuring a release profile was well-known and the specification did not identify any factors making release profiling an unpredictable exercise); Purdue Pharm. Prods. LP v. Actavis Elizabeth LLC, 2015 BL 273849, *52-53 (D.N.J. Mar. 27, 2015) (basing its finding that claimed plasma concentration were inherently obvious based on testimony that "a POSA could easily predict offset blood concentrations").

[11] See, e.g., Fresenius-Kabi USA, LLC v. AstraZeneca AB, IPR2017-01910, Paper 10 at 15-16 (P.T.A.B. Dec. 11, 2017) (finding claims directed to plasma concentrations from intramuscular injection of a pharmaceutical nonobvious in light of the unpredictability and unexpected results); Actavis LLC v. Abraxis Bioscience, Inc., IPR2017-01100, Paper 7, *11-13 (P.T.A.B., Oct. 11, 2017) (finding stability limitations for a particular formulation nonobvious and not inherent); Bidelivery Scis. Int'l, v. Aquestive Therapeutics, Inc., IPR2015-00169, Paper 89 at 28-29 (P.T.A.B. Feb. 7, 2019) (finding claims requiring substantially uniform distribution not inherently obvious because the prior art does not describe uniform thickness and the Petitioner did not provide evidenced showing that any of the drying processes described in the prior art necessarily produced a film having the uniform thickness requirement).

[12] PAR Pharm., Inc. v. TWI Pharm., Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2014).

[13] Millennium Pharmaceuticals, Inc. v. Sandoz Inc., 862 F.3d 1356 (Fed. Cir. 2017).

[14] Id. at 1362.

[15] Id. at 1367.

[16] Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A., 865 F.3d 1348 (Fed. Cir. 2017).

[17] Id. at 1355.

[18] Id.

[19] Hospira, Inc. v. Fresenius Kabi USA, LLC, Appeal No. 19-1329, ECF No. 66 at 4 (Feb. 20, 2020) ("This Court should rehear this case en banc to resolve that disagreement and set a clear standard for inherency in obviousness law. On the merits, the Court should hold that, as a matter of law, nonprior art examples are not enough to sustain a patent challenger's burden of proving inherency. Rather, the patentee bears the affirmative burden to extrapolate the inherent properties of the allegedly obvious combination, no matter how it is prepared.").

[20] *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("the inherency of an advantage and its obviousness are entirely different questions"); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983) ("Inherency and obviousness are distinct concepts"). see also Dan Burk and Mark Lemley, *Inherency*, 47 *William & Mary Law Review* 371 (2005) (arguing inherency should have almost no role in obviousness because hindsight is forbidden).

[21] *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. De C.V.*, 865 F.3d 1348 (Fed. Cir. 2017) ("in dismissing properties of the claimed invention as merely inherent, without further consideration as to unpredictability and unexpectedness, [the Board] erred as a matter of law"); *Application of Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977) (reversing because the Board made no showing as to the "predictability" of the appetite curbing property recited in the claims).

[22] *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020) (explaining that the reasonable expectations of a person of ordinary skill in the art are not a necessary or proper part of the inherency analysis because "[i]f a property of a composition is in fact inherent, there is no question of a reasonable expectation of success in achieving it").

[23] *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, Appeal No. 18-2361, ECF No. 75 at SAppx1 ("Now, the law on that is a little tricky, I think. There is law that says inherency is not inherently forbidden from being used in obviousness analysis, but it has to be employed with caution. And that kind of instruction, which is maddening, because it's not very informative, I have not done a lot of research, but that is my impression of roughly what the law is, and I would like you all to give me some briefing on that.") (Judge Bryson, sitting by designation).

[24] *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020) ("The court thus conflated the standards for inherency and reasonable expectation of success. However, that was harmless error that did not infect its inherency analysis and findings.").

[25] See, e.g., Matthew Bultman, *Federal Circuit Ruling Could Put Certain Drug Patents At Risk*, *Bloomberg Law* (Dec. 31, 2019), available at <https://news.bloomberglaw.com/ip-law/federal-circuit-ruling-could-put-certain-drug-patents-at-risk?context=search&index=1>.

[26] See, e.g., *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018) ("[I]t is Custopharm's burden to present clear and convincing evidence that the Articles necessarily disclosed the vehicle formulation to one of skill in the art."); *PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1382–83 (Fed. Cir. 2019) ("Because we find that the proposed, theoretical Binary Object Identifier look-up table that Apple and the Board rely on does not necessarily exist in Woodhill, the Board's reliance on inherency for that element in its obviousness analysis was improper."); see also *Luxshare Precision Industry Co., Ltd. v. Bing Xu Precision Co., Ltd.*, IPR2017-01657, Paper 47 (P.T.A.B. Jan. 10, 2019) (denying institution).