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Fed. Circ. Rulings Crystallize Polymorph Patent 'Obviousness'

By **Michael Green and John Molenda** (June 4, 2024, 3:20 PM EDT)


Michael Green


John Molenda

The fact that an active pharmaceutical ingredient may exist in more than one crystalline form, i.e., polymorphs, can play a key role in an innovator's patent lifecycle management strategy.[1]

Through a process called polymorph screening, innovators commonly generate and characterize polymorphs of their active pharmaceutical ingredient,[2] and ultimately patent those polymorphs with desirable chemical properties.

Challenges to such patents have been met with mixed success, particularly when the basis for the challenge is that it would have been obvious to obtain the claimed polymorphs by routine polymorph screening procedures.[3]

After the U.S. Court of Appeals for the Federal Circuit's 2019 decision in Grunenthal GmbH v. Alkem Laboratories Ltd., which rejected such an obviousness challenge to polymorph patent claims, some practitioners questioned the feasibility of obviousness-type challenges to polymorph patents.[4]

But the Federal Circuit's April decision in Salix Pharmaceuticals Ltd. v. Norwich Pharmaceuticals Inc. may have resolved at least some of that questioning.[5] That is because, in Salix, the Federal Circuit affirmed the invalidation of the asserted polymorph claims as obvious based in part on polymorphic screening-type arguments.

This article conducts an in-depth analysis of how Grunenthal and Salix approached the question of obviousness in the context of polymorph screening arguments, and provides key takeaways from those decisions.

Background

Before delving into the legal issues in the Grunenthal and Salix decisions, we first provide a brief overview of polymorph screening, the goal of which is to determine whether crystalline forms of an active pharmaceutical ingredient, or API, exist and, if so, characterize those forms using various analytical techniques.[6]

Polymorph screening employs the technique known as recrystallization, which involves dissolving the API in one or more solvents, while at the same time varying different reaction conditions, such as

temperature, pH, agitation and concentration.[7] If a crystalline form of the API is obtained, it can be characterized using analytical techniques such as X-ray powder diffraction, which provides a unique spectrum for each form.[8]

In fact, polymorphs are commonly claimed by the unique collection of spectral peaks associated with that polymorph.[9] Because different polymorphic forms can have different biological properties, such as dissolution and bioavailability, U.S. Food and Drug Administration guidelines indicate that innovators should screen their APIs for polymorphs.[10]

As will be discussed below, patent challengers have attacked polymorph patent claims as obvious, arguing that FDA guidelines provide a motivation to screen for polymorphs, and that such screening involves routine techniques that yield a reasonable expectation of success in obtaining the claimed polymorphs.

Innovators respond that such claims are nonobvious given that the techniques used to obtain polymorphs require the manipulation of numerous parameters, and there is no way to predict which polymorphs — if any — will arise and what their properties will be.

The Grunenthal Decision

In Grunenthal, the pertinent patent-at-issue was directed to the Form A polymorph of tapentadol hydrochloride, which is an API used to treat polyneuropathic pain and urinary incontinence.[11] The appellant Alkem alleged that the asserted polymorph claims were invalid as obvious in view of two references.[12]

The first reference was U.S. Patent No. 6,248,737, which disclosed the steps for making tapentadol hydrochloride, yielding a crystalline form of that compound known as Form β .[13]

The second reference was the Byrn article, which disclosed a polymorph screening methodology for determining whether polymorphs exist for a particular compound, including recrystallization solvents and the possible impact that variables, such as temperature, concentration, agitation and pH, could have on polymorph formation.[14]

The Federal Circuit focused its obviousness analysis on two issues: whether there was a reasonable expectation of success in obtaining the claimed Form A, and whether it would have been obvious to try to obtain that polymorph.[15][16]

As for reasonable expectation of success, Alkem argued that the U.S. District Court for the District of New Jersey erred in finding that there would have been no such expectation in obtaining the claimed Form A polymorph by performing Byrn's polymorph screening methods on the Form β polymorph disclosed in the '737 patent.[17]

The Federal Circuit disagreed, noting that Byrn failed to provide any guidance for how to vary the many specific parameters it discloses to obtain potential polymorphs for tapentadol hydrochloride.[18] Rather, the Federal Circuit determined that a person of skill would need to manipulate those parameters without a sense of what the result might be.[19]

Alkem also argued that a person of skill would have expected to obtain at least some Form A in reproducing the synthetic protocol for tapentadol hydrochloride in the '737 patent, because Form A is

more stable than Form β.[20] But the Federal Circuit rejected that argument because, inter alia, there was no known polymorphism of tapentadol hydrochloride as of the priority date and no evidence that the '737 patent's synthesis procedure results in any Form A.[21]

As for "obvious to try," Alkem asserted that producing Form A would have been obvious to try because Byrn discloses a finite number of recrystallization solvents.[22] The Federal Circuit again disagreed, holding that the district court did not err in finding that Byrn actually disclosed a huge number of options for polymorph screening — solvents or otherwise — with only general guidance and no detailed enabling methodology.[23]

The Federal Circuit thus affirmed the district court's obviousness determination.[24]

The reasoning in Grunenthal led some practitioners to question the feasibility of polymorph screening-type obviousness challenges.[25] Their viewpoints seemed supported by the Federal Circuit's **2022** nonprecedential decision in Pharmacyclics LLC v. Alvogen Inc., which followed the reasoning of Grunenthal in rejecting an obviousness challenge to polymorph patent claims.

But those practitioners may not have given sufficient credence to the court's statement in Grunenthal that "[o]ur decision today does not rule out the possibility that polymorph patents could be found obvious." And, in fact, that statement would appear particularly prescient in view of the Federal Circuit's recent Salix decision, which we discuss in detail below.

The Salix Decision

In Salix, the pertinent patent-at-issue was directed to rifaximin Form β, an API used to treat hepatic encephalopathy and various forms of diarrhea.[26] The generic manufacturer Norwich had alleged that the asserted polymorph claims were invalid as obvious in view of Cannata, a prior art reference that taught that rifaximin exists in crystalline form and has strong antibacterial properties, and further disclosed several crystallization procedures for rifaximin.[27]

The district court agreed with Norwich, holding that the evidence showed that (1) there was good reason to characterize the crystalline rifaximin obtained from the prior art procedures, (2) characterization was routine, and (3) Form β would have been detected upon performing the characterization.[28]

In assessing the correctness of the district court's obviousness decision, the Federal Circuit focused on two issues: whether (1) the court's Grunenthal and Pharmacyclics decisions in fact compelled a determination of nonobviousness, and (2) a person of skill would have had a reasonable expectation of success in obtaining the claimed rifaximin Form β.[29][30]

As to the first issue, the Federal Circuit disagreed with patentee Salix that Grunenthal and Pharmacyclics compelled a determination of nonobviousness.[31] The court noted that Grunenthal emphasized "the factual nature" of obviousness and pointed to Grunenthal's statement that the court did "not rule out the possibility that polymorph patents could be found obvious."[32]

The Federal Circuit also distinguished those cases, explaining that the issue in Grunenthal and Pharmacyclics was whether there was a reasonable expectation of success in producing the claimed form, while the issue here was whether there was a reasonable expectation of success in characterizing the claimed form.[33]

The Federal Circuit concluded that it appeared undisputed that Form β "can be readily produced" from the disclosures in the prior art Cannata reference, and that "it would have been well within the abilities of the skilled artisan to procure and characterize the B form of rifaximin."[34]

As to the second issue, the Federal Circuit also disagreed with Salix's argument that a person of skill would not have been expected to succeed at obtaining Form β, because (1) the polymorphic nature of rifaximin and the identity of Form β were both undisclosed, and (2) the polymorphic forms that might result from following the prior art procedures could not have been predicted.[35]

The Federal Circuit dismissed those arguments as suggesting that no unknown polymorph could ever be obvious, which wrongly assumes that a person of skill cannot reasonably expect what was previously unknown.[36] And, in affirming the district court's finding of reasonable expectation of success, the Federal Circuit held that

Salix has done no more than combine known elements of the prior art to verify readily accessible information concerning a compound already in the hands of those of ordinary skill in the art, and such routine efforts do not justify removing this polymorph from the public domain.[37]

But, channeling its earlier statement in Grunenthal as to the fact-specific nature of the obviousness analysis concerning polymorph patents, the Federal Circuit clarified that "[t]o be sure, we do not hold that there is always a reasonable expectation of success in accessing or characterizing polymorphs."[38]

Analysis and Takeaways

Taken together, Grunenthal and Salix provide helpful insight into how the Federal Circuit assesses the obviousness of polymorph patents, particularly the issue of reasonable expectation of success.

First and foremost, both cases make clear that such an assessment will turn on the specific facts at issue in a particular case. While Grunenthal said as much, practitioners nonetheless questioned the feasibility of obviousness-based challenges to polymorph patents. By confirming the fact-specific nature of the inquiry, as articulated in Grunenthal, and holding the claims at issue invalid, it would appear that Salix has, at least to some degree, quelled concerns about the viability of those challenges.

Moreover, Grunenthal and Salix provide some insight as to factors that may be pertinent to finding whether a person of skill would have a reasonable expectation of success in obtaining a claimed polymorph.

Such factors appear to include whether, as of the priority date, (1) the API was known to exist in polymorphic forms, (2) the art disclosed procedures for obtaining the claimed crystalline form, (3) the art provided any guidance as to which particular parameters for polymorph screening were likely to result in the claimed form, and (4) methods for characterizing crystalline forms were routine.

But again, Grunenthal and Salix make clear that those and any other factors that a court considers in evaluating obviousness must be viewed in the context of each specific case. As such, we anticipate that the issue of obviousness in the context of polymorph patents will continue to be vigorously litigated in cases going forward.

Michael Green is an associate at Steptoe LLP.

John Josef Molenda is a partner, and co-chair of the healthcare and life sciences group and lead of the New York intellectual property practice, at the firm.

Steptoe partner Vishal Gupta contributed to this article.

[1] Walter Cabri et al., Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study, 11 Organic Process Res. Dev. 64, 64 (2007) ("[T]he filing of patents claiming new crystalline forms, usually 4-6 years after the original product patent, is a typical strategy applied by [large pharmaceutical] companies to extend patent protection").

[2] Grünenthal GMBH v. Alkem Laboratories Ltd., 919 F.3d 1333, 1336 & n.1, 1337 (Fed. Cir. 2019) (providing overview of polymorphism and polymorph screening).

[3] See, e.g., Kowa Co., Ltd. v. Amneal Pharms., LLC, No. 14-CV-2758 (PAC), 2017 WL 10667089, at *23-*29 (S.D.N.Y. Sept. 19, 2017) (rejecting polymorph screening-based obviousness argument), aff'd, 745 F. App'x 168 (Fed. Cir. 2018); In re Armodafinil Pat. Litig. Inc. ('722 Pat. Litig.), 939 F. Supp. 2d 456, 488-503 (D. Del. 2013) (same).

[4] Luke T. Shannon & Taras A. Gracey, Federal Circuit Addresses Obviousness of Polymorphs in Grunenthal GmbH v. Alkem Labs. Ltd., No. 2017-1153 (Fed. Cir. Mar. 28, 2019), Nat. L. Rev. (April 4, 2019), available at https://natlawreview.com/article/federal-circuit-addresses-obviousness-polymorphs-grunenthal-gmbh-v-alkem-labs-ltd-no) ("In view of Grunenthal, ANDA filers should expect that already difficult obviousness challenges to polymorph patents will be even more difficult."); Amy L. Mahan, Polymorphic Patent Survives Obviousness Challenge, 22(4) IP Update 8, 9 (April 2019), available at https://www.mwe.com/pdf/ip-update-vol-23-april-2019/ ("Patents covering polymorphic compounds may become more difficult to invalidate in view of the Federal Circuit's decision—especially in situations where it is unknown whether a compound is polymorphic at all and there are no concrete steps in the literature to definitively determine that such polymorphism exists").

[5] Salix Pharmaceuticals, Ltd. v. Norwich Pharmaceuticals Inc., 98 F.4th 1056 (Fed. Cir. 2024).

[5] Grünenthal, 919 F.3d at 1337, 1341-42.

[6] Id.

[7] Id. at 1336.

[8] Id. at 1336 (noting that the asserted patent claims recite X-ray powder diffraction spectral patterns).

[9] Ctr. For Drug Evaluation and Res., Food and Drug Admin., Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (1987) at 31-35.

[10] Grünenthal, 919 F.3d at 1336.

[11] Id. at 1337.

[12] Id.

[13] Id.

[14] Id. at 1341.

[15] The Federal Circuit did not reach the issue of whether the FDA's guidance addressing polymorphs would have provided a motivation to conduct polymorph screening and thereby obtain Form A. Id.

[16] Id.

[17] Id. at 1342-43.

[18] Id.

[19] Id. at 1343.

[20] Id.

[21] Id. at 1345.

[22] Id.

[23] Id. at 1336.

[24] Shannon, supra note 5; Mahan, supra note 5.

[25] 98 F.4th at 1059-60, 1064.

[26] Id. at 1064.

[27] Id. at 1064-65.

[28] Id. at 1065-67.

[29] Salix did not appear to dispute that there would have been a motivation to investigate the existence of possible polymorphic forms of rifaximin. Id. at 1066.

[30] Id. at 1065.

[31] Id. (quoting Grünenthal, 919 F.3d at 1344-45).

[32] Id.

[33] Id. at 1066.

[34] Id.

[35] Id.

[36] Id. at 1066-67.

[37] Id. at 1066 (emphasis added).