Paper No. _____
Filed:

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PETITIONER

V.

GRÜNENTHAL GMBH

PATENT OWNER

CASE NO.: UNASSIGNED
PATENT NO. 7,994,364
FILED: DECEMBER 10, 2009
ISSUED: AUGUST 9, 2011
INVENTORS: ANDREAS FISCHER, *ET AL.*

TITLE: CRYSTALLINE FORMS OF (-)-(1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYLPROPYL)-PHENOL HYDROCHLORIDE

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 7,994,364

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Exhibit No.	Description
Exhibit 1017	U.S. Patent No. 6,248,737 to Helmut Bushmann *et al*., issued Jun. 19, 2001 ("*Bushmann 737*")
Exhibit 1018	U.S. Patent No. 6,344,558 to Helmut Bushmann *et al*., issued Feb. 5, 2002 ("*Bushmann 558*")
Exhibit 1019	Plaintiffs' Opening Claim Construction Brief, *Janssen Pharms., Inc. et al. v. Actavis Elizabeth LLC et al.*, 2-13-cv-04507 (D. NJ), D.I. No. 141 ("*Janssen Claim Construction Brief*")
Exhibit 1020	July 15, 2015 Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations listing for Nucynta ("Orange Book")

I. INTRODUCTION

Petitioner requests an *Inter Partes* Review ("IPR") of claims 1–4 and 24–27 (collectively, the "Challenged Claims") of U.S. Patent No. 7,994,364 (the "'364 Patent") (Ex. 1001) in accordance with 35 U.S.C. §§ 311–19 and 37 C.F.R. §§ 42.100 *et seq*.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A))

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '364 Patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR challenging the claims of the '364 Patent on the grounds identified in this Petition.

III. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that it has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition.

B. Related Judicial and Administrative Matters (37 C.F.R. § 42.8(b)(2))

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '364 Patent has been the subject of the following lawsuits: *Janssen Pharms., Inc. et al. v. Actavis Elizabeth LLC et al.*, D. NJ.-2-13-cv-04507 (filed Jul. 25, 3013); *Janssen Pharms., Inc. et al. v. Sandoz Inc. et al.*, D. NJ.-2-13-cv-06929 (filed Nov. 14, 2013);

Janssen Pharms., Inc. et al. v. Roxane Labs., Inc., D. Nev.-3-13-cv-00639 (filed Nov. 15, 2013); *Janssen Pharms., Inc. et al. v. Alkem Labs. Ltd.*, D. NJ-2-13-cv-07803 (filed Dec. 23, 2013); *Janssen Pharms., Inc. et al. v. Roxane Labs., Inc.*, D. NJ-2-14-cv-03941 (filed Jun. 19, 2014); and *Janssen Pharms., Inc. et al. v. Watson Labs., Inc.*, D. NJ-2-14-cv-04617 (filed Jul. 23, 2014).

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead counsel is Attorney 1. Back-up counsel is Attorney 2. Petitioner consents to electronic service.

IV. PAYMENT OF FEES (37 C.F.R. § 42.15(A) AND § 42.103)

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. _____. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of U.S. Patent No. 7,994,364

The ’364 Patent is titled “Crystalline Forms of (-)-(1R,2R)-3-(3-Dimethylamino-1-Ethyl-2-Methylpropyl)-Phenol Hydrochloride.” (Ex. 1001 at Front Cover.) The underlying application, U.S. Patent App. No. 12/364,777 (the “’777 Application”) was filed on Dec. 10, 2009. The ’777 Application is a continuation of U.S. Patent App. No. 12/274,747, filed on Nov. 20, 2008 (now

abandoned), which is a continuation of U.S. Patent App. No. 11/646,232, filed on Dec. 28, 2006 (now abandoned), which is a continuation of Application No. PCT/EP2005/006884, filed on Jun. 27, 2005. (*Id.*) The '777 Application claims priority back to European Patent App. No. 04015091, filed on Jun. 28, 2004. (*Id.*)

1. **The '364 Patent Specification**

The '364 Patent claims the crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride ("tapentadol HCl"), pharmaceutical compositions containing Form A, methods of producing Form A compounds, and methods of treating conditions by administering the compound, including methods for the treatment of pain. (*Id.* at Abstract.) The '364 Patent acknowledges that "U.S. Pat. Nos. 6,248,737 and 6,344,558 as well as European Patent EP 693 475 B1 [*German EP 475*; *EP 475*] disclose the substance and the synthesis of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride in example 25." (*Id.* at 1:46-49.)[1] However, the '364 Patent purports to disclose "a new form (Form A) of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride which is different from the form already

[1] The '364 Patent explains that "the 1R,2R configuration as shown in the drawing of the structure in example 25 is correct although the configuration is reported as (-)-(1R,2S) in U.S. Pat. No. 6,248,737 and (-)-(1S,2S) in U.S. Pat. No. 6,344,558 as well as in EP 693 475 B1." (Ex. 1001 at 1:50-54.)

known (Form B) obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737 and U.S. Pat. No. 6,344,558 as well as EP 693 475 B1." (*Id.* at 1:58-63.)

According to the '364 Patent, "[t]he new crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride can be identified by X-ray powder diffraction. The X-ray diffraction ("XRPD") pattern is shown in FIG. 1 [copied below] with the peak listing showing in Table 1 [also copied below]." (*Id.* at 2:14-18.)

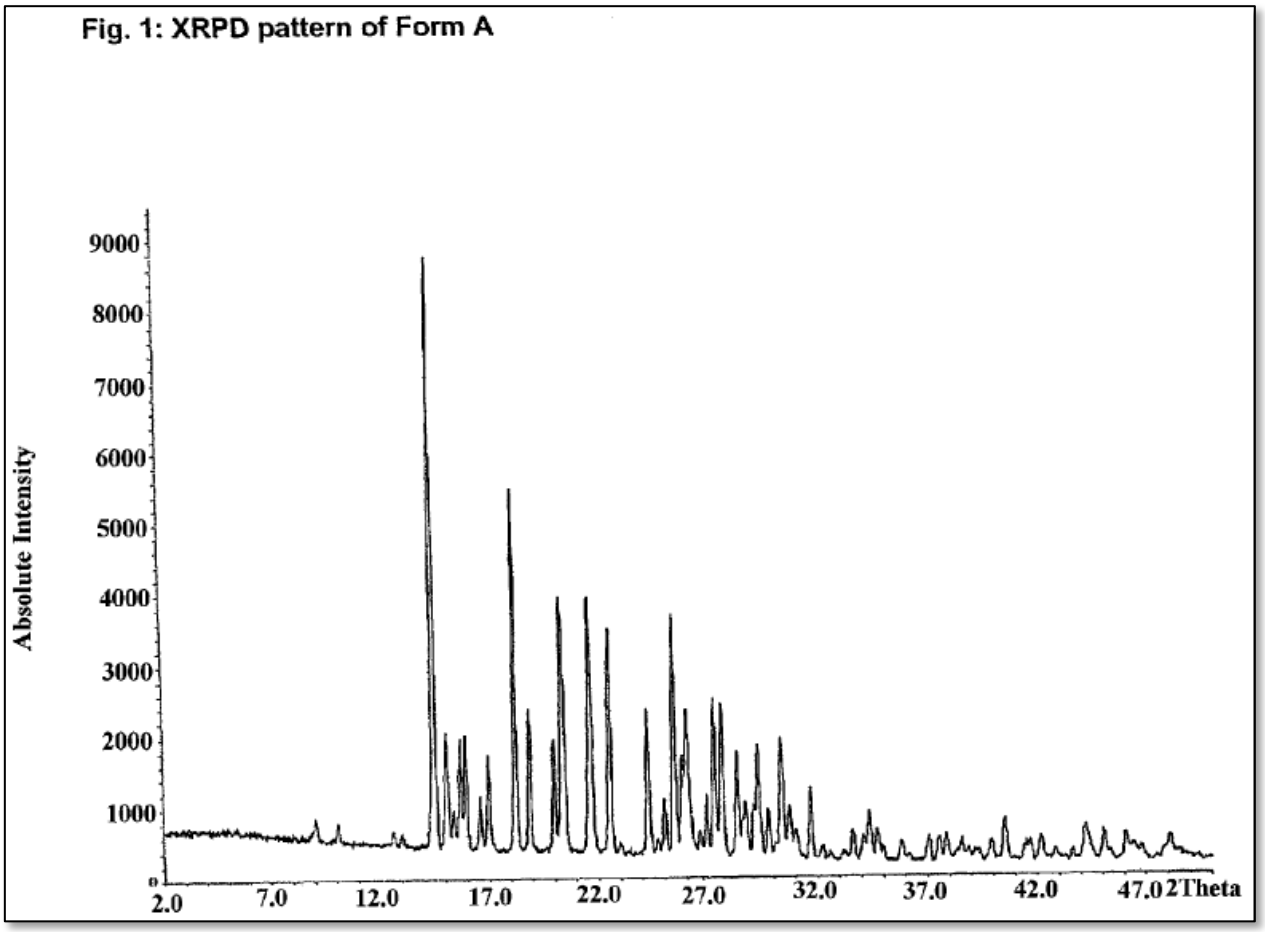


TABLE 1

Peak and Relative Intensity Listing (°2θ, peaks with I/I1 value of 10 and over)

Peak No.	A	I/I1	B	I/I1
1	9.07	10	14.58	100
2	10.11	9	14.94	9
3	14.51	100	15.42	19
4	15.08	24	15.76	27
5	15.39	11	16.05	8
6	15.69	22	16.77	14
7	15.96	24	18.01	60
8	16.62	13	19.60	39
9	17.00	20	20.18	27
10	18.24	63	20.98	19
11	18.88	28	21.43	14
12	20.00	23	21.99	65
13	20.39	47	23.71	4
14	21.66	47	24.73	43
15	22.54	41	25.10	14
16	24.27	28	25.71	21
17	25.03	13	26.29	10
18	25.47	43	26.81	5
19	25.84	20	27.76	20
20	26.04	27	28.19	39
21	26.94	13	29.20	12
22	27.29	29	29.86	13
23	27.63	28	30.28	5
24	28.33	20	30.58	6
25	28.72	12	31.15	22
26	29.09	12	32.41	6
27	29.29	21	32.91	5
28	29.76	11	33.17	6
29	30.37	23	34.34	6
30	30.74	11	35.88	9
31	31.70	14	36.29	7
32	34.37	11	39.08	9

The ’364 Patent explains:

To discriminate crystalline Form A of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride from

> Form B it is more advantageous to look at the unique peaks in the X-ray diffraction diagram, *i.e. e.g.* the lines with sufficient intensity at 2-theta values, where Form B does not show lines with significant intensity. Such characteristic X-ray lines (2-theta values) for Form A in a powder diffraction pattern when measured using Cu K_α radiation at ambient temperature are: 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2 [highlighted in Table 1, above].

(*Id.* at 2:27-36.) The ’364 Patent claims at least this “crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride” displaying the above “X-ray lines (2-theta values) for Form A” in each of the Challenged Claims, as shown below.

Additionally, the ’364 Patent allegedly provides procedures for obtaining tapentadol HCl’s Form A—found in Examples 1-6, as well as for obtaining tapentadol HCl’s Form B—found in Examples 7-9. Of note, Example 7 purports to obtain Form B by following Example 25 of *EP 475*—the anticipatory prior art reference relied upon in Ground 1, and discussed in more detail below.

2. **The ’364 Claims**

The ’364 Patent’s Challenged Claims includes 3 independent claims and 5 dependent claims. **Claim 1** is representative and is reproduced below.

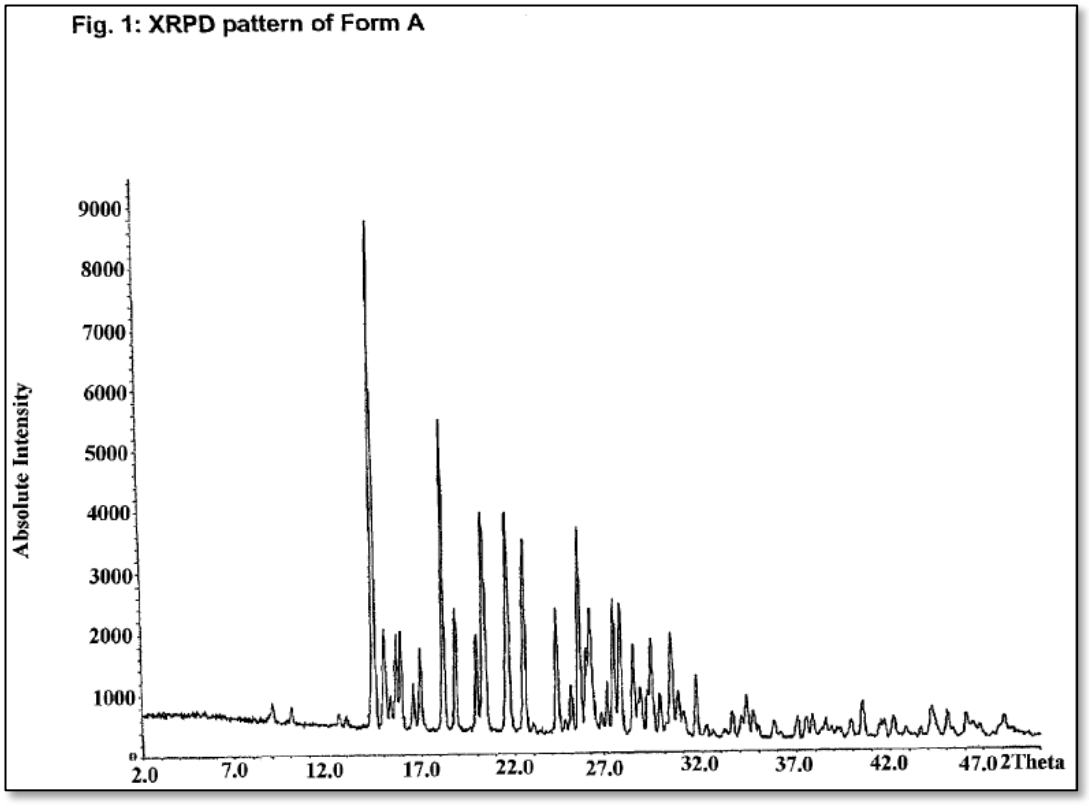
> A crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu

K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

(Ex. 1001 at 18:66-19:4.)

Claim 2 depends from claim 1 and adds the limitation that Form A exhibits "at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 22.5±0.2. (*Id.* at 19:7-10.)

Claim 3 depends from claim 1 and adds the limitation that Form A exhibits "an X-ray pattern (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1" (copied below). (*Id.* at 19:13-15.)



Claim 4 depends from claim 1 and adds the limitation that the Form A crystal has a monoclinic form. (*Id.* at 19:18-19.)

Claim 24 depends from claim 1 and is a product-by-process claim that adds the limitation that Form A is

> produced by the process of:
> dissolving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,
> heating the solution to the boiling point,
> removing the active carbon by filtering,
> stirring the solution at a temperature below 40° C.,
> removing part of the solvent residue by filtering and removing part of the solvent,
> leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize,
> redissolving the resulting crystals in acetonitrile,
> removing insoluble residue by filtering and removing part of the solvent, and
> leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize.

(*Id.* at 19:38-55.)

Independent **claim 25** requires a "solid pharmaceutical composition comprising, as an active ingredient," the crystalline Form A of claim 1, "and at least one suitable additive or auxiliary substance." (*Id.* at 19:56-63.)

Claim 26 depends from claim 25 and adds the limitation that Form A is

produced by the process of:
dissolving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,
heating the solution to the boiling point,
removing the active carbon by filtering,
stirring the solution at a temperature below 40° C.,
removing insoluble residue by filtering and removing part of the solvent, and
leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize, and
at least one suitable additive or auxiliary substance.

(*Id.* at 19:67-22:4.)

Independent **claim 27** requires a "method of treating or inhibiting pain or urinary incontinence, said method comprising the step of administering a pharmaceutically effective amount of "the crystalline Form A of claim 1 "to a subject in need thereof." (*Id.* at 22:5-13.)

3. **Prosecution History of the '364 Patent and European Counterpart**

The '777 Application that led to the '364 Patent received light treatment during prosecution. The only claims to ever receive a rejection were as-filed claims 26 and 27. (Ex. 1002 at 50.) For these two claims, the Examiner stated that the a pending 35 U.S.C. 112 rejection could "be removed by adding the word 'solid' in

front of the word 'pharmaceutical.'" (*Id.* at 51-53.) The applicant therefore amended claims 26 and 27 according to the Examiner's suggestion. (*Id.* at 58-64.)

Additionally, the applicant submitted an IDS containing information about "four clinical trials of a crystalline form of (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (CG5503) [that] were conducted in the United States through contract research organizations from 2001 to January 2003." (*Id.* at 64.) The applicant explained that "[a]t the time of these clinical trials, the crystalline material used to prepare the pharmaceutical dosage forms for these clinical trials was not tested to determine which crystalline form it was." (*Id.* at 54.) The applicant went on to state that, "[a]lthough tests have shown that even when the crystalline form B, produced as disclosed in US patent no. 6,248,737, is subjected to tableting, it retains its form B crystalline structure and does not convert to the crystalline form A …." (*Id.* at 65.) Additionally, the applicant remarked that "[e]xtreme stress tests of crystalline form B alone (*i.e.*, in the absence of any other tablet ingredients) for extended durations of 60 seconds have yielded mixtures of crystalline forms B and A, but under normal tableting conditions, no conversion to crystalline form A can be detected." (*Id.* at 65.) Importantly, these statements were made without any provocation from the Examiner, and without providing any data to support their veracity.

In direct contrast to the applicant's statements above, during prosecution of the '364 Patent's European counterpart Application No. 05 770 026.2, the European applicant (and owner of the '364 Patent)—Grünenthal GmbH—stated that "[t]he crystalline form B disclosed in D1 [*EP 475*] has the disadvantage that under the influence of pressure (which occurs e.g. in the manufacturing process for the drug tablet) polymorph B (crystalline form of D1 [EP 475]) is transformed in a mixture of the crystalline forms A and B." (Ex. 1004 at 1; *see* Ex. 1003 at 1 ("Also published as: … US799364").)

After the applicant's amendment to claims 26 and 27, the Examiner issued a Notice of Allowance. With authorization from a telephone interview, the Examiner further amended (1) claim 5 to require that "during the process the temperature is kept below + 40^{o}C, (2) claim 25 to require that Form A be "according to claim 1," and (3) claim 26 to require that Form be "according to claim 26." (*Id.* at 77-78.)

B. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279 (Fed. Cir. 2015). In applying such a standard, the broadest reasonable construction of claim language is not one that permits *any* reading, but instead is one that must be made "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re*

Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed. Cir. 2004) (citation omitted).

Unless otherwise noted, Petitioner accepts, for purposes of this IPR only, that the claim terms of the ’364 Patent are presumed to take on the ordinary and customary meaning that they would have to one of ordinary skill in the art.

C. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Petitioners request IPR under 35 U.S.C. § 311 of claims 1–4 and 24–27 of the ’364 Patent, and cancellation of these 8 claims as unpatentable.

2. Statutory Grounds of Challenge

Petitioners request IPR of claims 1–4 and 24–27 of the ’364 Patent in view of the following references, each of which is prior art to the ’364 Patent under pre-AIA 35 U.S.C. §§ 102(a) or (b) or 103. The Examiner did not rely on any of the prior art listed in the following chart as the basis of any rejection in any Office Action. (*See generally*, Ex. 1002.) Claims 1–4 and 24–27 are unpatentable under 35 U.S.C. § 102(b):

Ground	Proposed Rejections for the ’364 Patent	Exhibit Number(s)
1	Claims 1–4 and 24–27 are anticipated under 35 U.S.C. § 102(b) by European Patent No. 693 475 B1 (Ex. 1006, “*EP 475*”).	1006, 1007, 1008

2	Claims 1–4 and 24–27 are anticipated under 35 U.S.C. § 102(b) by International Patent Publication No. WO 09/035053 (Ex. 1009, "*Bartholomaeus*").	1009, 1010, 1011

D. Overview of the State of the Art and Prior Art References

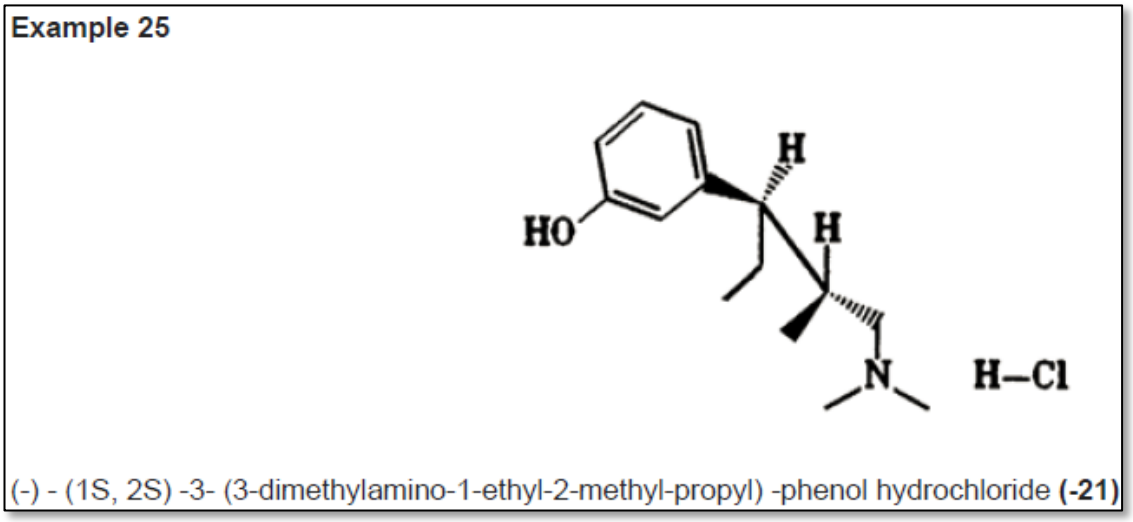
1. *EP 475* (Ex. 1006, Ex. 1007, Ex. 1008)

In early 1994, scientists at the assignee of the '364 Patent—Grünenthal GmbH ("Grünenthal"), allegedly first synthesized the pain killer tapentadol HCl. (Ex. 1019 at 7.) Grünenthal first described tapentadol HCl, also known as (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride, in German Patent App. No. DE 4426245, which was filed on July 23, 1994. This application served as a basis for priority for *EP 475*, which issued on January 24, 1996, to Grünenthal.[2] (Ex. 1006 at Cover; *see* Ex. 1007 for original German version of Ex. 1006 and Ex. 1008 for translation certification for Ex. 1006.) Grünenthal then repeated the *EP 475* disclosure in the various *EP 475*

[2] *EP 475* constitutes prior art under pre-AIA35 U.S.C. § 102(b) because it issued in 1996—eight years before the '364 Patent's earliest priority date. (Ex. 1006 at Cover.)

counterparts, which included U.S. Pat. Nos. 6,248,737 and 6,344,558. (*See* Ex. 1017; Ex. 1018.)

Along with other teachings, *EP 475* discloses the synthesis of tapentadol HCl in Example 25, as shown below:



(Ex. 1006 at XX.) *EP 475* then explains that it obtained tapentadol HCl "under the conditions cited in Example 24 from (-1), which was prepared as in Example 2." (Ex. 1006 at XX.) *EP 475* does not specify the polymorphic form of tapentadol HCl that was obtained by following the Example 25 procedure. (*See* Ex. 1006.)

2. ***Bartholomaeus* (Ex. 1009, 1010, 1011)**

Almost a decade after disclosing tapentadol HCl—and subsequently receiving patent protection for that disclosure—Grünenthal disclosed and attempted to obtain patent protection for an extended-release version of the same

drug.[3] In *Bartholomaeus*, Grünenthal explained that "3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)phenol is known from EP 0 693 475 B1 [*EP 475*]," and discloses "[a] pharmaceutical dosage form having delayed release (delayed release formulation) for oral application of the active ingredient 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol." (Ex. 1009 at 3:9, 3:19-22.) *Bartholomaeus* further discloses that the active ingredient is produced according to *EP 475*, stating that "[t]he active ingredient, 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, may be present as such, *i.e*. as a free base, but may also be present in the form of a pharmaceutically acceptable salt, for instance as hydrochloride. The production of the free base is known from EP 0 693 475 A1 [*EP 475*]." (Ex. 1009 at 8:8-11.) After production of the active ingredient, Example 1 of *Bartholomaeus* discloses:

> Matrix tablets having … (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol hydrochloride … were produced in a batch size of 1,000 tablets in the following manner: All components were weighed in and screened on a Quadro Comil U10 screening machine using a screen size of 0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 min ± 15 s at a speed of 20 ± 1 rpm, and ***pressed on a***

[3] *Bartholomaeus* constitutes prior art under pre-AIA35 U.S.C. § 102(b) because it was published on May 1, 2003—more than a year before the '364 Patent's earliest priority date. (Ex. 1009 at 1; *see* Ex. 1010 for original German version of Ex. 1009 and Ex. 1011 for translation certification for Ex. 1009.)

> ***Korsch EK0 press into tablets*** having a diameter of 10 mm, a radius of curvature of 8 mm, and a mean tablet weight of 310 mg.

(Ex. 1009 at 18:5-12 (emphasis added.)

E. Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") as of June 28, 2004—the earliest possible priority date for the '364 Patent—"would typically have a Ph.D. in fields relevant to small molecule drug development, such as biochemistry, medicinal chemistry, organic chemistry, or the equivalent, or a bachelor's degree in the same field(s) with four to six years of practical experience." (Ex. XX ¶ XX.) *See, e.g.*, *Bristol-Myers Squibb Co. v. Mylan Pharms. Inc.*, XX, 2013 U.S. Dist. LEXIS 188207, *11-12 (D. Del. Sept. 30, 2013). "A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills," but also take advantage of certain specialized skills of others on the team, to solve a given problem. (*Id*.)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: *EP 475* anticipates claims 1–4 and 24–27 of U.S. Patent No. 7,994,364 under 35 U.S.C. § 102(b).

1. *EP 475* anticipates independent claims 1 and 25.

Claim 1 of the '364 Patent requires:

> A crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu

K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

(Ex. 1001 at 18:66-19:4.)

a. *EP 475* Example 25 discloses a procedure for making tapentadol HCl

EP 475 discloses the synthesis of tapentadol HCl[4] in Example 25. (Ex. 1006 at XX.) *EP 475* then explains that it obtained the Example 25 tapentadol HLC "under the conditions cited in Example 24 from (-1), which was prepared as in

[4] Based on the *EP 475* disclosure, a POSA would have known that the drawing shown in Example 25 depicted tapentadol's (1R, 2R) configuration, even though the configuration is reported as (1S, 2S). (Ex. XX ¶ XX.) Indeed, Grünenthal similarly mislabeled the configuration in U.S. Pat. No. 6,344,558, and also mislabeled the configuration as (1R, 2S) in U.S. Pat. No. 6,248,737 (Ex. XX at XX; Ex. XX at XX.) In U.S. Reissue Patent RE39,593, which was filed on June 17, 2003, Grünenthal corrected this mistake with respect to U.S. Pat. No. 6,248,737—which claims priority to the same July 23, 1994 German Patent App. No. DE 44 26 245 as the '364 Patent. (Ex. 1016 at Cover, 19:24.) The '364 Patent confirms this, explaining that "the 1R,2R configuration as shown in the drawing of the structure in example 25 is correct although the configuration is reported as (-)-(1R,2S) in U.S. Pat. No. 6,248,737 and (-)-(1S,2S) in U.S. Pat. No. 6,344,558 as well as in EP 693 475 B1." (Ex. 1001 at 1:50-54.)

Example 2." (Ex. 1006 at XX.) That is, tapentadol HCl (*i.e.,* the (1R,2R) diastereomer) was produced using the same procedure set out to produce the HCl salt of the (1S,2S) diastereomer, starting with the (-1) intermediate produced in Example 2 instead of the (+1) intermediate. (*See generally* Examples 2 and 24.)

Example 24 sets forth the following process:

> 1st Step: (+)-(2R,3R)-[3-chloro-3-(-3-methoxyphenyl)-2-methylpentyl]-dimethylamine Hydrochloride(+22)
> 10 g (35 mmole) of (+1), prepared as in Example 2, were added to 10 ml thionyl chloride at room temperature. Nitrogen was subsequently passed over the reaction mixture for two hours to remove excess thionyl chloride. After a fresh addition of 10 ml thionyl chloride the reaction mixture was allowed to stand for 12 hours before excess thionyl chloride was again removed over a period of 2.5 hours by means of a stream of nitrogen. After drying, the residue was dissolved in 10 ml of ice-cold 2-butanone and mixed with stirring with 200 ml ether and then with 140 diisopropyl ether. The supernatant solvent phase was decanted off and the remaining oil was again taken up in 10 ml 2-butanone. After the addition of seed crystals, 300 ml diisopropyl ether were added drop-wise with vigorous stirring over three hours, whereupon the hydrochloride crystallized out. 9.8 g of (22) (91% theoretical) were obtained.
> m.p.: 120° C. (decomposition)
> $[\alpha]_D RT$=+24.7 ° (c=1.01; methanol)
> 2nd Step:

(+)-(2R,3S)-[3-(3-methoxyphenyl)-2-methylphentyl]-dimethylamine Hydrochloride(+23)

46 g of dried zinc chloride were dissolved in 580 ml of dry ether and subsequently added drop-wise to a slurry of 31 g sodium borohydride in 1800 ml ether. After stirring for 12 hours, 500 ml were removed by decantation from the zinc borohydride suspension obtained and added drop-wise to 9.8 g (32 mmole) of (+22) in 200 ml of dry ether. The reaction mixture was stirred for 72 hours at room temperature and then added drop-wise to 40 ml of a saturated ammonium chloride solution with cooling in an ice bath. After phase separation, the ether phase was washed twice with saturated brine; after drying over sodium sulphate the solvent was distilled off under vacuum. 7.3 g of an amine-borane complex were obtained, which were dissolved in 100 ml of dry methanol to isolate the free base. After the addition of 7.5 g triphenylphosphine the mixture was heated for 18 hours under reflux. After removing the solvent by distillation the residue was added to 100 ml of 5% hydrochloric acid, and the hydrochloric acid phase was subsequently washed twice with 50 ml ether. Thereafter the hydrochloric acid phase was made alkaline with concentrated sodium hydroxide solution whilst cooling in an ice bath, and was solvent-extracted twice with 50 ml dichloromethane. After drying the combined organic phases over sodium sulphate the solvent was distilled off under vacuum and the remaining residue (5.2 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 4.3 g of hydrochloride (+23) (50% theoretical) crystallized out.

m.p.: 163-164 ^{o} C.

$[\alpha]_D RT$=+25.20 (c=0.95; methanol)

3rd Step:

(+)-(1S,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol Hydrochloride(+21)

4.3g (15 mmole) of (+23) from step 2 were added to 100 ml of concentrated hydrobrombic acid. The mixture was then heated under reflux for two hours. After cooling to room temperature the reaction mixture was concentrated under the vacuum from a water pump. The residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained. After extracting twice with 50 ml dichloromethane in each case the combined organic phases were dried over sodium sulphate. Dichloromethane was then distilled off under vacuum and the residue (4 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 2.8 g of hydrochloride (+21) (98% theoretical) crystallized out.

m.p.: 194-196° C. (decomposition)

$[\alpha]_D RT$=+24.5 ° (c=1.10; methanol)

(Ex. 1006 at XX.)

EP 475 does not itself characterize the crystalline nature of the tapentadol HCl product produced according to Example 25. However, Grünenthal has alleged that the procedures of *EP 475* and Example 25 produces *only* the Form B polymorph. (Ex. 1004 at 1.) Notwithstanding that, Dr. Expert notes that the "crystalline identity of tapentadol HCl produced in Example 25 – via the synthetic procedure set forth in Example 24 – will be determined in the final step of the

procedure. The fact that the Example 24 procedure is long and includes the production of at least 2 intermediates over 3 steps is irrelevant; the only portion of the synthesis that will impart a polymorphic identity to tapentadol HCl is the latter half of step 3, wherein the free base (generated *in situ*) is taken up in 2-butanone and trimethylchlorosilane (TMSCl)/water is added." (Ex. XX. ¶ XX.)

b. *EP 475's* Example 25 procedure for making tapentadol HCl inherently produces Form A, anticipating the '364 Patent

(a) Methods and results from performing Example 25 of *EP 475*

EP 475 does not specify what tapentadol HCl polymorph(s) it obtained by following Example 25. (*See* Ex. 1006.) However, Drs. Expert and Expert2—performing the synthetic procedures set forth in *EP 475* at least 12 times—*always* obtained at least a mixture of *both* Form A and Form B. (Ex. XX. ¶¶ XX; Ex. XX. ¶¶ XX.)

Specifically, to perform *EP 475* Example 25, Dr. Expert obtained a research sample of tapentadol HCl, and ran X-ray powder diffraction ("XRPD") on the sample to determine its polymorphic form. (Ex. XX. ¶ XX.) In so doing, Dr. Expert discovered that the sample consisted entirely of Form A, matching the Form A XRDP pattern described in Figure 1 of the '364 patent (Ex. XX. ¶ XX.)

Dr. Expert2 obtained a portion of the research sample from Dr. Expert, and observed that the tapentadol HCl was a fine white solid, melting at 204 – 207 °C. (Ex. XX. ¶ XX.)

Dr. Expert2 then followed the procedure of Example 25 (via Example 24) in *EP 475* in an attempt to: (i) generate the tapentadol free base, and (ii) precipitate crystalline Form B of tapentadol HCl. (Ex. XX. ¶ XX.) As discussed in greater detail below, Drs. Expert and Expert2 observed the production of the Form A polymorph each and every time they attempted to generate tapentadol HCl from the tapentadol free base in accordance with the procedures set forth in *EP 475*.

As explained above, *EP 475* discloses the preparation of tapentadol HCl "under the conditions cited in Example 24 from (-1), which was prepared as in Example 2." (Ex. 1006 at XX.) Steps 1-3 of Example 24 teach the preparation of tapentadol intermediates, wherein the first half of step 3 generates the tapentadol free base:

> 4.3 g (15 mmol) of [the tapentadol intermediate] from step 2 [was] added to 100 ml of concentrated hydrobromic acid. The mixture was then heated under reflux for two hours. After cooling to room temperature the reaction mixture was concentrated under the vacuum from a water pump. The residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained [to provide the tapentadol free base].

(Ex. 1006 at 31-32; Ex. XX. ¶ XX.)

Because Dr. Expert2's starting material was tapentadol HCl, he was able to prepare the tapentadol free base by exposing the HCl salt to the basic conditions set forth in the first part of step 3 in Example 24. Upon generating the free base, Dr. Expert2 continued the synthesis by following the crystallization portion of Example 24's Step 3 (as referenced by Example 25):

> After extracting twice with 50 ml dichloromethane in each case, the combined organic phases were dried over sodium sulfate. Dichloromethane was then distilled off under vacuum and the residue (4 g) was taken up in 2-butanone. After the addition of trimethylchlorosilane/water, 3.8 g of hydrochloride (+21) (98% theoretical) crystallized out.

(Ex. 1006 at 32; Ex. XX. ¶ XX.)

Based on the foregoing teachings, Dr. Expert2 commenced the synthetic procedure by mixing 300 mg tapentadol HCl (from the research sample) with 4.5 ml freshly prepared saturated aqueous sodium bicarbonate, and then extracted this mixture three times with 3 ml dichloromethane. (Ex. XX. ¶ XX.) He then dried the combined dichloromethane extracts over sodium sulfate, filtered, and evaporated the solvent *in vacuo* to give the free base of tapentadol (257 mg, 100% yield) as a colorless oil which solidified after storage at 5 °C. (Ex. XX. ¶ XX.) Dr. Expert2 observed that these crystals melted at 86 – 88 °C. (Ex. XX. ¶ XX.)

Then, Dr. Expert2 followed the *EP 475* disclosure in an attempt to create tapentadol HCl (and particularly, Form B) from the tapentadol free base. Because

Example 24 did not define the particular reagent:reagent ratio used during the crystallization step, Dr. Expert2 was able to look to other examples in the *EP 475*'s specification (e.g., Example 1) to obtain specific ratios of 2-butanone : TMSCl/water. (Ex. XX. ¶ XX.). Dr. Expert2's Example 25 crystallization procedures are set forth below:

- Dr. Expert2 dissolved the tapentadol free base (109 mg, 0.49 mmol) in 2-butanone (1.0 mL), and added water (15 mg) and TMSCl (67 mg, 0.62 mmol) in one portion. (Ex. XX. ¶ XX.) An oily precipitate formed immediately which became crystalline in about 1 minute. (Ex. XX. ¶ XX.) After 10 minutes, Dr. Expert2 collected the precipitate, rinsed it with 2-butanone, and dried it in air to obtain tapentadol HCl (111 mg, 87 % yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **83:17 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)
- Dr. Expert2 dissolved the tapentadol free base (35 mg, 0.16 mmol) in 2-butanone (0.5 mL), and then added water (5 mg) and TMSCl (22 µL, 0.174 mmol) over 10 minutes while stirring and scratching the reaction container. (Ex. XX. ¶ XX.) After 30 minutes, Dr. Expert2 collected the precipitate, rinsed it with 2-butanone, and dried it in air to obtain tapentadol HCl (31

mg, 76 % yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **65:35 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)

Thus, Dr. Expert2 was unable to produce "pure" or "substantially pure" crystalline Form B tapentadol HCl in accordance with the procedures set forth in Example 24/25 of *EP 475*. Even when varying the addition time of TMSCl/water in accordance with common practice, Dr. Expert2 always produced at least some tapentadol HCl Form A. (Ex. XX. ¶ XX.)

Next, Dr. Expert2 attempted to produce pure Form B tapentadol HCl using other alternative crystallization techniques described in *EP 475*. For instance, examples in *EP 475* describe the preparation of actives via the free base solution's *addition to* a TMSCl/water mixture – as opposed adding TMSCl/water to the free base/2-butanone solution as described in Example 24/25. (*See, e.g.*, Ex. 1006 at 7 (Example 1).) In accordance with those general procedures, Dr. Expert2 carried out the following crystallization procedures:

- Dr. Expert2 dissolved the tapentadol free base (30 mg, 0.16 mmol) in 2-butanone (0.45 mL) and added this solution to a mixture of TMSCl (22.7 µL, 0.180 mmol) and water (3.3 µL). (Ex. XX. ¶ XX.) After about 18 hours

at 5 °C, Dr. Expert2 collected the precipitate, rinsed it with 2-butanone, and dried it in air to obtain tapentadol hydrochloride (XX mg, XX % yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **100:0 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)

- Dr. Expert2 repeated the procedure immediately above to obtain tapentadol hydrochloride (7 mg, 20% yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **100:0 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)
- Dr. Expert2 again repeated the procedure above, but cooled the mixture to 5°C for 3 days, to obtain tapentadol hydrochloride (8 mg, 23% yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **100:0 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)
- Dr. Expert2 repeated the procedure immediately above to obtain tapentadol hydrochloride (30 mg, 86% yield). (Ex. XX. ¶ XX.) Dr. Expert conducted an

XRPD analysis of the resulting tapentadol HCl using Cu K_α radiation. (Ex. XX. ¶ XX.) The XRPD pattern indicated the presence of both the Form A and Form B tapentadol HCl polymorphs, in **79:21 ratio of Form A to Form B**. (Ex. XX. ¶ XX.)

Finally, Dr. Expert2 attempted to prepare Form B tapentadol HCl by implementing general crystallization techniques described in *EP 475*. (Ex. 1005 at 5; Ex. XX. ¶ XX.) For example, using "physiologically acceptable acids," Dr. Expert2 implemented no less than 6 additional synthetic procedures in which he converted the tapentadol free base (prepared in accordance with the procedures of Example 24) into tapentadol HCl. (Ex. XX. ¶ XX.) In no case was he able to achieve a **Form A to Form B ratio** that was better than **31:69.**

In summary, Dr. Expert2 prepared tapentadol HCl by crystallizing the tapentadol free base in accordance with the procedures set forth in *EP 47*5 and Example 24/25 therein. The tapentadol HCl synthesis was conducted at least 12 times using these procedures, with each iteration producing a mixture of the Form A and Form B polymorphs. Thus, identifiable quantities of the Form A polymorph were consistently produced *each and every time* when following the synthetic procedures for tapentadol HCl described in *EP 475*.

(b) An analysis of XRPD patterns demonstrates that following *EP 475* procedures – including Example 25 – produces both Forms A and B of tapentadol HCl

"A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (citation omitted). Here, even though *EP 475* only explicitly discloses how to make tapentadol HCl without reference to any particular polymorph, the *EP 475* anticipates claims 1-4 and 24-27 of the '364 Patent because following *EP 475*'s synthetic procedures, including Example 24/25, produces at least some Form A of tapentadol HCl. *See id.* (Reversing the district court and finding inherent anticipation of a PHC hemihydrate claim "even though the [prior art] discloses how to make PHC anhydrate and does not discuss PHC hemihydrate. PHC hemihydrate was not even discovered until years after the [prior art] patent was filed. Nonetheless, the [prior art] anticipates claim 1 of the '723 patent because the [prior art] inherently discloses PHC hemihydrate.").

The Federal Circuit has noted that "one of the principles underlying the doctrine of inherent anticipation is to ensure that 'the public remains free to make, use or sell prior art compositions or processes, regardless of whether or not they

understand their complete makeup or the underlying scientific principles which allow them to operate.'" *SmithKline Beecham Corp.*, 403 F.3d at 1346 (quoting *Atlas Powder* XX, 190 F.3d at 1348). Because Grünenthal's *Bushmann 737* patent (reissued as RE 39,593, with both being U.S. counterparts to *EP 475*) inherently discloses both Forms A and B of tapentadol HCl and expires prior to the '364 Patent, "[i]nvalidating [the claims] of the ['364] patent for inherent anticipation by [*EP 475*] furthers this policy of allowing the public to practice expired patents." *SmithKline Beecham Corp.*, 403 F.3d at 1346. (*See* Ex. 1020 at 1.)

As the XRPD patterns in Dr. Expert's report demonstrate, following the Example 24/25 synthesis in *EP 475* – and other general procedures described therein – at best produces a mixture of both Forms A and B of tapentadol HCl. (Ex. XX. ¶ XX.) The Form A and Form B overlays (generated from the Form A and Form B peaks listed in Table I of the '364 Patent), when placed on the obtained XRPD patterns below, demonstrate the peaks resulting from the presence of Form A and Form B, respectively. (Ex. XX. ¶ XX.)

Additionally, the obtained XRPD patterns contain each of the "unique peaks in the X-ray diffraction diagram, *i.e.* the [Form A] lines with sufficient intensity at 2-theta values, where Form B does not show lines with significant intensity." (Ex. 1001 at 2:30-32; Ex. XX. ¶ XX.) As the '364 Patent explains, "[s]uch characteristic X-ray lines (2-theta values) for Form A in a powder diffraction pattern when

measured using Cu K_α radiation at ambient temperature are: 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2." (Ex. 1001 at 2:32-36.) These characteristic Form A peaks are clearly present in the XRPD patterns obtained by Drs. Expert and Expert2. (Ex. XX. ¶ XX.)

Because claim 1 of the '364 Patent requires only "crystalline Form A" "exhibiting at least [the above] X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation, *EP 475*'s disclosure of a procedure that naturally results in this crystalline compound inherently anticipates claim 1. (Ex. 1001 at 18:66-19:4; Ex. XX. ¶ XX.) *See SmithKline Beecham Corp.*, 403 F.3d at 1343 (to prove inherent anticipation, Petitioner must prove that "the disclosure of the prior art is sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product.") (quotation omitted).

Even though Grünenthal may not have realized that, through its disclosure in *EP 475*, it had inherently disclosed to a POSA how to obtain the tapentadol HCl Form A that it later claimed in the '364 Patent, such realization is not necessary for the *EP 475* disclosure to have inherently anticipated the '364 Patent claims. Rather, "inherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created." *SmithKline Beecham Corp.*, 403 F.3d at 1343.

To the extent the Patent Owner attempts to argue that the *EP 475* somehow, somewhere, discloses a synthetic procedure in which "substantially pure" Form B tapentadol HCl could be produced, such an argument would be an irrelevant red herring. Nor does it matter that *EP 475* provided alternatives for producing the desired HCl salt that differed from the synthesis of tapentadol HCl in Example 25, as demonstrated by Dr. Expert. As noted by the Federal Circuit, "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation only requires an enabling disclosure." *Schering Corp. v. Geneva Pharms., Inc*., 339 F.3d 1373, 1380 (Fed. Cir. 2003). Thus, in addition to Example 24/25, *EP 475* suffices as anticipatory prior art because it discloses several enabling methods in which tapentadol HCl Form B would be consistently produced, as effectively demonstrated by Drs. Expert and Expert2. The fact that other methods of preparing tapentadol HCl exist – including those that may produce substantially pure Form B – is of no moment.

Petitioner recognizes that Examples 7-9 of the '364 Patent disclose three different procedures for allegedly obtaining Form B tapentadol HCl—including Example 7 that follows the procedure in *EP 475*'s Example 25—and that Figure 4 of the '364 Patent shows an XRPD pattern of allegedly "pure" or "substantially pure" Form B tapentadol HCl. This Figure 4 XRPD pattern is in contrast to the mixed Form A/Form B XRPD patterns Petitioner obtained by following *EP 475*'s

Example 24/25. However, the **'364 Patent provides no evidence relating to Example 7—the only example following the *EP 475* method for obtaining tapentadol HCl—showing that the crystalline solid obtained from the Example 7 procedure is the Form B polymorph having the purity shown in Figure 4** (as opposed to the mixed Form A/Form B Petitioner obtained). (Ex. XX ¶ XX.) In fact, the '364 Patent is completely devoid of any indication as to how the polymorph identified as Form B in Figure 4 was prepared, let alone an explicit teaching linking the Figure 4 XRPD pattern to Example 7 and the synthetic procedure of *EP 475*. At best, Example 7 confirms that "Form B … was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis," without any indication as to yield or % purity. (Ex. XX ¶ XX.)

Thus, a POSA would not reasonably conclude that the '364 Patent's Figure 4 Form B XRPD pattern was produced using the Example 7 procedure, as derived from *EP 475*'s Example 25. (Ex. XX ¶ XX.) Moreover, Petitioner need not prove the impossibility of producing substantially pure Form B – to the exclusion of Form A – to demonstrate inherency; instead, Petitioner's results demonstrating that every natural repetition of *EP 475*'s synthetic procedures by a POSA resulted in at least some Form A demonstrates inherent anticipation. *SmithKline Beecham Corp.*, 403 F.3d at 1343 (reversing the district court's finding of no anticipation of PCH hemihydrate based on a PCH anhydrate disclosure, and holding that for inherency,

"Apotex did not need to prove that it was impossible to make PHC anhydrate in the United States that contained no PHC hemihydrate, but merely that the disclosure of the prior art is sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product.") (quotation omitted); *see Atlas Powder* XX, 190 F.3d at 1349-50 (affirming inherent anticipation despite a finding that the inherent element could be avoided by taking "extraordinary measures" when practicing the prior art.").

(c) Melting Point

Petitioner notes that Dr. Expert2 observed a melting point for the tapentadol HCl other than the 168-170° C disclosed in *EP 475*'s Example 25. (Ex. XX ¶ XX.) This does not affect Petitioner's inherent anticipation analysis, however, because a "[m]ere difference in physical property is well known conventional variation for the same pure substance, and [additionally] the solvent used for preparation, and the degree of purification can have an [e]ffect on the physical properties of the product." *Ex Parte Reddy*, XX, 2010 Pat. App. LEXIS 13975, *9 (Pat. App. Mar. 31, 2010) (quotation omitted). Additionally, because the '364 Patent's "claims do not require a specific amount of crystalline compound or purity of the compound[, and] … the degree of purification can have an [e]ffect on the physical properties of the product, such as melting point," there is no reason for a POSA to believe that, in light of the obtained XRPD patterns, that Petitioner's experts have not

consistently obtained tapentadol HCl Form A by following *EP 475*'s procedures. *Id.* at *9-10. (Ex. XX ¶ XX.)

Moreover, the Patent Owner also admits that it would be improper to give weight to the different observed melting points for tapentadol HCl, since "observed melting points and optical rotations could vary each time a compound is synthesized and tested." (Ex. 1019 at 34.) In ANDA litigation relating to the '364 patent, the Patent Owner stated that "'(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (-21)' refers to 'the chemical compound (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride depicted by the structural formula identified by the number (-21) in Example 25 of the '593 patent.'" (Ex. 1019 at 31; *see* Ex. 1016 at Cover.) In so arguing, the Patent Owner stated that adopting "observed melting points and optical rotations … as claim limitations would improperly narrow the patent claims." (Ex. 1019 at 34.) The Patent Owner further admitted:

> [T]he reported melting point range and optical rotation are likely affected by whatever impurities were present in the tested product from Example 25. One of skill in the art would recognize that these data points are highly dependent upon the conditions of a single experiment, and that ***observed melting points and optical rotations could vary each time a compound is synthesized and tested***.

(Ex. 1019 at 34 (emphasis added).) Thus, despite a different observed melting points, Petitioner's demonstration—through the more reliable XRPD analysis—

that it consistently obtained tapentadol HCl Form A through *EP 475*'s procedures is sufficient to demonstrate inherent anticipation of the '364 Patent's claim 1.

c. Claim 25

Claim 25 of the '364 Patent merely requires "[a] solid pharmaceutical composition comprising, as an active ingredient," the crystalline Form A of claim 1, "and at least one suitable additive or auxiliary substance." (19:56-63.) According to the '364 patent, "one or more suitable additive and/or auxiliary substance" may include "for example carrier materials, fillers, solvents, diluents, coloring agents and/or binders. …" (4:23-28.)

As shown with respect to claim 1, *EP 475* inherently discloses tapentadol HCl Form A. *EP 475* further discloses:

> In addition to at least one 1-phenyl-3-dimethylaminopropane compound of formula I, the analgesics according to the invention may contain ***carriers, fillers, solvents, diluents, colorants and/or binders***. The selection of auxiliary substances and of the amounts of the same to be used depends on whether the drug is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or locally, for example for infections of the skin, of the mucous membranes or of the eye. Preparations in the form of tablets, dragees, capsules, granules, drops, liquids and syrups are suitable for oral application.

(Ex. 1006 at 9 (emphasis added).) Thus, *EP 475* explicitly discloses a solid[5] pharmaceutical composition comprising "at least one suitable additive or auxiliary substance" in addition to the inherently disclosed Form A, anticipating claim 25. (Ex. XX ¶ XX.)

2. ***EP 475* anticipates dependent claims 2–4.**

a. Claim 2

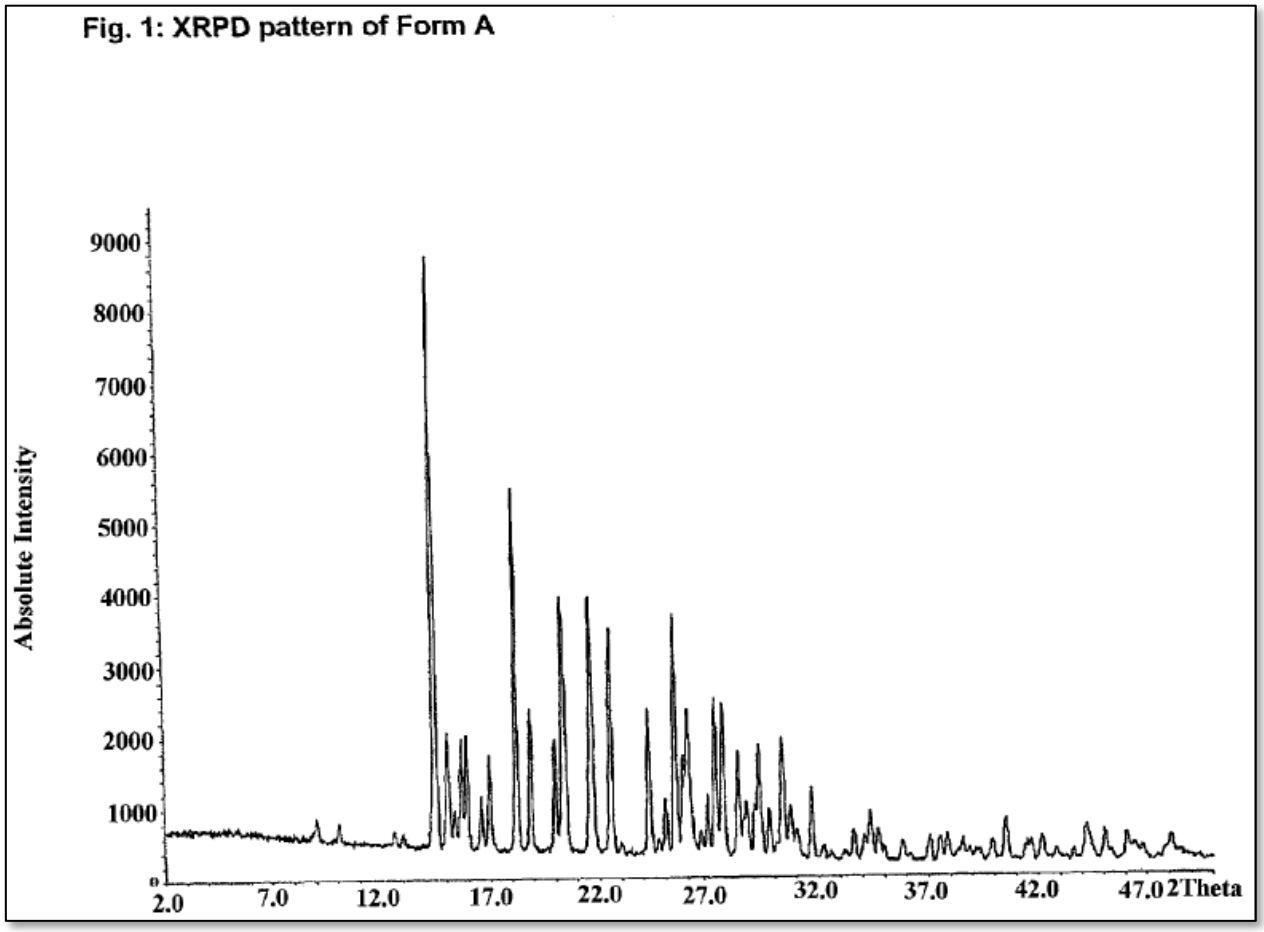
Claim 2 depends from claim 1 and adds the limitation that Form A exhibits "at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 22.5±0.2." (*Id.* at 19:7-10.)

As shown with respect to claim 1, *EP 475* inherently discloses tapentadol HCl Form A. As the XRPD patterns obtained through this analysis show, the Form A obtained through *EP 475*'s procedures exhibits X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at at least 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 22.5±0.2, anticipating claim 2 of the '364 Patent. (Ex. XX ¶ XX.) These Form A peaks are confirmed by the XRPD pattern obtained by Drs. Expert and Expert2. (Ex. XX. ¶ XX.)

[5] A POSA at the time of the '364 Patent's priority date would understand that a tablet is one form of a "solid pharmaceutical composition," as in claim 25.

b. Claim 3

Claim 3 depends from claim 1 and adds the limitation that Form A exhibits "an X-ray pattern (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1" (copied below). (*Id.* at 19:13-15.)



As shown with respect to claim 1, *EP 475* inherently discloses tapentadol HCl Form A. As the XRPD patterns obtained through this analysis show, the Form A obtained through *EP 475*'s Example 25 exhibits an X-ray pattern (2-theta

values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1. (Ex. XX ¶ XX.)

Because the XRPD patterns obtained by Petitioner contain mixtures of the Form A and Form B polymorphs, the Patent Owner may attempt to argue that those patterns do not appear to be "essentially the same" as that provided in FIG. 1. However, claim 3 only requires that the ***Form A XRPD pattern*** be essentially the same that that depicted in FIG. 1. Indeed, the Form A and Form B overlays (generated from the Form A and Form B peaks listed in Table 1 of the '364 patent) – when placed on the Petitioner's XRPD patterns for the Form A/B mixture – demonstrate the independent presence of peaks representative of Form A. (Ex. XX ¶ XX.) Thus, the existence of any Form B peaks on Petitioner's XRPD patterns do not detract from the *presence of the relevant Form A peaks*. (Ex. XX ¶ XX.)

Further, Patent Owner may attempt to argue that the XRPD patterns obtained by Petitioner are not "essentially the same" as that provided in FIG. 1 of the '364 patent due to slight differences in peak locations and peak intensities. However, in the pending ANDA litigations related to the '364 patent, the Patent Owner admitted that "X-ray pattern (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1" has its plain meaning, and does not require "having essentially the same peak location and intensities." (Ex. 1019 at 36.) The Patent Owner further admitted that

"a person of ordinary skill in the art could have considered two XRPD patterns to be 'essentially the same' even if the peak locations and intensities differed. For example, intensities 'may vary considerably' and still be considered a match." (Ex. 1019 at 39.) Additionally, according to the Patent Owner, "[o]ne of ordinary skill in the art would have known that two test results could be 'essentially the same' even where the peaks in one pattern were broader or narrower than the peaks in the other pattern." (Ex. 1019 at 40.) Petitioner agrees with Patent Owner, and notes that, to a POSA, the Form A obtained through *EP 475*'s procedures exhibits an XRPD pattern essentially the same as that provided in FIG. 1, despite any alleged differences in peak locations, intensities, and breadth. (Ex. XX ¶ XX.)

Thus, for at least these additional reasons, a POSA at the time of the earliest priority date of the '364 patent would have understood that Petitioner's Form A XRPD patterns, obtained by following the procedures set forth in *EP 475*, are essentially the same at those provided in FIG. 1.

c. Claim 4

Claim 4 depends from claim 1 and adds the limitation that the Form A crystal has a monoclinic form. (*Id.* at 19:18-19.)

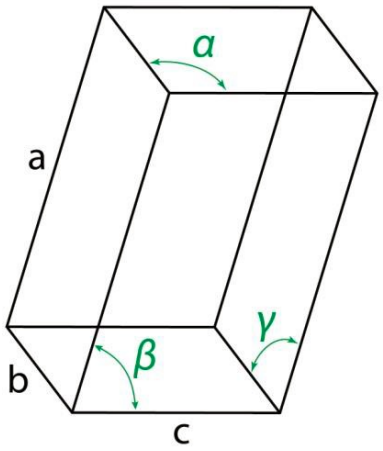
As shown above with respect to claim 1, *EP 475* inherently discloses tapentadol HCl Form A. The '364 Patent admits that the Form A polymorph has a monoclinic form, stating: "Crystal structure analysis of Form A of (-)-(1R,2R)-3-(3

dimethylamino-1-ethyl-2 -methylpropyl)-phenol hydrochloride showed monoclinic crystals." (Ex. 1001 at 2:54-56.) Moreover, as confirmed by Dr. Expert, "the form – *i.e*. shape – of a polymorph's crystals is an inherent characteristic of that particular polymorph. Said differently, the same polymorphs – as confirmed by XRPD patterns – will invariably exhibit the same crystalline shape." (Ex. XX ¶ XX.)

Consequently, because *EP 475* inherently discloses tapentadol HCl Form A, and Form A is known to have a monoclinic form, *EP 475* also inherently discloses tapentadol HCl Form A having a monoclinic form, anticipating claim 4. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.").

Additionally, in the ANDA litigations discussed above with respect to claim 3, the Patent Owner admitted:

> The phrase "monoclinic form" is a term of art in the field of crystallography. Its plain meaning is described in the scientific literature. *See, e.g.*, J. Glusker & K. Trueblood, *Crystal Structure Analysis: A Primer* 232 (Oxford University Press 1985) ("monoclinic form" means "a unit cell in which there is a two-fold rotation axis parallel to one cell axis (usually chosen as *b*).") …. An example of a monoclinic unit cell is shown below:



… Nothing in the specification (or elsewhere in the intrinsic evidence) suggested that the inventors wished to depart from the conventional meaning of "monoclinic form." (Ex. 1019 at 41-42 (citation omitted).) In so stating, the Patent Owner argued that "monoclinic form," as used in this claim, "could encompass unit cells of many different shapes and sizes," and should not "limit that broad claim term to a single unit cell having the precise parameters described in column 2, lines 58 to 61 of the '364 patent specification." (Ex. 1019 at 42.) Petitioner agrees. Thus, any observed variations from the particular monoclinic form disclosed in the '364 patent do not affect Petitioner's anticipation analysis.

3. ***EP 475* anticipates dependent claims 24 and 26.**

Claim 24 depends from claim 1 and adds the limitation that Form A is

produced by the process of:
dissolving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,

heating the solution to the boiling point,
removing the active carbon by filtering,
stirring the solution at a temperature below 40° C.,
removing part of the solvent residue by filtering and removing part of the solvent,
leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize,
redissolving the resulting crystals in acetonitrile,
removing insoluble residue by filtering and removing part of the solvent, and
leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize.

(*Id.* at 19:38-55.)

Claim 26 depends from claim 25 and adds the limitation that Form A is

produced by the process of:
dissolving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,
heating the solution to the boiling point,
removing the active carbon by filtering,
stirring the solution at a temperature below 40° C.,
removing insoluble residue by filtering and removing part of the solvent, and
leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize, and
at least one suitable additive or auxiliary substance.

(*Id.* at 19:67-22:4.)

Claims 24 and **26** are product-by-process claims, which means they are "defined at least in part in terms of the method or process by which [the claimed product was] made." *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (quoting *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 158 (1989)). "In determining validity of a product-by-process claim, the focus is on the product and not the process of making it. That is because of the long-standing rule that an old product is not patentable even if it is made by a new process." *Greenliant Sys., Inc.*, 692 F.3d at 1268 (quotation omitted); *see SmithKline Beecham Corp.*, 439 F.3d at 1317 ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming … the product as produced by a particular process."). "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). As shown above with respect to claims 1 and 25, *EP 475* inherently discloses tapentadol HCl Form A—consequently, *EP 475* inherently anticipates claims 24 and 26. (Ex. XX. ¶ XX.)

4. ***EP 475* anticipates independent claim 27.**

Independent **claim 27** requires "[a] method of treating or inhibiting pain or urinary incontinence, said method comprising the step of administering a

pharmaceutically effective amount of "the crystalline Form A of claim 1 "to a subject in need thereof." (*Id.* at 22:5-13.)

As shown with respect to claim 1, *EP 475* inherently discloses tapentadol HCl Form A. *EP 475* also explicitly discloses administering the compounds disclosed therein as a "method of treating or inhibiting pain" "to a subject in need thereof," anticipating claim 27. (*See, e.g.*, Ex. 1006 at 36 ("The analgesic effectiveness of the compounds according to the invention was investigated … For each dose of substance, each animals received, 30 minutes after the oral administration of a compound according to the invention… The number of pain-induced stretching movements (writhing reaction = straightening of the body with stretching of the rear extremities) was counted"); Ex. 1006 at 2 ("The underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain").) (Ex. 1006 at 1.)

Whether or not a skilled artisan would have appreciated the inherent presence of the Form A polymorph in *EP 475* at the time the '364 patent was filed is irrelevant. As previously discussed, a POSA considering *EP 475* would have prepared tapentadol HCl in accordance with the procedures set forth therein (e.g., Example 24/25) – resulting in at least some tapentadol HCl Form A – and administered the resulting crystalline product for "treating or inhibiting pain." *See supra*. In doing so, the skilled artisan would be inherently treating or inhibiting

pain by administering the Form A polymorph, whether or not realized by the POSA at the time of administration. Thus, claim 27 is inherently anticipated by *EP 475*.

B. Ground 2: *Bartholomaeus* anticipates claims 1–4 and 24–27 of U.S. Patent No. 7,994,364 under 35 U.S.C. § 102(b).

1. *Bartholomaeus* anticipates independent claims 1 and 25.

Claim 1 of the '364 Patent requires:

> A crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

(Ex. 1001 at 18:66-19:4.)

Bartholomaeus discloses that the active ingredient is produced according to *EP 475*—the procedure discussed above in Ground 1—stating that "[t]he active ingredient, 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, may be present as such, *i.e*. as a free base, but may also be present in the form of a pharmaceutically acceptable salt, for instance as hydrochloride. The production of the free base is known from EP 0 693 475 A1 [*EP 475*]." (Ex. 1009 at 6:8-11.) *Bartholomaeus* also notes that *EP 475* includes certain procedures for the production of the HCl

salt. (Ex. 1009 at 6:11-13.)[6] In addition, after production of the active ingredient, Example 1 of *Bartholomaeus* discloses:

> Matrix tablets having … (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol hydrochloride [tapentadol HCl]… were produced in a batch size of 1,000 tablets in the following manner: All components were weighed in and screened on a Quadro Comil U10 screening machine using a screen size of 0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 min ± 15 s at a speed of 20 ± 1 rpm, and ***pressed on a Korsch EK0 press into tablets*** having a diameter of 10 mm, a radius of curvature of 8 mm, and a mean tablet weight of 310 mg.

(Ex. 1009 at 18:5-12 (emphasis added.)

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[6] The synthesis of tapentadol HCl provided in *EP 475*, and incorporated by reference in *Bartholomaeus*, should be considered as part of *Bartholomaeus'* disclosure for purposes of a novelty analysis under Section 102(b). *See, e.g.*, *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331 (Fed. Cir. 2009) (finding that material not explicitly contained in a single document may still be considered for purposes of anticipation if incorporated by reference, provided that the document "identify with particularity what specific material it incorporates and clearly indicate where that material is found.") *Bartholomaeus* expressly incorporates *EP 475* (Ex. 1009 at 6:8-11.).

During prosecution of the '364 Patent's European counterpart, Application No. 05 770 026.2, the European applicant (and owner of the '364 Patent)—Grünenthal—asserted that the crystalline form of tapentadol HCl prepared in D1 [*EP 475*] was Form B. (Ex. 1004 at 1.) Additionally, Grünenthal admitted that "[t]he crystalline form B disclosed in D1 [*EP 475*[7]] has the disadvantage that ***under the influence of pressure (which occurs e.g. in the manufacturing process for the drug tablet) polymorph B (crystalline form of D1 [EP 475]) is transformed in a mixture of the crystalline forms A and B***." (*Id*. at 1 (emphasis added); *see* Ex. 1003 at 1 ("Also published as: … US799364").) This statement is consistent with a POSA's knowledge—at the time of the '364 Patent's earliest possible priority date—that pressure, such as that caused by tableting, could cause polymorphic interconversions. (Ex. XX. ¶ XX.) Indeed, Grünenthal further acknowledged that "***all form B batches exposed to pressures of 2 tons***" resulted in at least some interconversion to the Form A polymorph. (Ex. 1004 at 2 (emphasis added).)

In summary, *Bartholomaeus* – by incorporating the teachings of *EP 475* – discloses the preparation of tapentadol HCl, which Grünenthal has asserted is the

[7] "D1"—the prior art reference identifier used in Ex. 1004—is the designation chosen by the European Patent Office ("EPO") to refer to EP 693 475 B1 [*EP 475*]. (*See* Ex. 1005 at 2 ("D1: EP-B-0 693 475").)

Form B polymorph. Hence, in Example 1, *Bartholomaeus* implicitly describes the formation of matrix tablets comprising the use of Form B polymorph of tapentadol HCl, which includes subjecting the Form B polymorph to the high pressures of a Korsch EK0 press during tableting.

Although *Bartholomaeus* does not expressly describe the operation of its disclosed Korsch press, a POSA at the time of the '364 Patent's earliest possible priority date would have known that such an eccentric press forms tablets by applying compression forces to compositions comprising the desired active ingredient. (Ex. XX. ¶ XX.) Indeed, a POSA also would have understood that the Korsch EKO eccentric press is capable of achieving compression forces of up to 30 kN, which is ***more than 3 tons*** (approx. 6,700 lbs). (Ex. XX. ¶ XX; *see, e.g.*, http://www.labx.com/product/korsch-tablet-press.)

Thus, at the very least, *Bartholomaeus* would have enabled a POSA following the procedure of Example 1 to i) prepare a matrix composition comprising Form B of tapentadol HCl, and ii) expose the composition to pressures of 6,000 lbs or more in a Korsch EK0 press to form a tablet. Upon exposure to such high tableting pressures – as admitted by Grünenthal – the tapentadol HCl Form B in the composition would have at least partially converted to Form A during the procedure. (Ex. XX. ¶ XX.) *See In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) ("A reference anticipates a claim if it discloses the claimed invention

'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'") (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962). Whether or not Grünenthal actually produced at least some Form A when carrying out the procedure of Example 1 is irrelevant to the analysis because "[a]nticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation only requires an enabling disclosure." *Schering Corp.*, 339 F.3d at 1380.

As discussed in Ground 1, any disclosure of Form A would have inherently disclosed the "characteristic X-ray lines (2-theta values) for Form A in a powder diffraction pattern when measured using Cu K_α radiation at ambient temperature are: 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2," anticipating claim 1 and the relevant XRPD pattern. (Ex. 1001 at 2:32-36; Ex. XX. ¶ XX.) *See Atlas Powder Co.*, 190 F.3d at 1347 ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.").

Claim 25 of the '364 Patent merely requires "A solid pharmaceutical composition comprising, as an active ingredient," the crystalline Form A of claim 1, "and at least one suitable additive or auxiliary substance." (*Id.* at 19:56-63.)

As shown with respect to claim 1, *Bartholomaeus* inherently discloses tapentadol HCl Form A. *Bartholomaeus* further discloses in Example 1 "Matrix tablets" containing "Hydroxypropyl methylcellulose," "Microcrystalline cellulose," "Highly disperse silicon dioxide," and "Magnesium stearate." (Ex. 1009 at 18.) Thus, *Bartholomaeus* explicitly discloses a solid[8] pharmaceutical composition comprising "at least one suitable additive or auxiliary substance" in addition to the inherently disclosed Form A, anticipating claim 25. (Ex. XX ¶ XX.) (*Compare to* Ex. 1001 at 4:24-30 (stating that suitable additives and auxiliary substances include "carrier materials, fillers, solvents, diluents, coloring agents and/or binders, and may be administered as liquid medicament preparations in the form of injectable solutions, drops or juices, as semi-solid medicament preparations in the form of granules, tablets, pellets, patches, capsules, plasters or aerosols.")

2. ***Bartholomaeus* anticipates dependent claims 2–4.**

Claim 2 depends from claim 1 and adds the limitation that Form A exhibits "at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 22.5±0.2." (*Id.* at 19:7-10.)

[8] A POSA at the time of the '364 Patent's priority date would understand that a tablet is one form of a "solid pharmaceutical composition," as in claim 25.

As previously discussed with respect to claim 1 and in Ground 1, any disclosure of Form A—such as that inherently disclosed by *Bartholomaeus*—would have disclosed "at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 14.5±0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 22.5±0.2," anticipating claim 2 requiring this XRPD pattern. (Ex. 1001 at 19:7-10; Ex. XX. ¶ XX.) *See Atlas Powder Co.*, 190 F.3d at 1347.

Claim 3 depends from claim 1 and adds the limitation that Form A exhibits "an X-ray pattern (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1" (copied above). (*Id.* at 19:13-15.)

As previously discussed with respect to claim 1 and in Ground 1, any disclosure of Form A—such as that inherently disclosed by *Bartholomaeus*—would have disclosed "an X-ray pattern (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation essentially the same as that provided in FIG. 1" anticipating claim 3 requiring this XRPD pattern. (Ex. 1001 at 19:13-15; Ex. XX. ¶ XX.) *See Atlas Powder Co.*, 190 F.3d at 1347.

Claim 4 depends from claim 1 and adds the limitation that the Form A crystal has a monoclinic form. (*Id.* at 19:18-19.)

As previously discussed with respect to claim 1 and in Ground 1, any disclosure of Form A—such as that inherently disclosed by *Bartholomaeus*—

would have disclosed Form A having "a monoclinic form," anticipating this claim 4 requirement. (Ex. 1001 at 19:18-19; Ex. XX. ¶ XX.) *See Atlas Powder Co.*, 190 F.3d at 1347.

3. ***Bartholomaeus* anticipates dependent claims 24 and 26.**

Claim 24 depends from claim 1 and adds the limitation that Form A is

> produced by the process of:
> dissolving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,
> heating the solution to the boiling point,
> removing the active carbon by filtering,
> stirring the solution at a temperature below 40° C.,
> removing part of the solvent residue by filtering and removing part of the solvent,
> leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize,
> redissolving the resulting crystals in acetonitrile,
> removing insoluble residue by filtering and removing part of the solvent, and
> leaving (−) (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize.

(*Id.* at 19:38-55.)

Claim 26 depends from claim 25 and adds the limitation that Form A is

> produced by the process of:

dissolving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon,
heating the solution to the boiling point,
removing the active carbon by filtering,
stirring the solution at a temperature below 40° C.,
removing insoluble residue by filtering and removing part of the solvent, and
leaving (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystalize, and
at least one suitable additive or auxiliary substance.

(*Id.* at 19:67-22:4.)

As discussed in Ground 1, **Claims 24** and **26** are product-by-process claims, which means they are "defined at least in part in terms of the method or process by which [the claimed product was] made." *Greenliant Sys., Inc.*, 692 F.3d at 1268 (Fed. Cir. 2012) (quotation omitted). "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d at 697. Because, as shown with respect to claims 1 and 25, *Bartholomaeus* inherently discloses tapentadol HCl Form A—the product of claims 24 and 26, *Bartholomaeus* inherently anticipates claims 24 and 26. (Ex. XX. ¶ XX.)

4. ***Bartholomaeus* anticipates independent claim 27.**

Independent **claim 27** requires "[a] method of treating or inhibiting pain or urinary incontinence, said method comprising the step of administering a pharmaceutically effective amount of "the crystalline Form A of claim 1 "to a subject in need thereof." (*Id.* at 22:5-13.)

As shown with respect to claim 1, *Bartholomaeus* inherently discloses tapentadol HCl Form A. *Bartholomaeus* also explicitly discloses administering this compound as a "method of treating or inhibiting pain" "to a subject in need thereof," anticipating claim 27. (*See, e.g.*, Ex. 1009 at 5:27-6:4 ("The inventive formulation consequently permits pain management therapy, during the course of which the analgesic 3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol must be administered only once daily, e.g. at intervals of 24 h, or twice daily, preferably at intervals of 12 hours, to ensure a sufficient concentration of the active ingredient in plasma."). For at least those reasons, *Bartholomaeus* inherently anticipates claim 27.

VII. CONCLUSION

Thus, Petitioners respectfully request *inter partes* review of claims 1–4 and 24–27 of U.S. Patent No. 7,994,364.

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CERTIFICATE OF SERVICE

I hereby certify that on _____, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 7,994,364, including all exhibits, was served via FedEx, overnight delivery, upon the following:

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