



UNITED STATES PATENT AND TRADEMARK OFFICE

Making a Prima Facie Case (e.g. In Polymorph Cases)

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Impetus For Training

- Sampling of Board Decision addressing Polymorphs:
 - » These Board decisions were used in developing our recent polymorph training;
 - » Examiners were interested in a more detailed review of these cases;
 - » We feel that, regardless of the Board's decision, both the examiner and Board did a good job and, while these cases concern crystalline forms, the ideas we want to discuss are generally applicable to all subject matter.



Prima Facie Case

- (“[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant... If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent.”). See also *Fregeau v. Mossinghoff*, 776 F.2d 1034, 227 USPQ 848 (Fed. Cir. 1985) (applying *prima facie* case law to [35 U.S.C. 101](#)); *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984).
- See MPEP 2107.02 (in the context of 101).



Fundamentals and No Per Se Rules

- Examination is on a case by case basis;
- During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification.
 - See MPEP § 904.01 and § 2111 – § 2116.01 for case law pertinent to claim analysis.
- Consistent with case law, it is office policy not to employ *per se* rules to make technical rejections. See MPEP 2116.01.



112 ¶ 1: *Written Description/Enablement*

Statement of Statutory Basis, 35 U.S.C. 112, First Paragraph

The following is a quotation of the first paragraph of [35 U.S.C. 112](#):

The specification shall contain a *written description* of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable* any person skilled in the art to which it pertains, or with which *it is most nearly connected*, to make and use the same,



Written Description: Test

- To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.
 - See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116; MPEP 2163.



Written Description: Factors

- **Relevant Factors to consider when analyzing claims for compliance with the Written Description requirement:**
 - a. Actual reduction to practice
 - b. Disclosure of drawings or structural chemical formulas
 - c. Sufficient relevant identifying characteristics: include:
 - complete/partial structure; physical/chemical properties;
 - structure-function correlation;
 - d. Method of making the claimed invention;
 - e. Level of skill and knowledge in the art;
 - f. Predictability in the art

See MPEP 2163.



112 ¶ 1: *Written Description (Genus)*

- For each claim drawn to a genus, consider the above-recited factors to determine whether there is disclosure of a representative number of species which would lead one skilled in the art to conclude that the applicant was in possession of the claimed invention.
 - The number of species required to represent a genus will vary, depending on the level of skill and knowledge in the art and the variability among the claimed genus.
 - For instance, fewer species will be required where the skill and knowledge in the art is high, and more species will be required where the claimed genus is highly variable.



112 ¶ 1: *Written Description*

(a) *Written Description (Ex Parte Chern)*



Ex Parte Chern et al: Solvates: Written Description

- Based on: 11/999637 *Ex Parte Chern et al.*: effective filing date 4/7/06(decided 10/23/11) (Written Description rejection reversed).
- 1. A method of treating disease X in a mammalian subject in need thereof comprising administering to the subject a pharmaceutical composition comprising an effective amount of compound Y or a pharmaceutical salt or solvate thereof.
- The Examiner rejected claim 1 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.



Ex Parte Chern et. al: Written Description (Rejection)

- Specification does not disclose chemical structures or how to make a particular solvate of compound Y; and the
- Formation of a particular solvate of a given compound is unpredictable citing:
 - a. Vippagunta et al, "Crystalline Solids", *Advanced Drug Delivery Reviews* 2001, 48, 1-26, at pp 1, 11-12, and 18 (general art acceptance that forming solvates, polymorphs or hydrates of a compound is unpredictable);
 - b. Braga et al, "Making Crystals from Crystals: a green route to crystal engineering and polymorphism", *Chem Commun* 2005, pp 3635- 3645) at 3640, " ... if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent."
 - c. Seddon, K.R., "Pseudopolymorph: a Polemic", *Crystal Growth & Design*, 2004, 4(6), pp 1087, (the state of the art is such that in this century there should not be any doubt as to the chemical identity of a material).



Ex Parte Chern et. al: Written Description (Rebuttal)

- Appellants argue that:
 1. the term “solvate” is not describing a desired result but is a precise definition by chemical name; and
 2. the Federal Circuit has made it clear that using a chemical name is sufficient to distinguish a genus from other materials.



Ex Parte Chern et al: Written Description cont.

- Board's *Findings of Fact*
 1. Specification teaches that the term “solvate” means a compound of the present invention or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of solvent, e.g., water or organic solvent, bound by non-covalent intermolecular forces”;
 2. *Vippagunta* teaches that:
 - i. “[m]ost organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms” (*Vippagunta* 4, col. 1); and
 - ii. that “[p]redicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult.”(*Vippagunta* 18, col. 1.)



Ex Parte Chern et al: Written Description cont.

- Board's Findings of Fact (cont.)
3. Braga teaches that: "One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to predict whether a new species crystallizes from solution with one or more molecules of solvent. However, while serendipitous polymorphism and solvate formation are very common ... intentional polymorphism is more difficult, as it requires the purposed investigation of the conditions to obtain different crystals for the same species." (Braga 3640, col. 2.);
 4. *Seddon* teaches that the "term 'solvate' has been around for centuries, is universally understood, and is a perfect descriptor for these materials" (*Seddon* 1087).



Ex Parte Chern et al. : Written Description cont.

- In the Board's opinion, *Capon v. Eshhar*, 418 F3d 1349, 76 USPQ2 1078 (Fed. Cir. 2005) and *Ariad Pharmaceuticals Inc. v. Eli Lilly & Co.*, 598 F3d 1336, 94 USPQ2d 1161 (Fed. Cir. 2010) control the instant situation.
- As in *Capon*, Appellants do not claim their inventive contribution is to provide solvates of compound Y. Instead, the inventive contribution is asserted to be the use of compound Y to treat disease X.
 - *Capon* teaches that the Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes. *Capon*, 418 F.3d at 1358.



Ex Parte Chern et. al: Written Description cont.

- Board's opinion cont.:
- The instant claims are drawn to a specific pharmaceutical, compound Y, to treat a specific disease, which may also include solvates of compound Y.
 - Here, a specific chemical structure is required as the active pharmaceutical agent, compound Y, and a particular disease is identified.
- Thus, the instant situation is substantially different than that in *Ariad*, for example, where the invention was drawn to an NF- κ B inhibitor where:
 - no chemical name or structure of the inhibitor was disclosed; with only vague discussions of potential inhibitors; and
 - no particular diseases were identified. See *Ariad*, 598 F.3d at 1353-1356.



Ex Parte Chern: Summary

- Although, there was no disclosure of actual compound Y solvates as pointed out by the Examiner; WD was met where:
 - solvates share the compound Y structure;
 - the compound Y structure correlated to the claimed use to treat disease X;
 - inventive contribution did not reside in possession of a solvate of compound Y.



Ex Parte Chern et al: Written Description cont.

- Take home: a court is inclined to find adequate written description for crystalline forms (e.g. solvates, polymorphs) of a claimed structured compound
 - if the compound provides sufficient structure for bioactivity (e.g. a structure/function correlation exists); and
 - is not the point of novelty.
- This is contrasted with *Ariad* which was a purely functionally claimed inhibitor without any structure being claimed or disclosed.



112 ¶ 1: *Enablement*

(b) *Enablement* (Ex Parte Cai)



Enablement Test

- “The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art *without undue experimentation.*”
 - See: *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); MPEP 2164.



Enablement: Factors

- These factors include, but are not limited to:
 - (A) The breadth of the claims;
 - (B) The nature of the invention;
 - (C) The state of the prior art;
 - (D) The level of one of ordinary skill;
 - (E) The level of predictability in the art;
 - (F) The amount of direction provided by the inventor;
 - (G) The existence of working examples; and
 - (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
- See: *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); MPEP 2164.01.



Ex Parte Cai et al: Polymorph/Solvates/Hydrates: Enablement

- Based on: 11/852433: Ex Parte Cai et al. : effective filing date: 9/11/06: decided 12/6/11 (enablement rejection reversed):

Claim 1 is the only independent claim and is directed to a “compound represented by formula (I).”

- specification defines “compound” to include solvates, hydrates and polymorphs.
- The Examiner rejects claim 1 under 35 U.S.C. § 112, first paragraph, on the basis that the specification, while enabling for a compound of (I) (alone) or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a hydrate, solvate or polymorph thereof.



Ex Parte Cai et al: Enablement cont.

The Examiner reasons that, based on the Specification's definition of "compound" ... the claims read on "presently unknown compounds embraced by the terms solvates, hydrates, and polymorphs".

- The Examiner finds that "the formation, composition and therapeutic activity of solvates (e.g. hydrates) and polymorphs is unpredictable"; that they can differ in properties such as dissolution and therapeutic effect; that it is unpredictable "whether a given compound will even form a hydrate, solvate or polymorph" and whether they "will possess the same beneficial properties that make a given compound a drug candidate".
- The Specification does not provide guidance or working examples that teach making hydrates, solvates, or polymorphs; and that "a study of hydrates, solvates, and polymorphs requires a full research program and is well beyond that of routine experimentation".
- The Examiner concludes that undue experimentation would be required to practice the full scope of the claimed invention



Ex Parte Cai et al: Enablement cont.

Board Analysis:

- The Examiner’s finding that a study of hydrates, solvates, and polymorphs requires “a full research program” is based on guidelines that address experimentation required for “marketing approval of new drug products” ; such experimentation is not required by § 112;
- The Examiner’s argument that the claims read on “presently unknown compounds embraced by the terms solvates, hydrates, and polymorphs” was not persuasive since:
 - future state of the art cannot be relied on to show non-enablement of a claim as of its effective filing date (*In re Hogan*, 559 F.2d 595 (CCPA 1977); and thus a possible future state of the art cannot be relied on either. See Bd decision, p. 15.
 - NOTE: in *Hogan* newly discovered post-filing prior art of an amorphous form did not non-enable applicants’ claim to a solid drug formulation in which the crystalline form was exemplified.



Ex Parte Cai et al: Enablement cont.

Board Opinion:

The evidence of record shows that high-throughput methods of crystal growth and analysis were known in the art at the time the instant application was filed.

- Rodríguez-Spong *Adv. Drug Delivery Rev.* 56 (2004) 241-274 at 264 states that such methods allowed skilled workers to test thousands of crystallization conditions using robotic liquid handling and automated screening through optical image analysis and Raman microscopy.
- Thus, the Examiner's finding that it is unpredictable whether hydrates, solvates, and polymorphs exist appears to be moot, since thousands of different crystallization conditions can be tested via automated, and therefore routine, experimentation.



Ex Parte Cai et al: Enablement cont.

- Board Held: the Examiner has not carried the burden of showing that undue experimentation would be required to make or use the full scope of the claimed compounds.
- Solvates, hydrates, and polymorphs of a compound are the same compound, in different physical forms ... which share "chemical identity" and are indistinguishable when dissolved. Some forms of a compound might dissolve more readily than others and different forms may even differ in therapeutic activity, but the Examiner has not adequately explained why these differences would result in the need for more experimentation than is routine in this art to use solvates, hydrates, or polymorphs of the claimed compounds in the same manner as the forms that the Examiner has indicated to be enabled.



Ex Parte Cai: Summary

- Although, the Examiner correctly pointed to the potential breadth of the claim and lack of guidance in the specification toward “how to make” the prior art can be used to help applicant enable his/her invention.
 - Here, the prior art provides the means to screen for the presence or absence of formula I solvates, hydrates or polymorphs;
 - Note also that the point of novelty was the formula I compound; and not the solvates/hydrates/polymorphs.



Ex Parte Cai et al: Enablement-Summary cont.

- Take home: despite lack of any working examples of actual existence of hydrates, solvates and polymorphs or guidance as to how to make they were enabled because it would not constitute “undue experimentation” to screen using high-throughput methods of crystal growth and analysis known in the art.



102: Anticipation

(3) 102 and 103 Caselaw

(a) 102 (Ex Parte Pfrenge)



Ex parte Pfrengle et al. (Anticipation)

10/976624 (Ex parte Pfrengle et al. : effective filing date (12/10/03)
decided 10/27/10: (102 reversed).

- Claim 1. Anhydrous crystalline compound which is characterized in that the X-ray powder diagram has values $d = 6.02 \text{ \AA}$; 4.95 \AA ; 4.78 \AA ; 3.93 \AA and 3.83 \AA .
- Rejected under 35 U.S.C. § 102(b) as anticipated by Reference A.
- Held: A preponderance of the evidence does not support the Examiner's position that the crystalline compound produced by Reference A is the same crystalline form of the compound as recited in claim 1.



Ex parte Pfrengle et al. (Anticipation)

Anticipation Rejection Analysis:

1. The Examiner makes a *prima facie* case of anticipation:
 - Although Reference A crystalline form was prepared by a different process than Appellants, as the Examiner notes, the Reference A process uses anhydrous solvents in a tightly sealed reaction vessel, after which the crystals are dried under reduced pressure ... (e.g. the prior art process made the compound in an analogous manner as in the specification).
 - Thus, it was reasonable to shift to Appellants the burden to show that the Reference A anhydrous compound lacked the X-ray powder diffraction data recited in claim 1.



Ex parte Pfrengle et al. (Anticipation)

2. Appellants demonstrated Reference A lacked the instantly claimed X-ray diffraction signature:
 - 132 Declaration states that the Reference A method results in a composition that does not have the X-ray powder diffraction data required in claim 1; and
 - Additional evidence that the crystalline form recited in claim 1 also differs from the Reference A crystals with respect to dynamic vapor sorption measurements.



Ex parte Pfrengle: Summary

- The Examiner made a *prima facie* case of anticipation by comparing the similarities between the prior art method and that used by applicant to make the analagous compound.
- However, applicant was successfully able to rebut the *prima facie* case by providing empirical evidence demonstrating the failure of the prior art method to achieve the instantly claimed crystalline parameters.



Ex parte Pfrengle et al. : Anticipation- Summary cont.

- Take home message:
 - Examiner can make a *prima facie* case of anticipation using a reference teaching an analogous prior art method of making a crystalline compound as instantly claimed shifting the burden to applicant to provide evidence (e.g. in a 132 declaration) to distinguish the claimed crystal from the prior art crystal.
- NOTE: absent the crystalline claimed parameters, the Examiner's *prima facie* anticipation rejection, in all likelihood, would have been affirmed (possible exception: specification definition clearly defining the instant crystalline compound as necessarily possessing the instantly claimed crystalline parameters).



102/103

(3) *102 and 103 Caselaw*

(b) *102/103 (Ex Parte Reddy)*



Ex parte Reddy et al. : 102/103

- 10/647449: (effective filing date: 8/25/03): decided : 3/29/10 Ex parte Reddy et al. : 102/103 affirmed
1. A compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1.
 2. The compound of claim 1, having an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09 , 6.81 ± 0.09 , 7.80 ± 0.09 , ... , 30.26 ± 0.09 , 35.50 ± 0.09 , and 38.74 ± 0.09 degrees.
 38. A compound which is an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4.



Ex parte Reddy et al. : 102/103

- *Anticipation*
 1. Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Grell et al. US 5,312,924.
 2. Claim 38 is rejected under 35 U.S.C. § 102(b) as anticipated by Grell et al. US 5,312,924.
- *Obviousness*
 3. Claim 1 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Grell '924 et al. US 5,312,924 in view of Grell et al. J. Med. Chem (Grell 2) and Brittain.



Ex parte Reddy et al. : 102 (claim 1)

Claim 1

- The Examiner provides reference evidence that polymorphs are different crystalline forms of the same substance, and finds with respect to the crystalline compound of claim 1, that the infrared spectra of Figure 3 of the present application and Figure 4, parts 1 and 2 of Grell '924 are the same within the margin of error of each other.
- The Examiner finds that Grell '924 employed alcoholic solvents as well as haloalkanes in various process of making the product for example: in example 1, col. 16, line 49, tetrachloride was used; in example 2 col. 20, line 33, chloroform was used; in example 3, col. 21, line 40, dichlorobenzene was used; in example 11, col. 32, line 48, ethanol was used.
- Therefore, both polymorphic forms, how to prepare them, and the different solvent systems are found through out the reference. The species of specific solvents rendered the claims of using haloalkane and alcoholic system *prima facie* obvious.



Ex parte Reddy et al. : 102 (claim 1)

- Appellants argue that the compound of Grell '924 and the claim 1 compound have different melting points and therefore are different compounds.
- The Examiner responds, arguing that “[m]ere difference in physical property is well known conventional variation for the same pure substance” and that the solvent used for preparation, and the degree of purification can have an affect on the physical properties of the product.



Ex parte Reddy et al. : 102 (claim 1)

Board Reasoned (anticipation of claim 1):

- Claim 1 does not require a specific amount of crystalline compound or purity of the compound.
 - If the solids or crystals of Grell '924 have even a small portion of the claimed compound in the product, the product is anticipated.
 - Moreover, Appellants have not disputed the Examiner's finding that the degree of purification can have an affect on the physical properties of the product, such as melting point.
- Thus, we do not find that Appellants have provided evidence that the compound of Figure 4 of Grell '924 is not the crystalline form of (S)-repaglinide of claim 1.



Ex parte Reddy et al. : 102 (claim 38)

Board Reasoned (anticipation of Claim 38)

- The Examiner finds that process of obtaining a non-crystalline solid (amorphous), (S)-repaglinide in Example 12 of Grell '924 (col. 89-90) is the same as that disclosed in the Specification, i.e., dissolving the compound in ethanol and evaporating the solvent. (Ans. 4.)
- Because the non-crystalline compounds are made by the same process, the Examiner has provided sufficient evidence to shift the burden to Appellants to show that the compound of claim 38 is not the compound disclosed in Grell '924.
- Appellants have not provided evidence that the compound of Example 12 of Grell '924 is not the claimed amorphous form of (S)-repaglinide.



Ex parte Reddy et al. : 102 (claims 1 and 38)

- Anticipation of claims 1 and 38: Board (affirmed): ANALYSIS
- The Examiner finds that Grell '924 teaches the compound of claim 1; and with respect to claim 38, the Examiner finds that process of obtaining a non-crystalline solid (amorphous), (S)-repaglinide in Example 12 of Grell '924 (col. 89-90) is the same as that disclosed in the Specification,
 - Appellants contend that the Examiner has failed to provide evidence that the compound of Grell '924 is amorphous (S)-repaglinide as in claim 38 or crystalline repaglinide as in claim 1.
- We conclude that the Examiner has provided sufficient evidence to shift the burden to Appellants to show that the compounds of claims 1 and 38 are not the compound disclosed in Grell '924.



Ex parte Reddy et al. : 103 (claim 1)

- Obviousness of claim 1: Board (affirmed): ANALYSIS
- For the reasons provided above, we conclude that Appellants have not provided evidence that the compound of Figure 4 of Grell '924 is not the crystalline form of (S)-repaglinide of claim 1.
- Anticipation being the epitome of obviousness, the obviousness rejection is affirmed.



Ex parte Reddy: 102/103 Summary

- Consistent with the prior *Pfrenge* case, the Examiner provided a *prima facie* case of anticipation by comparing the prior art method of making the instant compound crystal with that disclosed by applicant.
- Here, unlike *Pfrenge*, applicant failed to provide empirical evidence to demonstrate that the prior art method would not produce the instantly claimed crystalline parameters.



Ex parte Reddy: 102/103 Summary cont.

- Take home: pursuant to MPEP 2112 (Requirements of Rejection Based on Inherency; Burden of Proof):
 - A rejection under 35 U.S.C. 102/103 can be made when the prior art product seems to be identical except that the prior art is silent as to an inherent characteristic (e.g. X-ray diffraction pattern or amorphous).
 - Examiner must provide rationale or evidence tending to show inherency
 - the burden of proof is similar to that required with respect to product-by-process claims;
 - Examiner's *prima facie* showing shifts the burden to the applicant to show an unobvious difference.



Questions

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