Presenting a live 90-minute webinar with interactive Q&A

Drug Substance Patents: FDA Guidance, Protecting Composition-of-Matter Patents, Drafting Solid Form Claims

THURSDAY, OCTOBER 26, 2017

1pm Eastern  |  12pm Central  |  11am Mountain  |  10am Pacific

Today’s faculty features:

Eyal H. Barash, Barash Law, Lafayette, Ind.

Dr. Steef Boerrigter, Senior Research Investigator, Materials Science, SSCI, West Lafayette, Ind.

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Drug Substance Patents
Polymorphs and Cocrystals

Dr. Steef Boerrigter
stephan.boerrigter@amriglobal.com
SSCI - AMRI

- Solid State Chemical Information
- Founded by Prof. Stephen Byrn, Purdue University, 1991
- Specializes in solid-state aspects in drug development
- ~100 employees
- West Lafayette, IN
- Division of Albany Molecular Research, Inc.
Polymorphism

Analytical and Solid State Services
Drug Molecules Tend to Crystallize

Aspirin

Ibuprofen (Advil)
Most Can Crystallize into Different Structures: Polymorphism

Acetaminophen / Paracetamol (Tylenol)
Most Can Crystallize into Different Structures: Solvates

Acetaminophen / Paracetamol (Tylenol)

Monohydrate  Dihydrate  Trihydrate

Pyridine Solvate

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Cocrystals

Analytical and Solid State Services
Cocrystals

- paracetamol:citric acid cocrystal
- paracetamol:oxalic acid cocrystal
FDA Draft Guidance on Cocrystals, Aug 2016

Regulatory Classification of Pharmaceutical Co-Crystals
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.reginfo.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5001 tele, Rockville, MD 20852. All comments should be identified with the docket number in the notice of availability that publish in the Federal Register. For questions regarding this draft document, contact (CDER) Richard E. Lafontain 201-352-1697.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2016
Pharmaceutical Quality (CMC)
Revision 1


27-fold solubility enhancement to pterostilbene; sustained over 5 hours

1:1 pterostilbene:caffeine co-crystal
Schultheiss et al, 2010

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Drug Substance Patents: Leveraging New FDA Guidance, Protecting Composition of Matter Patents, Drafting Solid Form Claims

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October 26, 2017
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Solid Form Patents As Drug Substance Patents in the Orange Book

• Challenge
  • Many drug products are approved in the US with no or limited drug substance patent protection
  • For typical small-molecule exits for composition of matter assets, drug substance patents provide the greatest value. Why?
    • Drug referencing via ANDA walks into infringement
    • Species claims least likely to be declared invalid as a general rule
    • Valuable in deal making!

• Opportunity
  • Solid Form patents may be used to “reset” the composition of matter clock
  • Solid form patents (e.g., salt, cocrystal, and polymorphs) are listed as drug substance patents in the Orange Book
  • They may be narrower than the “organic” chemical compound patent
Drug Substance Patents with Later-Expiring Solid Form Patents – 2015 Drug Approvals
(Not including HW extensions)

- Corlanor®
  - No organic chemistry DS patent protection
  - Solid form protection to 2026
- Addyi®
  - No organic chemistry DS patent protection
  - Solid form protection to 2022
- Entresto®
  - No organic chemistry DS patent protection
  - Solid form protection to 2027
- Farydak®
  - Organic chemistry DS patent protection to 2021
  - Solid form protection to 2028
- Zurampic®
  - Organic chemistry DS patent protection to 2025
  - Solid form protection to 2032
Farxiga®

- NCE is dapagliflozin propanediol
- Approved on January 8, 2014
- NCE Exclusivity until January 8, 2019
## Patent Data

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Composition of Matter Claims

From Label

Claim 1 of 7,919,598 — expires December 16, 2029
1. A crystalline (S)-propylene glycol ((S)-PG) solvate compound la (form SC-3)

Claim 1 of 6,515,117 — expires October 4, 2020
1. A compound having the structure

or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.
Regulatory Scheme at FDA

- Polymorphs

- Salts
  - Applications Covered by Section 505(b)(2) October 1999 (Draft)

- Cocrystals
  - Final Guidance of 2013 recently revised
Polymorphs at FDA

• “Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice.” (p. 2).

• “Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate.” (p. 2).
Polymorphs and “Sameness” at FDA

- ANDA must contain reference to an active ingredient that is the “same as” that in the Reference Listed Drug (RLD)
- Polymorphs of a drug substance differ in solid-state structure, but not chemical structure.
- “[D]ifferences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals.” (p. 5).
Salts at FDA

- Draft 1999 Guidance on 505(b)(2) applications
  - “A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted” (21 U.S.C. 355(b)(2)).” (p. 2).
  - Example includes “An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety” (p. 5).
Salts at FDA – Not Same

• “Active Moiety”
  • "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance’ (21 CFR 314.108(a)).” (p. 11) (Emphasis Added).

• 21 CFR 320.1(c)
  • “Pharmaceutical equivalents means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e. , the same salt or ester of the same therapeutic moiety . . . that deliver identical amounts of the active drug ingredient over the identical dosing period. . . .” (Emphasis Added).
Cocrystals?

- Many comments to the Draft version of the original FDA Guidance argued there is no functional difference between a cocrystal and a salt.
- Based on the “complex” and “clathrate” language of the 505(b)(2) Guidance, many had proceeded under the belief that FDA would regulate cocrystals as salts.
- FDA Guidance of 2013, therefore, came as a great surprise to the Industry.
Cocrystal Guidance of 2013

• “Regulatory Classification of Pharmaceutical Co-Crystals” April 2013
  • Co-crystals are to be treated as drug product intermediates with the coformers are viewed as excipients
  • Data should be submitted confirming that the API and the “excipient” exist in neutral states and interact nonionically
  • “Assurance that complete dissociation of the API from its excipient occurs prior to reaching the site of action for pharmacological activity.” (p. 3).

• Negative response from Industry
  • Draft Guidance had more than 20 responses critical of the Guidance
Ramifications of 2013 Guidance

• Problems with Cocrystal as “Drug Product Intermediate” (same as “in process material” as per footnote 7.)
  • Makes what scientists would normally consider drug substance – “drug product”
  • Different rules, regulations and practices for making and processing drug substance and drug product
  • Typically done in different facilities
  • Chilling effect on cocrystal development
Revisiting the Guidance - 2016

- In August of 2016, FDA replaced the 2013 Guidance with a DRAFT Guidance, whose review period just closed
  - Cocrystals viewed as “special case” of solvates where coformer is non-volatile
  - Data to confirm co-crystal rather than salt still present
  - Assurance that API dissociation occurs before reaching site of pharmacological activity which can generally be done with in an intro evaluation based on dissolution or solubility data (no reference to “excipient”)
  - Cocrystal will be viewed similarly as a polymorph of the API and not a new API
2016 Draft Revision

- Responds to overwhelming industry criticism to change definition of co-crystal to be drug substance rather than drug product
  - Makes the regulatory path much clearer allowing for a fit into current regulatory guidances and ICH guidelines much easier
- There is still the issue of how to characterize whether a salt or cocrystal is made since the answer dictates whether the active ingredient is the same or not
Cocrystals – A European Approach

• EMA published a “Reflection Paper” on Cocrystals on 21 May 2015
  • Cocrystals are viewed as multi-component crystals with solvates and hydrates being a subclass and are considered drug substance
  • Cocrystals and salts are viewed on a “continuum”
  • “Cocrystals, hydrates and solvates will therefore be considered eligible for generic applications in the same way as salts are... unless they differ with respect to safety and/or efficacy.” (Page 6 of Paper).

• Note, EMA and FDA differ on the use of salts
  • “The different salts... of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.” (Page 3 of Paper).
Cocrystals and Patents

• Cocrystals as Drug Substance
  • Drug substance patents with potential listing in the Orange Book

• Cocrystals as “Polymorphs”
  • Bioequivalent polymorphs to the polymorph in the RLD may reference the RLD
  • The potential cocrystal “design-around” space is much larger than the typical design-around single-component polymorph space
Example 1

- Compound X is on the market – there are two polymorphs Form I and II and Innovator has both forms covered – drug launch in 2016
- Generic does cocystal screen and finds a succinic acid cocystal.
- The succinic acid cocystal not covered by polymorph patents
- The succinic acid cocystal is bioequivalent so an ANDA is filed referencing Innovator’s data and is approved
- Generic launches product and files patent on the succinic acid cocystal
- Nothing Innovator can do with its polymorph patents to stop Generic
Example 1A

- Generic 2 sees this and screens and finds fumaric acid cocrystal
- It files another ANDA on its cocrystal since its formulated product is also bioequivalent
- Innovator cannot stop this with its polymorph patent
- Generic 1 cannot stop this with its succinic acid cocrystal patent
- Generic 2 patents its fumaric acid cocrystal
Options

- Get a genus claim covering cocrystals
- A genus claim is valuable to protect against a design-around that can reference safety and efficacy data
- Valuable IP to both innovators and generics
- What are some ways to think about generic claiming?
Enablement

_In re Wright_, 999 F.2d 1557 (Fed. Cir. 1993)

- Patent claimed method of making vaccines directed against all RNA viruses.
- Single working example in application directed to a specific avian RNA virus.
- Court will not grant such broad claim scope in unpredictable art, no reasonable expectation of success for such an extrapolation.
- Thus, harder to get a broad claim in an unpredictable art – working examples become increasingly important.
- Solid forms are typically considered an unpredictable “art”
Example 1 - Succinic, Fumaric, Maleic

- Common Features:
  - All carboxylic acids
  - All di-acids
  - All four carbons
Sample Independent Claims

- A cocrystal of Compound X and a coformer
- A cocrystal of Compound X and an organic acid coformer
- A cocrystal of Compound X and an organic diacid coformer
- A cocrystal of Compound X and a four-carbon organic acid coformer
- A cocrystal of Compound X and a coformer selected from the group consisting of succinic acid, fumaric acid, and maleic acid.
- Crystalline X: coformer (etc.)
Cocrystal X: Patent Claiming

Polymorphs I, II and III

Cocrystal Genus

Succinic Cocrystal (1:1)

Fumaric Cocrystal (1:1)

Maleic Cocrystal (1:1)

Succinic Cocrystal (2:1)
Genus Cocystal Claims

- Multiple Cocrystals
  - Was only a single cocryystal made in the screen or 5 or 6?
- Teaching multiple methods of making cocrystals
- Good claim and specification drafting
- Identifying trends (i.e., C4 carboxylic acids)
- Was a method used to “reduce” search space based on hydrogen-bonding interactions, for example
- What was valuable and what was not valuable?
- Consider including hydrates and solvates
Composition of Matter Claims

Claim 1 of 7,919,598 – expires December 16, 2029
1. A crystalline (S)-propylene glycol ((S)-PG) solvate compound 1a (form SC-3)

Claim 1 of 6,515,117 – expires October 4, 2020
1. A compound having the structure

or a pharmaceutically acceptable salt, a stereoisomer thereof, or a prodrug ester thereof.
Claim 1 of 7,919,598 – expires December 16, 2029

1. A crystalline (S)-propylene glycol ((S)-PG) solvate compound 1a (form SC-3)

Claims 4-7 of 7,919,598 – expires December 16, 2029

4. The crystalline (S)-PG compound 1a (form SC-3) according to claim 1 characterized by peaks in the powder x-ray diffraction pattern at 2θ values of 3.8±0.1, 7.6±0.1, 8.1±0.1, 8.7±0.1, 15.2±0.1, 15.7±0.1, 17.1±0.1, 18.9±0.1 and 20.1±0.1.

5. The crystalline (S)-PG compound 1a (form SC-3) according to claim 1 characterized by a solid state 13C NMR spectrum having substantially similar peak positions at 16.2, 17.6, 39.3, 60.9, 63.3, 69.8, 76.9, 78.7, 79.4, 113.8, 123.6, 129.3, 130.5, 132.0, 135.7, 139.1 and 158.0 ppm.

6. The crystalline (S)-PG compound 1a (form SC-3) according to claim 1 characterized by a differential scanning calorimetry thermogram having an endotherm in the range of about 50º C. to about 78º C. or as shown in FIG. 7.

7. The crystalline (S)-PG compound 1a (form SC-3) according to claim 1 characterized by a thermal gravimetric analysis curve with about 18.7% weight loss from about room temperature up to about 240º C. or as shown in FIG. 5.
Data Claiming – How Solid Form Claims Differ from Chemical Structure Claims

U.S. Patent No. 9,353,090
Data Claiming – How Solid Form Claims Differ from Chemical Structure Claims

Compare to U.S. Patent Number 9,314,525

- No good language exists to define crystalline forms to pharmaceutical scientists which is as robust and commonly accepted as organic nomenclature for covalently bound compounds
- Unit cells not a convenient way to discuss solid forms in Pharma
- So, we use data as a surrogate for nomenclature
- The quality, amount, and type of data are critical when patenting solid forms

1. Picropodophyllin polymorph C having an X-ray powder diffraction pattern exhibiting peaks at 5.5, 7.0, 8.3, 11.0, 11.6 and 11.8±0.2° 2θ.
2. Picropodophyllin polymorph C according to claim 1, wherein the polymorph exhibits a peak at 5.4±0.2° 2θ.
3. Picropodophyllin polymorph C according to claim 2, wherein the polymorph exhibits peaks at 5.4 and 6.9±0.2° 2θ.
4. Picropodophyllin polymorph C according to claim 2, wherein the polymorph exhibits peaks at 5.4, 6.9, 8.2, 9.7, 10.0, 10.9, 11.5 and 11.7±0.2° 2θ.
5. Picropodophyllin polymorph C exhibiting an X-ray powder diffraction pattern as shown in FIG. 3.
6. Picropodophyllin polymorph C exhibiting an X-ray powder diffraction pattern as shown in FIG. 4.
7. Picropodophyllin polymorph C according to claim 6, wherein the polymorph has an IR spectrum exhibiting a peak at 1773.8 cm⁻¹.
Claims with Data Limitations
(Single Peak Used to Prove Infringement)

1. Form 2 ranitidine hydrochloride characterised by an infra-red spectrum as a mull in mineral oil showing the following main peaks:

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Glaxo v. Novopharm
110 F. 3d 1562 (Fed. Cir. 1997)

"It is elementary patent law that all limitations are material. The single-peak analysis was thus insufficient because, as the district court correctly noted, in order to prove infringement Glaxo was required to establish the presence of each limitation of the asserted claims." Id. at 1566

- Twenty-nine peaks
- Nineteen end in 0
- Several – OH stretches claimed
Inherency (Species of Novelty) the typical scenario

• Patent 1 contains 50 examples, including Example 10 which teaches a synthetic scheme and ends with a “white crystalline solid” but provides no analytical data
• Example 10 is carried forward into the clinic and is approved by the regulatory authorities
• A polymorph screen is later done and two forms are found, I and II and a patent is filed on those forms
• Is such a patent valid? Issue = what was the form of Example 10 in Patent 1?
• If it was Form II, then Form II not patentable even though nobody knew what form it was at the time Patent 1 was filed/issued!
• See Ex Parte Reguri, Appeal No. 2007-0313
Qualities of the Invention Cannot be Obvious

Would Aspirin be obvious over Methyl Salicylate?
• Representative Claim (linezolid)
  17. Crystalline Linezolid characterized by data selected from the group
      consisting of: an X-ray powder diffraction pattern having peaks at about 4.7,
      15.7, and 21.7 ± 0.2 degrees 2 theta, an FTIR spectrum having peaks at about
      3090, 1524, 1335, 1195, 1115, 1081, 940, 927, 802, and 752 cm⁻¹ and an
      FTRaman spectrum having peaks at about 2957, 2859, 880, 752 and 715 cm⁻¹.

• Examiner finds claims obvious because:
  • Barbachyn teaches same chemical composition of linezolid, having just a
    different arrangement or different molecular conformations
  • Brittain teaches that “mere difference in physical property is well known
    conventional variation of the same pure substance (see Brittain p.1-2).”
    (p.11).
  • Thus, in absence of a showing of unexpected results, the claimed Form X
    would be obvious
Ex Parte Aronhime Appeal 2009-003073
(October 19, 2009)

• Board Reverses

• None of the references suggest crystalline Form X and when a specific polymorph is claimed, “the prior art must make obvious the specific form that is claimed if the claim is to be held unpatentable under § 103.” (p. 13).

• No such showing by Examiner and, therefore, “no basis exists to require Appellants to provide evidence of unexpected results for the claimed product.” (p.13).

• Examiner erred in finding “crystalline Form X linezolid to be obvious based on Barbachyn and Brittain.” (p. 14).
Sanofi-Synthelabo v. Apotex, Inc.,
492 F.Supp.2d 353 (S.D.N.Y. 2007)
(affirmed on appeal)

Predictability and Salts:

I. Berge = "[T]here is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." Id. at 374.

II. Forming "a crystalline salt is important for an orally administered drug such as clopidrogel" due to its affect on solubility. Id.

III. "The prior art teaches – and both parties' experts agreed and the Court finds – that whether a crystalline material will form. . . the type of crystalline material that will form, and the properties . . . are all unpredictable." Id.
In re Armodafanil
939 F. Supp. 2d 456 (D. Del. 2013)

- Polymorphism is unpredictable
- Large number of experiments needed and non-linear dependence on experimental conditions
- Cannot predict how to make a specific polymorph or predict its properties
- No reasonable expectation of success in obtaining Form I
- See also Merck & Cie v. Watson Laboratories, Inc. 125 F. Supp. 3d 503 (D. Del. 2013) (rev’d on other grounds)
In Re Depomed Patent Litigation (Civil Action No. 13-4507, D. New Jersey (Sept. 30, 2016)

- Form A tapentadol HCl found non-obvious over prior art patent directed to tapentadol HCl and an article by S. Byrn (founder of SSCI) on polymorph screening

- "In sum, Plaintiffs demonstrated that, while each individual technique performed during a polymorph screen may be routine, polymorph screening consists of an unpredictable application of those routine techniques."

- "Plaintiffs further showed that the results of the polymorph screen — i.e., the determination of the structure and properties of the polymorph forms of tapentadol hydrochloride — would have been impossible to predict."

- "As "predictability is a touchstone of obviousness," Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009), Defendants have failed to meet their burden of demonstrating that the specific polymorph Form A of tapentadol hydrochloride was obvious."
Conclusion

• Solid Forms are increasingly being used to protect drug substance assets
• FDA has made the use of cocrystals more attractive by reclassifying as drug substance
• Cocrystals have the potential of creating more opportunities to find new and improved drug delivery properties than salts or single-component polymorphs
• Protecting solid forms may be more important than ever with cocrystals
• Inherency less problematic *a priori* with cocrystals than single-component polymorphs
• Non-obviousness advantageous to patentees today, but should always prepare for unexpected results as is the law in the EU
Thank You