Patenting and Litigating Pharmaceutical Salts

April 28th, 2022
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Dr. Stephen R. Byrn
Charles B. Jordan Professor of Medicinal Chemistry in the Department of Industrial and Physical Pharmacy, Purdue University

Dr. Stephen R. Byrn is Charles B. Jordan Professor of Medicinal Chemistry in the Department of Industrial and Physical Pharmacy, Purdue University. Dr. Byrn set in motion the development of the field of Solid State Chemistry of Drugs with his books, short courses, and papers on the subject the first of which were published in the mid-1970’s. He has also educated over 50 Ph. D. students and postdoctoral fellows. Dr. Byrn has had numerous grants including one of the first 13 NIH Centers for AIDS Research. Dr. Byrn is cofounder of Purdue’s graduate programs in regulatory and quality compliance. These programs are now part of the Biotechnology Innovation and Regulatory Science (BIRS) center and MS program at Purdue and in Africa. He is also cofounder of the Sustainable Medicines in Africa project in Tanzania. Dr. Byrn has served as chair of the Pharmaceutical Sciences Advisory Committee to the FDA and chaired several USP committees. Dr. Byrn is also cofounder of SSCI, Inc. (Solid State Chemical Information) and Improved Pharma, LLC.

Dr. Steven Zeman
European and German Patent Attorney, Grünecker

Dr. Steven Zeman is qualified as a German and European patent attorney and is a partner in the life science and chemical practice group of Grünecker. A US native, Dr. Zeman holds a B.S. in Chemistry/Biochemistry from the University of California at San Diego, an M.S. in Chemistry from Yale University, and a Ph.D. in Chemistry from Yale University, where his research focused on the interaction between small molecule anticancer drugs and DNA, developing new methodology for studying such interactions. Dr. Zeman has authored or co-authored numerous scientific publications, articles and regular columns on patent-related topics in European and international IP journals. Along with several other colleagues at Grünecker, Dr. Zeman co-authored the book Protecting and Enforcing Life Science Inventions in Europe: From Antibodies to Zebrafish, C.H. Beck, Hart, Nomos, Helbing Lichtenhahn, 2015. Dr. Zeman lectures regularly on IP-related topics in the US and Asia.
Eyal Barash
Patent Attorney and Founder, Barash Law LLC

Eyal Barash founded Barash Law LLC in 2009 to be a “roving” in-house General and IP counsel to early and mid-stage start-ups primarily coming out of the Purdue Research Park in West Lafayette, Indiana. He advises or has advised more than 20 start-up companies from Purdue alone and taken them through multiple stages of development including in-licenses, out-licenses, public offerings, private sales and public exits. In 2018, one of Eyal’s clients, Endocyte, Inc. was sold to Novartis for over $2B. Eyal was chief patent counsel to Endocyte for almost 10 years. Eyal is also a prolific speaker and lecturer, giving presentations primarily in life science IP throughout the globe. He has a particular interest in drug repositioning and repurposing and lectures on this topic frequently. Eyal’s current clients have a global footprint and are in the pharmaceutical, medical device, energy, defense, and agriculture sectors.

Gene Quinn
President, IPWatchdog, Inc.

Gene Quinn is a patent attorney and a leading commentator on patent law and innovation policy. Mr. Quinn has twice been named one of the top 50 most influential people in IP by Managing IP Magazine, in both 2014 and 2019. From 2017-2020, Mr. Quinn has also been recognized by IAM Magazine as one of the top 300 IP strategists in the world, and in 2021 he was recognized by IAM in their inaugural Strategy 300 Global Leaders list. Mr. Quinn founded IPWatchdog.com in 1999, and he is currently President & CEO of IPWatchdog, Inc. According to IAM Magazine, Mr. Quinn “has reshaped the IP debate in the United States in a way that has forced policy makers to carefully consider the macroeconomic effects of IP law and its potential to drive innovation and economic activity.”
Noteworthy Salt Related Papers

- *Solution Rate of Theophylline Salts*, 1958 – Eino Nelson
  - Salts increase solution rate and bioavailability

- *Pharmaceutical Salts*, 1977 – Berge, Bighley, Monkhouse
  - More than 50 approved commercially marketed salts

  - Federal Circuit ruled this paper did not render solid form screening obvious
# Patented Salts and Scientific Significance

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<thead>
<tr>
<th>Patented Salt</th>
<th>Scientific Significance</th>
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<tbody>
<tr>
<td>Ranitidine hydrochloride</td>
<td>Could not make pure Form I after Form II appeared in the same facility</td>
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<tr>
<td>Paroxetine hydrochloride</td>
<td>Facile transformation of anhydrous form to the hemihydrate in the presence of water</td>
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<tr>
<td>Clopidogrel bisulfate</td>
<td>Unique bisulfate structure with unsalified proton</td>
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<tr>
<td>Amlodipine besylate</td>
<td>Initial group of salts discovered - maleate, second group of salts - besylate</td>
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<tr>
<td>Atorvastatin calcium</td>
<td>Over 20 polymorphs discovered</td>
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<tr>
<td>Bedaquiline fumarate</td>
<td>Initial salt - fumarate, second group of 4 salts, third group of 4 additional salts</td>
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Salt Patents at the USPTO

“Pharmaceutically Acceptable Salt”

*Extrapolated from 4/22/22
13. The compound according to claim 1, wherein the compound is 3-(4-chlorophenyl)propyl-3-piperidinopropyl-ether, or its pharmaceutically acceptable salts, hydrates, or hydrated salts, or its optical isomers, racemates, diastereoisomers or enantiomers.
Pharmaceutical Salt Inventions in the EPO: General Orientation

- Central concept: Legal patentability requirements for pharmaceutical salts in the EPO are no different than for other technical fields.
- Specifics relate to technical information needed to satisfy these legal requirements.
- Consider legal requirements for inventive step (Art. 56 EPC) and sufficiency of disclosure (Art. 83 EPC)
  - EPO still assesses inventive step of claimed subject matter by the „problem-solution approach“:
    
    *Would the skilled person have been motivated to modify the prior art to achieve the technical effect caused by the claim's distinguishing feature(s), i.e. the feature(s) making the claim novel?*
  
  - EPO still assesses sufficiency of disclosure by considering:
    
    *Whether the skilled person has all the information needed to reliably obtain and characterize the claimed subject matter.*

Consider some specifics … →
Generic Relationship of Claim to Prior Art: EPO’s Problem-Solution Approach

Step 1:
Identify

Step 2:
Determine distinguishing feature by which claim is novel.

Step 3:
What **technical effect** is associated with this feature?
→ Technical effect X.

Step 4:
Formulate **objective technical problem**:
“Skilled person wants to achieve X”

Step 5:
Would prior art have motivated the skilled person to achieve X as claimed?

Key difference to USPTO:
Inventive step linked to technical effect.
No structural non-obviousness!

NO → inventive.
YES → obvious.
What Does This Mean for Pharmaceutical Salts?

Step 1: Identify

Teaching

- Closest prior art
- Claimed invention

Step 2: Determine distinguishing feature by which claim is novel.

Step 3: What technical effect is associated with this feature?

→ Technical effect \( X \).

Step 4: Formulate objective technical problem:

"Skilled person wants to achieve \( X \)"

Step 5: Would prior art have motivated the skilled person to achieve \( X \) as claimed?

NO → inventive.

YES → obvious.

Key difference to USPTO:

Inventive step linked to technical effect.

No structural non-obviousness!
What Does This Mean for Pharmaceutical Salts?

Sufficiency of disclosure (Art. 83 EPC)

What does skilled person need to reproducibly put claimed invention into practice without undue burden?

Some examples:

• Full compound (structure or IUPAC name)
• NMR/MS
• X-ray diffraction data, including XRPD (including wavelength / source) in form of diffractogram and 2θ values with variation.
• Differential scanning calorimetry (DSC) / Differential thermal analysis (DTA) (including heating rate)

Features best in claim, but at least in description, with all information necessary to perform using common general knowlegde.

Possible technical effects for inventive step

Improved - milling, granulation
- lyophilization
- pulverization
- hygroscopicity
- stability (e.g. to heat)
- filterability
- machine processability (e.g. tableting)

Improved - solubility
- bioavailability
- toxicity
- PK
Novelty and Inherency

• Issue often turns on what the prior art teaches inherently

• Typical scenario
  • P/A teaches the formation of Compound but silent on crystalline form
  • Claim at issue is to crystalline form of Compound or crystalline salt of Compound
  • Question: By practicing the prior art, does one necessarily produce the claimed crystalline material in question
    • See SmithKline Beecham v. Apotex 404 F.3d 1331 (2005)
    • Reproduction of prior art references
    • Don’t forget your chemistry
      • Cannot produce an HCl salt if the prior art only teaches a free base
Grunenthal GMBH v. Alkem Labs. Ltd.  
919 F.3d 1333 (2019)

• **Claim 1.** 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 Kα 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.  

[Tapentadol HCl Form A]  
• Prior Art = Tapentadol HCl Form B + 1995 Byrn article on polymorph screening generally  
• Standard = Reasonable Expectation of Success or obvious to try

• **Reasonable Expectation of Success**  
  • FC: No. Only Form B known. Why? (i) POSA would not know THCl polymorphic; (ii) no idea how the many variables in polymorph screening would affect rec. of THCl

• **Obvious to Try**  
  • FC: No. General approach and “finite” number of solvents still yields “a huge number of possible choices”
Thank You!

Steve Byrn  
sbyrn@purdue.edu

Eyal Barash  
eyal.barash@ebarashlaw.com

Steve Zeman  
zeman@grunecker.de