PATENT OWNER'S DEMONSTRATIVES

Liquidia Technologies, Inc. v. United Therapeutics Corp.

IPR2020-00770 – U.S. Patent No. 9,604,901

June 23, 2021

UT EX2037

CHALLENGED CLAIMS OF THE '901 PATENT

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and
wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim **1**, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim **1**.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim **1**.

5. The product of claim **4**, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim **1**, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim **1** at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim **6**, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim **1**, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim **8**, wherein the salt of treprostinil is a diethanolamine salt.

EX1001 (901 Patent), 17:24-18:29; Paper 12 (POR), 1.

CHALLENGED CLAIMS 1-9

- **Ground 1:** Obviousness over Phares
- **Ground 2:** Obviousness over Moriarty in view of Phares

Paper 1 (Petition), 2-3, 25; *id.*, 29-48 (Ground 1); *id.*, 49-75 (Ground 2); EX1002 (Winkler), ¶¶62-141 (Ground 1); *id.*, ¶¶142-238 (Ground 2); Paper 12 (POR), 1-2, 27-51 (Ground 1), 51-66 (Ground 2).

GROUNDS FOR INSTITUTION

- **Ground 1:** Obviousness over Phares
  - **Claims 1-9, no demonstration of reasonable likelihood of obviousness**
    - The “best course of action here is to permit the parties to fully develop the record during trial before resolving these disputes.”
- **Ground 2:** Obviousness over Moriarty in view of Phares
  - **Claims 1-5 and 8-9**
  - **Claims 6-7, no demonstration of reasonable likelihood of obviousness**
    - “we are not persuaded”

Paper 7 (Institution Decision), 22-28 (Ground 2, claims 1-5 + 8-9), 28-29 (claims 6 + 7), 30-31 (Ground 1).

LIQUIDIA FAILED TO CARRY ITS BURDENS

LIQUIDIA HAS FAILED TO PROVE ITS PRIMA FACIE CASE

- **Closed impurity claim limitations:**
  - Neither Moriarty nor Phares teach an impurity profile.
- **Salt Formation:**
  - Moriarty does not teach contacting a solution of treprostinil with a base to form a salt of treprostinil.
  - Moriarty does not teach isolating a salt of treprostinil.
- **Scale:**
  - Phares does not teach a single reaction that yields even 1 gram of product after purification, let alone a reaction relevant to treprostinil diethanolamine.
- **Storage:**
  - Neither Moriarty nor Phares teach storage.
  - Phares suggests instability due to polymorphs and hygroscopicity, drastically complicating the manufacture, storage, and stability of pharmaceutical batches and products.

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Paper 12 (POR), 27-51 (Ground 1), 51-66 (Ground 2).

LIQUIDIA'S SLOPPINESS IS FATAL TO THEIR PETITION

- Didn't establish that a translation was correct
- Didn't have sworn testimony from Dr. Winkler
- Provided unintelligible testimony from Dr. Hall-Ellis
- Didn't establish that their art was actual prior art

Paper 31 (MtE), 2-10; Paper 12 (POR), 17-22.

LIQUIDIA IMPROPERLY ATTEMPTS TO SHIFT BURDEN OF PROOF

- **Petitioner bears the burden for:**
  - Unpatentability over printed publication prior art
  - Collateral estoppel

"In an inter partes review instituted under this chapter, **the petitioner shall have the burden** of proving a proposition of unpatentability by a preponderance of the evidence."

- *35 U.S.C. §316(e)*

Paper 6 (POPR), 7, 57; Paper 12 (POR), 28-29, 48, 63.

LEVEL OF ORDINARY SKILL IN THE ART

COMPARING THE PROFFERED POSA DEFINITIONS

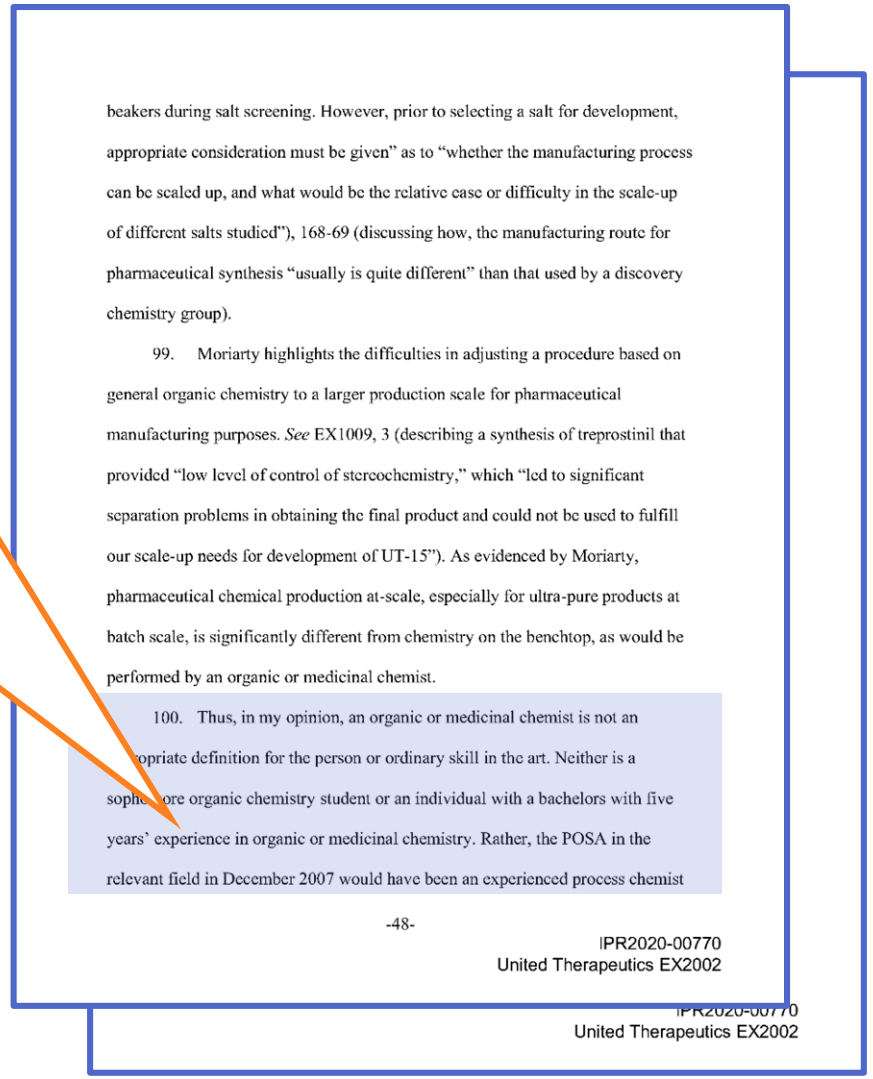
- **Dr. Pinal:** Consistent with claims, specification, and asserted art
- **Dr. Winkler:** Self-serving and unsupported by evidence
- **Dr. Hall-Ellis:** Bizarre

Paper 6 (POPR), 55-57; Paper 12 (POR), 1-2; Paper 25 (Sur-Reply), 13-16.

DR. PINAL ACTUALLY CONSIDERED BACKGROUNDS OF THOSE IN THE ASSERTED ART + REAL PROBLEMS IN THE FIELD

"[T]he POSA in the relevant field in December 2007 would have been an **experienced process chemist or chemical engineer**. This individual must have had **experience in the production and manufacture of pharmaceutical compositions and pharmaceutical products**."

- Dr. Pinal



beakers during salt screening. However, prior to selecting a salt for development, appropriate consideration must be given" as to "whether the manufacturing process can be scaled up, and what would be the relative ease or difficulty in the scale-up of different salts studied"), 168-69 (discussing how, the manufacturing route for pharmaceutical synthesis "usually is quite different" than that used by a discovery chemistry group).

99. Moriarty highlights the difficulties in adjusting a procedure based on general organic chemistry to a larger production scale for pharmaceutical manufacturing purposes. *See* EX1009, 3 (describing a synthesis of treprostinil that provided "low level of control of stereochemistry," which "led to significant separation problems in obtaining the final product and could not be used to fulfill our scale-up needs for development of UT-15"). As evidenced by Moriarty, pharmaceutical chemical production at-scale, especially for ultra-pure products at batch scale, is significantly different from chemistry on the benchtop, as would be performed by an organic or medicinal chemist.

100. Thus, in my opinion, an organic or medicinal chemist is not an appropriate definition for the person or ordinary skill in the art. Neither is a sophomore organic chemistry student or an individual with a bachelors with five years' experience in organic or medicinal chemistry. Rather, the POSA in the relevant field in December 2007 would have been an experienced process chemist

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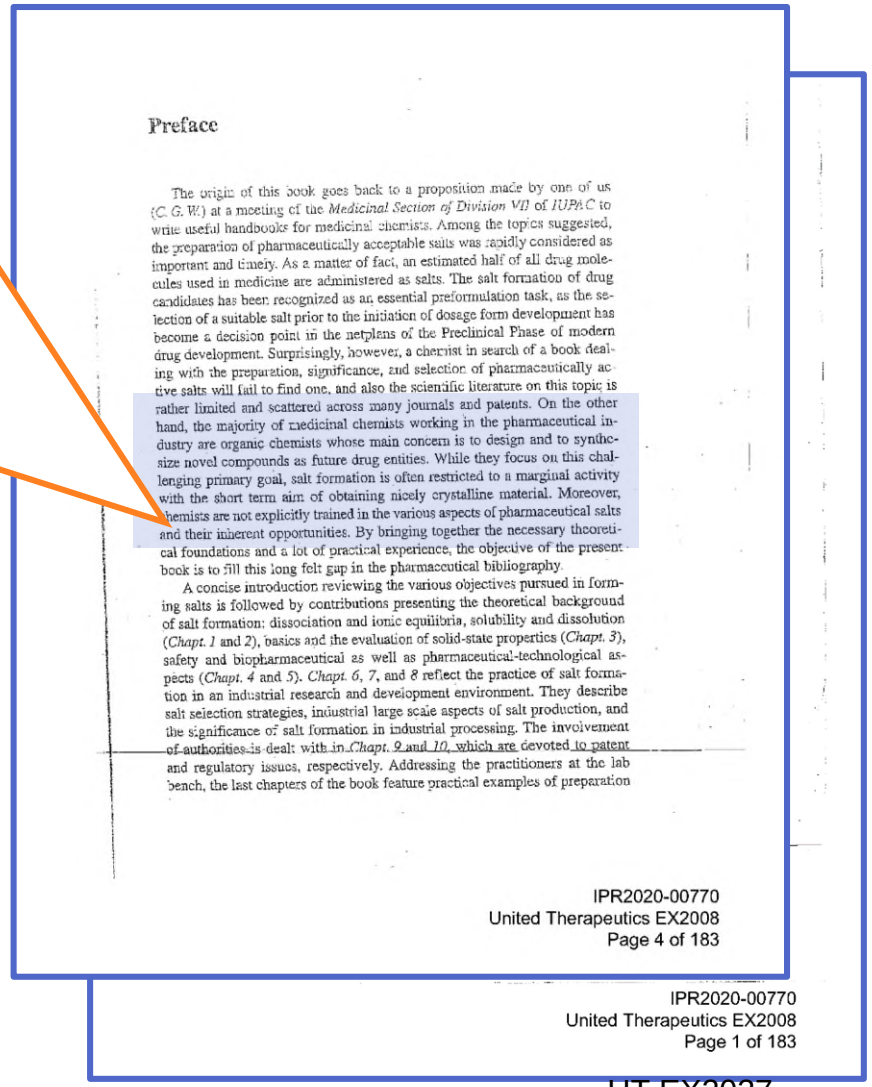
EX2002, ¶100; Paper 12 (POR), 22-27; Paper 25 (Sur-Reply), 13-16.

DR. PINAL'S OPINION IS SUPPORTED BY EVIDENCE

"**[T]he majority of medicinal chemists working in the pharmaceutical industry are organic chemists whose main concern is to design and to synthesize novel compounds as future drug entities**. While they focus on this challenging primary goal, salt formation is often restricted to a marginal activity with the short term aim of obtaining nicely crystalline material. Moreover, **chemists are not explicitly trained in the various aspects of pharmaceutical salts** and their inherent opportunities."

- Stahl



Preface

The origin of this book goes back to a proposition made by one of us (C. G. W.) at a meeting of the *Medicinal Section of Division VI* of *IUPAC* to write useful handbooks for medicinal chemists. Among the topics suggested, the preparation of pharmaceutically acceptable salts was rapidly considered as important and timely. As a matter of fact, an estimated half of all drug molecules used in medicine are administered as salts. The salt formation of drug candidates has been recognized as an essential preformulation task, as the selection of a suitable salt prior to the initiation of dosage form development has become a decision point in the netplans of the Preclinical Phase of modern drug development. Surprisingly, however, a chemist in search of a book dealing with the preparation, significance, and selection of pharmaceutically active salts will fail to find one, and also the scientific literature on this topic is rather limited and scattered across many journals and patents. On the other hand, the majority of medicinal chemists working in the pharmaceutical industry are organic chemists whose main concern is to design and to synthesize novel compounds as future drug entities. While they focus on this challenging primary goal, salt formation is often restricted to a marginal activity with the short term aim of obtaining nicely crystalline material. Moreover, chemists are not explicitly trained in the various aspects of pharmaceutical salts and their inherent opportunities. By bringing together the necessary theoretical foundations and a lot of practical experience, the objective of the present book is to fill this long felt gap in the pharmaceutical bibliography.

A concise introduction reviewing the various objectives pursued in forming salts is followed by contributions presenting the theoretical background of salt formation: dissociation and ionic equilibria, solubility and dissolution (*Chapt. 1* and *2*), basics and the evaluation of solid-state properties (*Chapt. 3*), safety and biopharmaceutical as well as pharmaceutical-technological aspects (*Chapt. 4* and *5*). *Chapt. 6*, *7*, and *8* reflect the practice of salt formation in an industrial research and development environment. They describe salt selection strategies, industrial large scale aspects of salt production, and the significance of salt formation in industrial processing. The involvement of authorities is dealt with in *Chapt. 9* and *10*, which are devoted to patent and regulatory issues, respectively. Addressing the practitioners at the lab bench, the last chapters of the book feature practical examples of preparation

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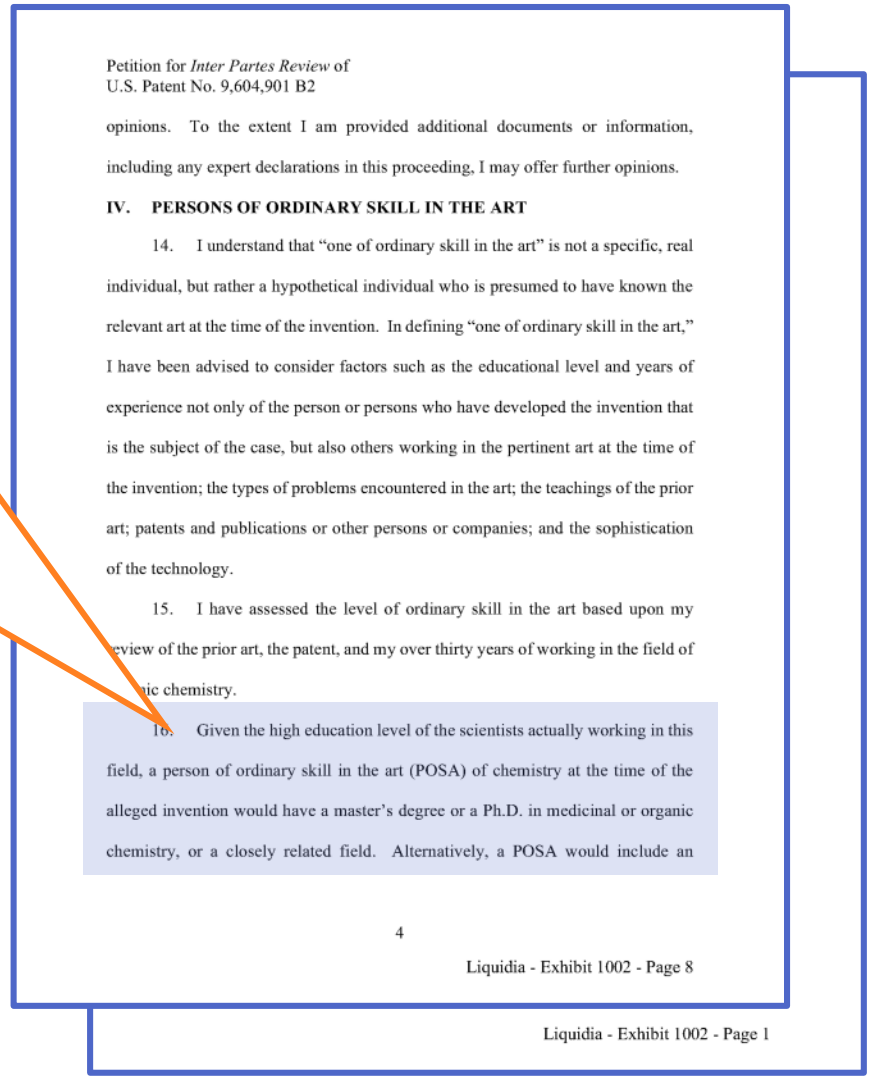
EX2008 (Stahl), iv; Paper 12 (POR), 22-27; Paper 25 (Sur-Reply), 13-16; EX2002 (Pinal), ¶94.

DR. WINKLER'S SELF-SERVING POSA DEFINITION

"[A] person of ordinary skill in the art (POSA) of **chemistry** at the time of the alleged invention would have a **master's degree or a Ph.D. in medicinal or organic chemistry**, or a closely related field."

- Dr. Winkler



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opinions. To the extent I am provided additional documents or information, including any expert declarations in this proceeding, I may offer further opinions.

IV. PERSONS OF ORDINARY SKILL IN THE ART

14. I understand that "one of ordinary skill in the art" is not a specific, real individual, but rather a hypothetical individual who is presumed to have known the relevant art at the time of the invention. In defining "one of ordinary skill in the art," I have been advised to consider factors such as the educational level and years of experience not only of the person or persons who have developed the invention that is the subject of the case, but also others working in the pertinent art at the time of the invention; the types of problems encountered in the art; the teachings of the prior art; patents and publications or other persons or companies; and the sophistication of the technology.

15. I have assessed the level of ordinary skill in the art based upon my review of the prior art, the patent, and my over thirty years of working in the field of ...ic chemistry.

16. Given the high education level of the scientists actually working in this field, a person of ordinary skill in the art (POSA) of chemistry at the time of the alleged invention would have a master's degree or a Ph.D. in medicinal or organic chemistry, or a closely related field. Alternatively, a POSA would include an

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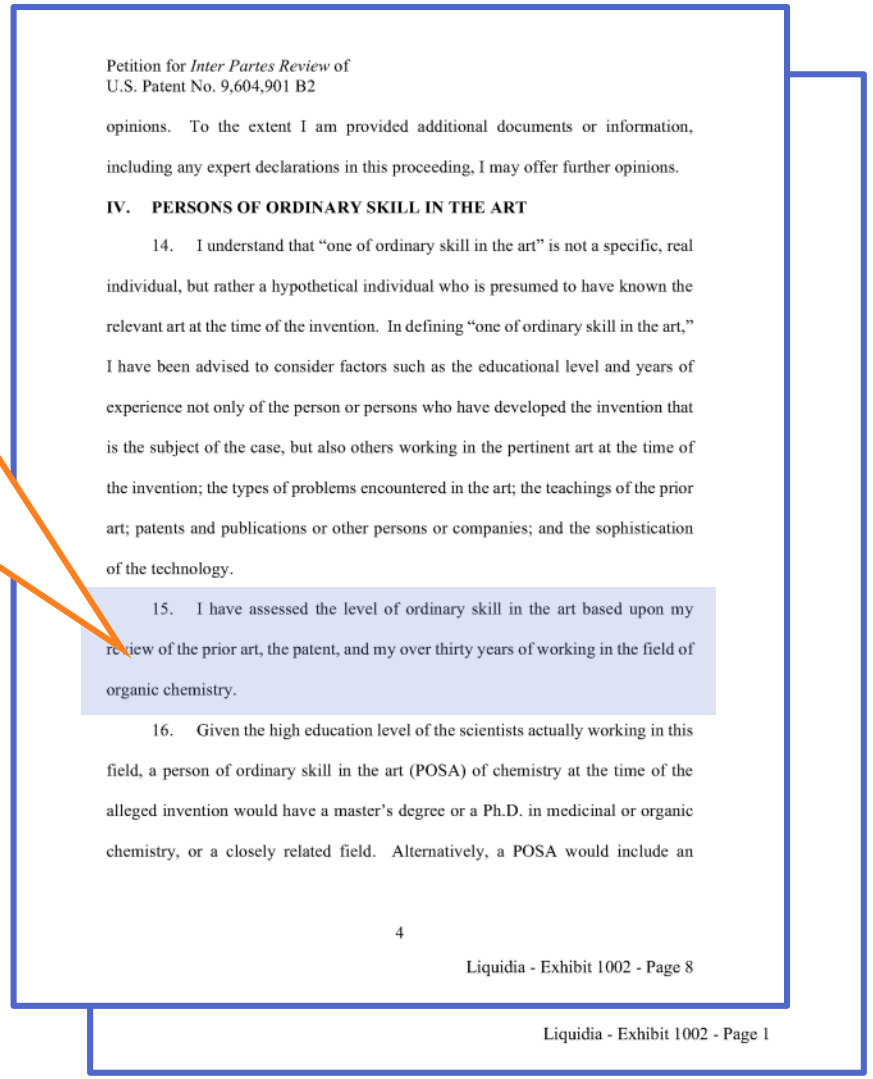
EX1002, ¶¶16-17; Paper 1 (Petition), 25; Paper 12 (POR), 1, 22-27; Paper 25 (Sur-Reply), 13-16.

DR. WINKLER'S SELF-SERVING POSA DEFINITION

"I have assessed the level of ordinary skill in the art based upon my review of the prior art, the patent, and **my over thirty years of working in the field of organic chemistry**."

- Dr. Winkler



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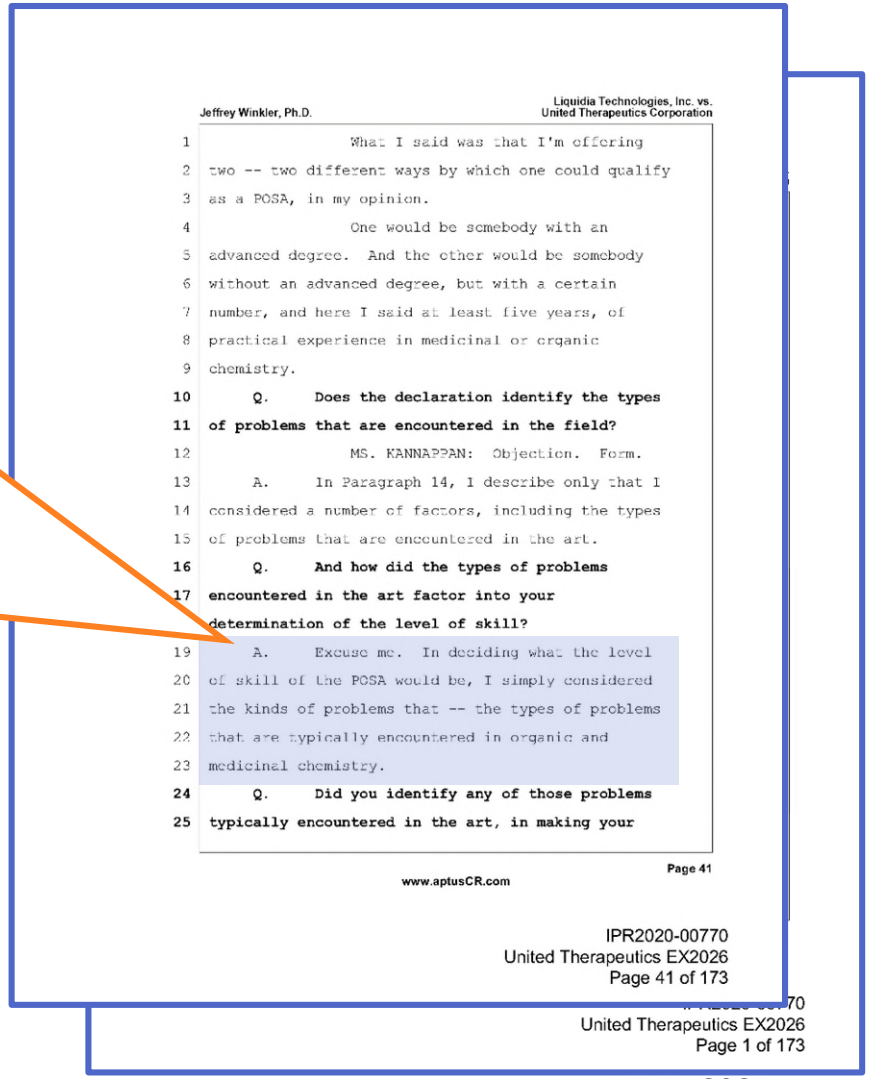
EX1002 (Winkler), ¶¶14-15; Paper 1 (Petition), 25; Paper 12 (POR), 1, 22-27; Paper 25 (Sur-Reply), 13-16.

DR. WINKLER ASSUMES WHAT HE WAS OFFERED TO PROVE

"In deciding what the level of skill of the POSA would be, I simply considered the kinds of problems that – the types of **problems that are typically encountered in organic and medicinal chemistry**."

- Dr. Winkler



Jeffrey Winkler, Ph.D. — Liquidia Technologies, Inc. vs. United Therapeutics Corporation

What I said was that I'm offering two -- two different ways by which one could qualify as a POSA, in my opinion.

One would be somebody with an advanced degree. And the other would be somebody without an advanced degree, but with a certain number, and here I said at least five years, of practical experience in medicinal or organic chemistry.

Q. Does the declaration identify the types of problems that are encountered in the field?

MS. KANNAPPAN: Objection. Form.

A. In Paragraph 14, I describe only that I considered a number of factors, including the types of problems that are encountered in the art.

Q. And how did the types of problems encountered in the art factor into your determination of the level of skill?

A. Excuse me. In deciding what the level of skill of the POSA would be, I simply considered the kinds of problems that -- the types of problems that are typically encountered in organic and medicinal chemistry.

Q. Did you identify any of those problems typically encountered in the art, in making your

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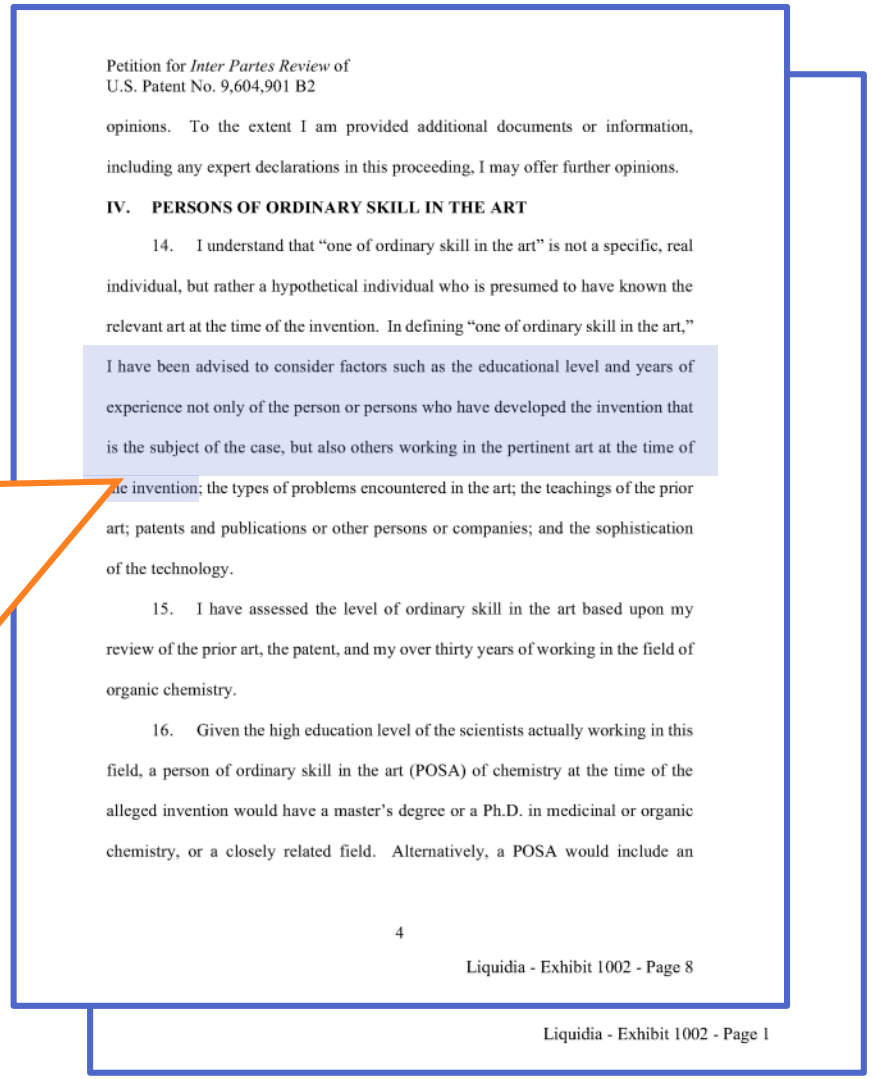
EX2026 (Winkler Depo #1), 41:10-23; Paper 1 (Petition), 25; Paper 12 (POR), 1, 22-27; Paper 25 (Sur-Reply), 13-16.

DR. WINKLER'S UNSUPPORTED POSA DEFINITION

"I have been advised to consider factors such as the **educational level and years of experience not only of the person or persons who have developed the invention,** but also **others working in the pertinent art** at the time of the invention…"

- Dr. Winkler



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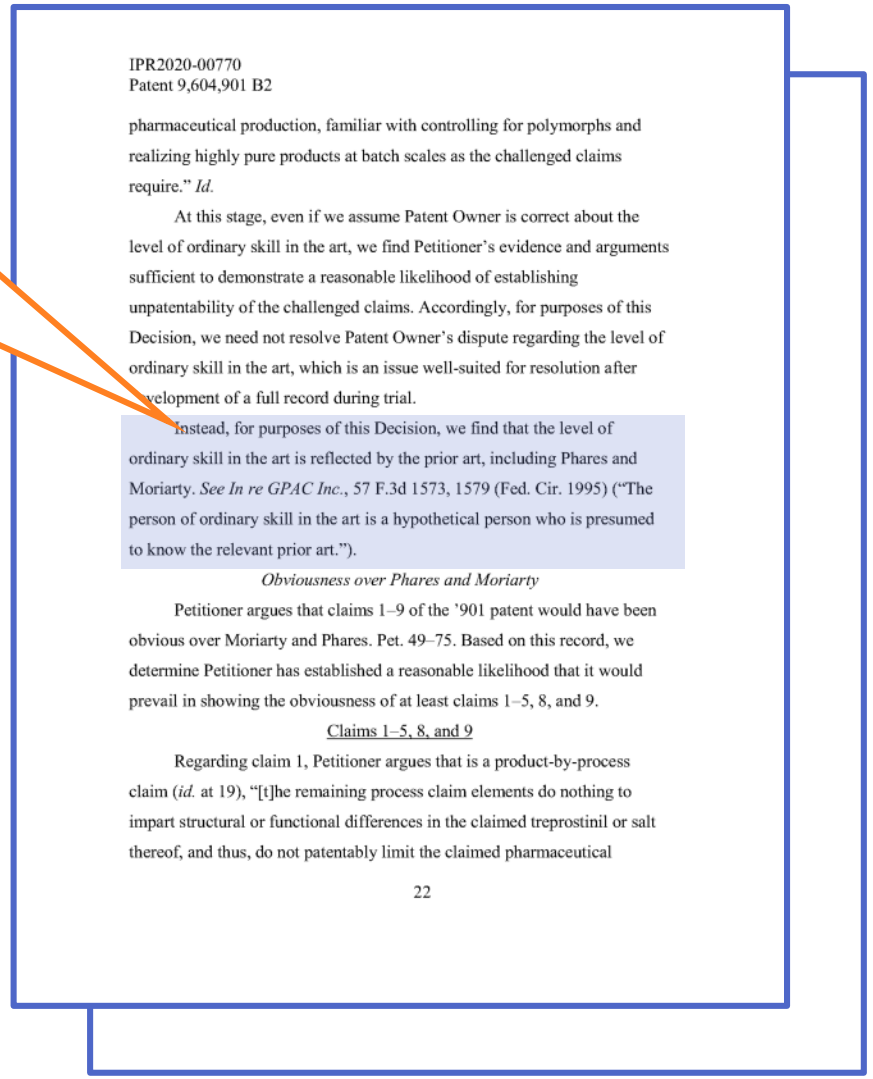
EX1002 (Winkler), ¶¶14-15; Paper 1 (Petition), 25; Paper 12 (POR), 1, 22-27; Paper 25 (Sur-Reply), 13-16.

PARTIES + BOARD AGREE POSA DEFINITION SHOULD BE CONSISTENT WITH PRIOR ART

"[W]e find that the level of ordinary skill in the art is **reflected by the prior art, including Phares and Moriarty**."

- Institution Decision



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pharmaceutical production, familiar with controlling for polymorphs and realizing highly pure products at batch scales as the challenged claims require." *Id.*

At this stage, even if we assume Patent Owner is correct about the level of ordinary skill in the art, we find Petitioner's evidence and arguments sufficient to demonstrate a reasonable likelihood of establishing unpatentability of the challenged claims. Accordingly, for purposes of this Decision, we need not resolve Patent Owner's dispute regarding the level of ordinary skill in the art, which is an issue well-suited for resolution after development of a full record during trial.

Instead, for purposes of this Decision, we find that the level of ordinary skill in the art is reflected by the prior art, including Phares and Moriarty. *See In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) ("The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art.").

Obviousness over Phares and Moriarty

Petitioner argues that claims 1–9 of the '901 patent would have been obvious over Moriarty and Phares. Pet. 49–75. Based on this record, we determine Petitioner has established a reasonable likelihood that it would prevail in showing the obviousness of at least claims 1–5, 8, and 9.

Claims 1–5, 8, and 9

Regarding claim 1, Petitioner argues that is a product-by-process claim (*id.* at 19), "[t]he remaining process claim elements do nothing to impart structural or functional differences in the claimed treprostinil or salt thereof, and thus, do not patentably limit the claimed pharmaceutical

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Paper 7 (Institution Decision), 22; Paper 12 (POR), 22-23; Paper 25 (Sur-Reply), 13-16.

LEVEL OF SKILL REFLECTED BY THE ART

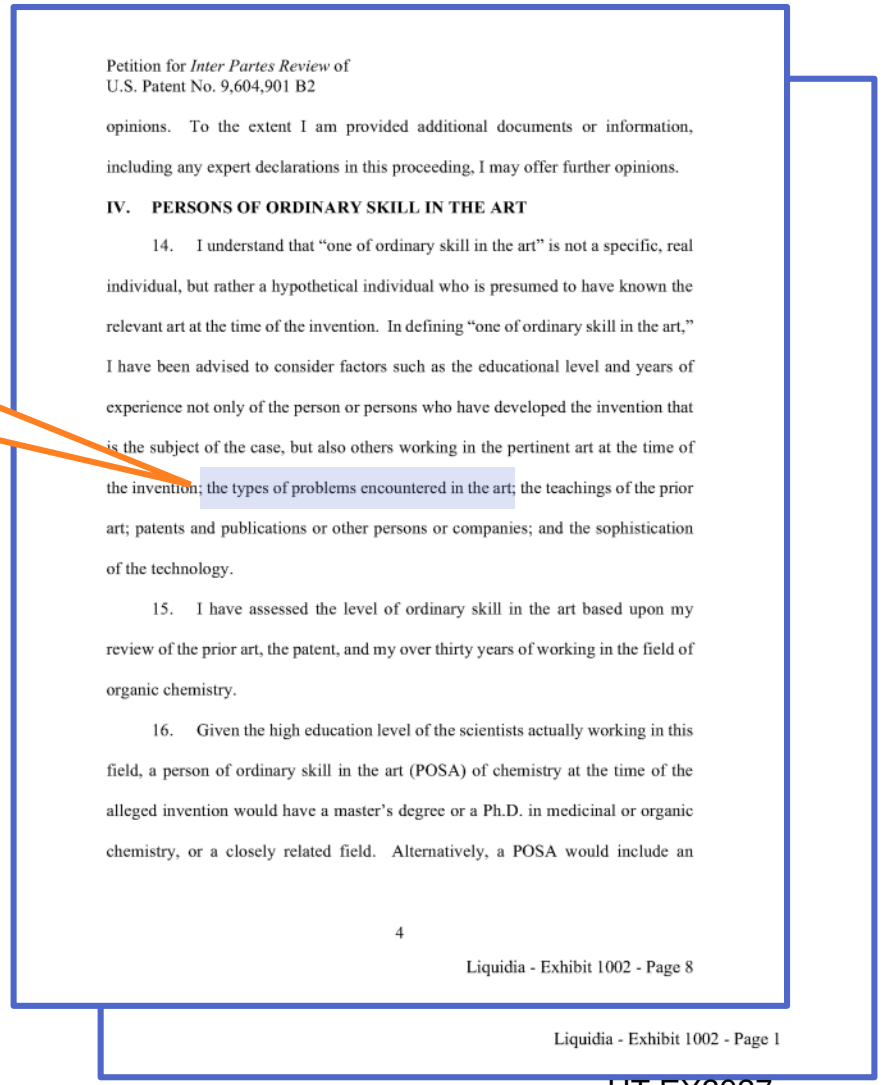
KEN PHARES	DAVID MOTTOLA	BOB MORIARTY
▪ **Ph.D. Pharmaceutical Chemistry** ▪ **VP of Pharmaceutical Development for ~20 years** – Managed process scale-up – Coordinated pharmaceutical development from API characterization to drug product development process scale-up.	▪ **Ph.D. Pharmacology** ▪ Guided product development from startup ▪ R&D leadership, including quality and process improvement	▪ **President and founder of Steroids Limited, 1989-2014** – Commercial organic synthesis ▪ Professor emeritus of University of Illinois, Chicago

EX2029-31 (LinkedIns); EX2032 (Winkler Depo #2), 225:16-239:21; Paper 25 (Sur-Reply), 13-14.

DR. WINKLER DOESN'T KNOW WHAT HE DOESN'T KNOW

"…the types of **problems encountered** in the art…"

- Dr. Winkler



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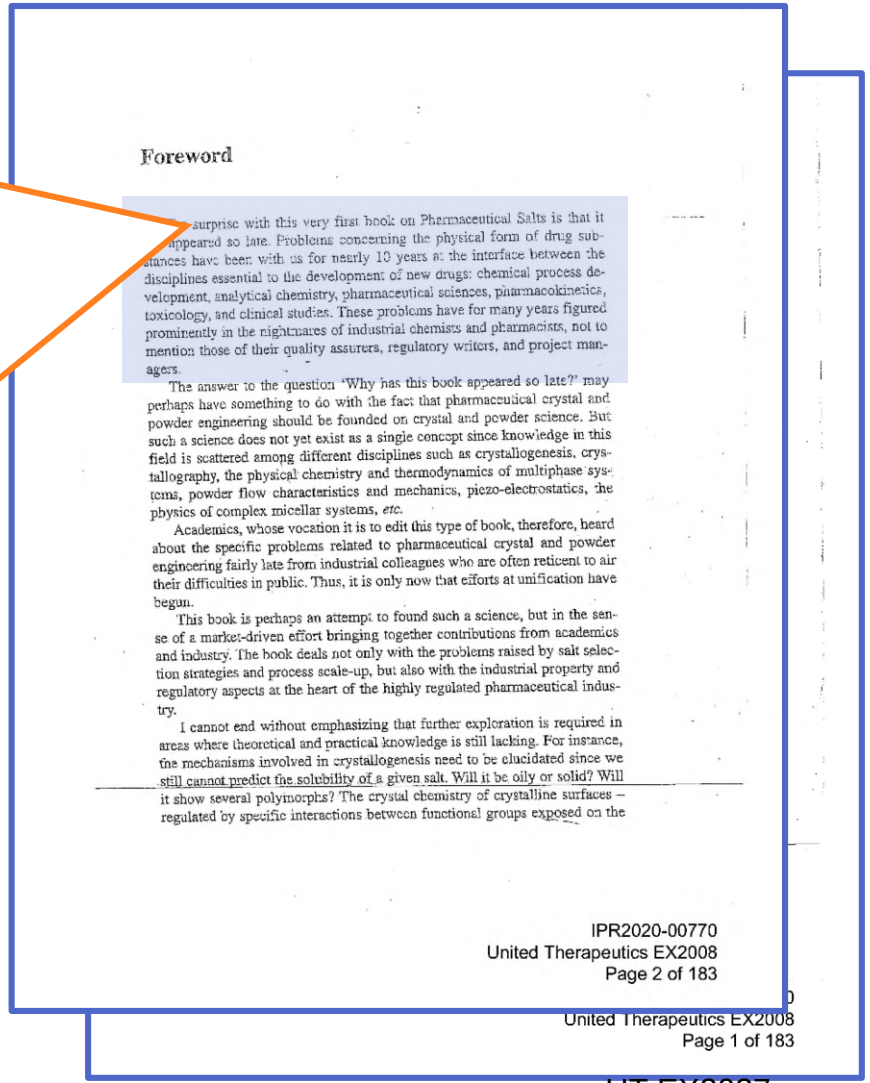
EX1002 (Winkler), ¶¶14-15; Paper 12 (POR), 24-26; Paper 25 (Sur-Reply), 13-16.

PROBLEMS IN THE ART ARE NOT ONES ORGANIC + MEDICINAL CHEMISTS KNOW HOW TO SOLVE

"Problems concerning the physical form of drug substances have been with us for nearly 10 years at the **interface between the disciplines essential to the development of new drugs: chemical process development, analytical chemistry, pharmaceutical sciences, pharmacokinetic, toxicology, and clinical studies**. These problems have for many years figured prominently in the **nightmares of industrial chemists and pharmacists**, not to mention those of their quality assurers, regulatory writers, and project managers."

- Stahl



Foreword

The surprise with this very first book on Pharmaceutical Salts is that it appeared so late. Problems concerning the physical form of drug substances have been with us for nearly 10 years at the interface between the disciplines essential to the development of new drugs: chemical process development, analytical chemistry, pharmaceutical sciences, pharmacokinetics, toxicology, and clinical studies. These problems have for many years figured prominently in the nightmares of industrial chemists and pharmacists, not to mention those of their quality assurers, regulatory writers, and project managers.

The answer to the question 'Why has this book appeared so late?' may perhaps have something to do with the fact that pharmaceutical crystal and powder engineering should be founded on crystal and powder science. But such a science does not yet exist as a single concept since knowledge in this field is scattered among different disciplines such as crystallogenesis, crystallography, the physical chemistry and thermodynamics of multiphase systems, powder flow characteristics and mechanics, piezo-electrostatics, the physics of complex micellar systems, *etc.*

Academics, whose vocation it is to edit this type of book, therefore, heard about the specific problems related to pharmaceutical crystal and powder engineering fairly late from industrial colleagues who are often reticent to air their difficulties in public. Thus, it is only now that efforts at unification have begun.

This book is perhaps an attempt to found such a science, but in the sense of a market-driven effort bringing together contributions from academics and industry. The book deals not only with the problems raised by salt selection strategies and process scale-up, but also with the industrial property and regulatory aspects at the heart of the highly regulated pharmaceutical industry.

I cannot end without emphasizing that further exploration is required in areas where theoretical and practical knowledge is still lacking. For instance, the mechanisms involved in crystallogenesis need to be elucidated since we still cannot predict the solubility of a given salt. Will it be oily or solid? Will it show several polymorphs? The crystal chemistry of crystalline surfaces – regulated by specific interactions between functional groups exposed on the

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EX2008 (Stahl), iv; Paper 1 (Petition), 25; Paper 12 (POR), 24-26; Paper 25 (Sur-Reply), 13-16; EX2002 (Pinal), ¶94.

PROBLEMS HERE ARE NOT ONES ACADEMICS KNOW HOW TO SOLVE

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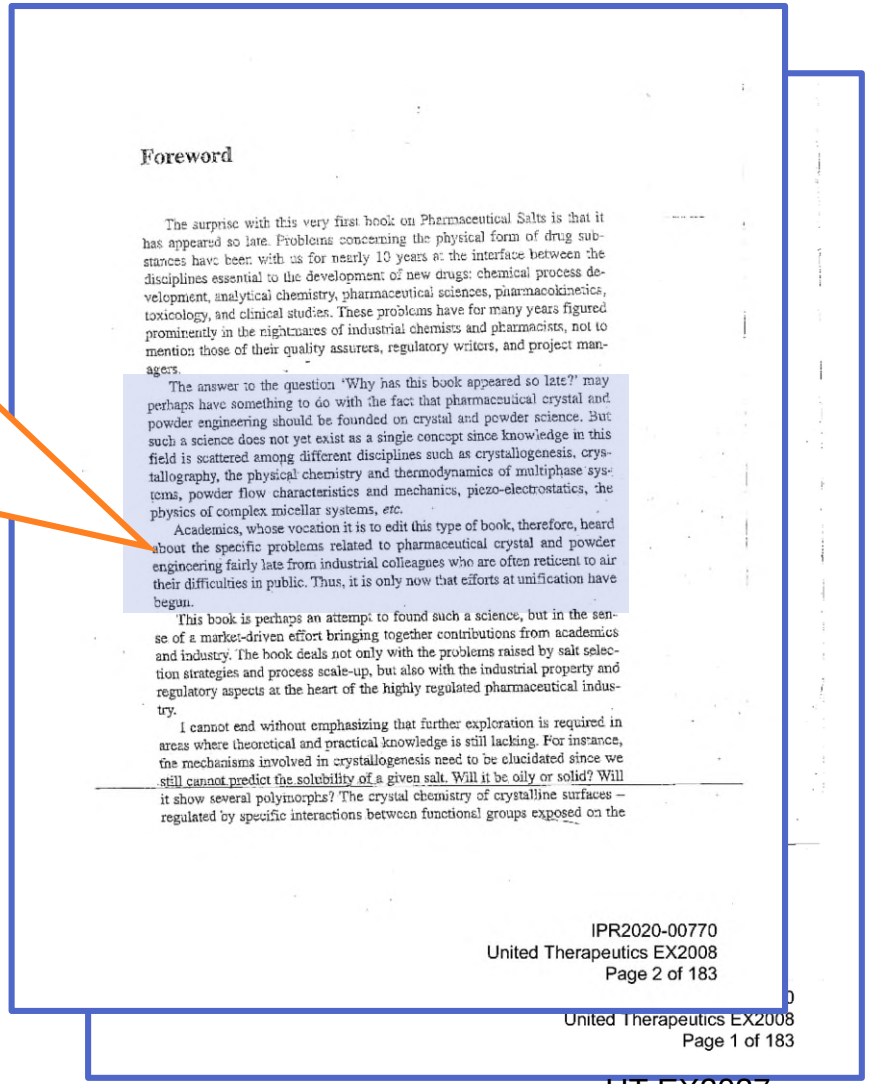
- Stahl



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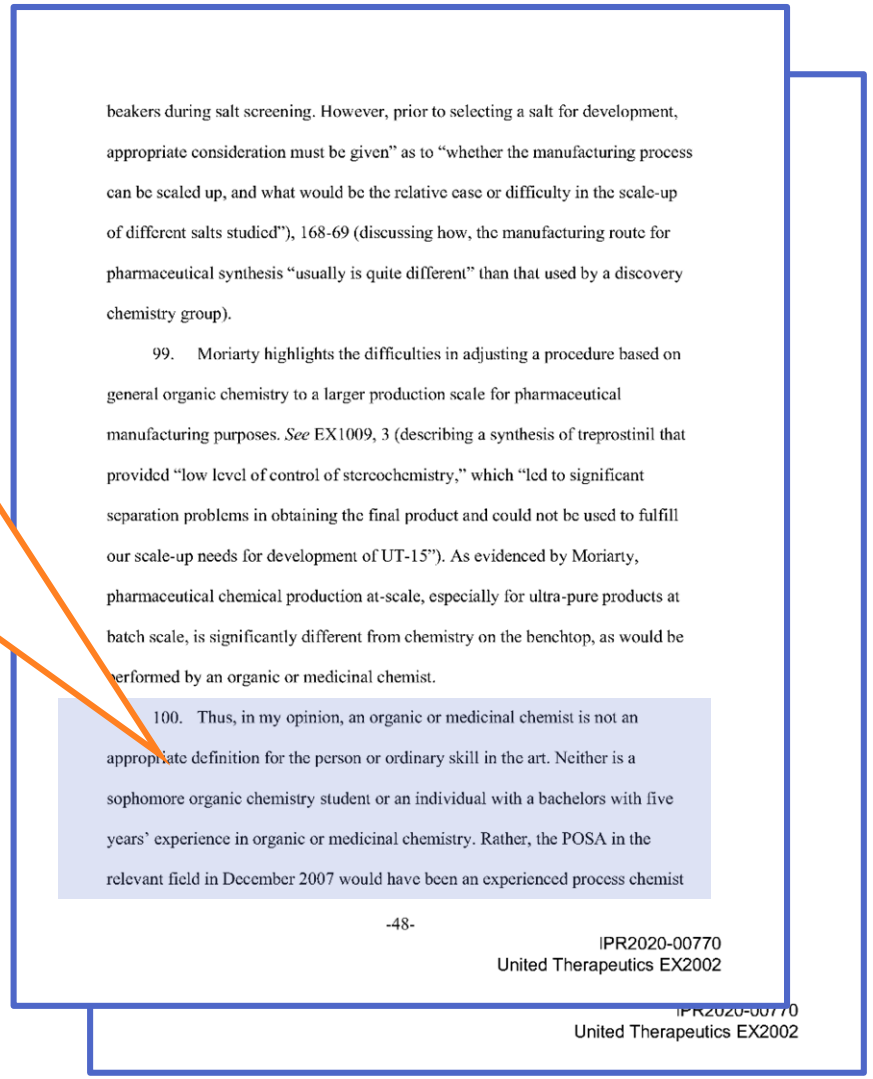
EX2008 (Stahl), iv; Paper 12 (POR), 24-26; Paper 25 (Sur-Reply), 13-16; EX2002 (Pinal), ¶94.

RELEVANT EVIDENCE SUPPORTS DR. PINAL'S CONCLUSIONS…

"[I]n my opinion, **an organic or medicinal chemist is not an appropriate definition for the person of ordinary skill in the art**. Neither is a sophomore organic chemistry student or an individual with a bachelors with five years' experience in organic chemistry."

- Dr. Pinal



beakers during salt screening. However, prior to selecting a salt for development, appropriate consideration must be given" as to "whether the manufacturing process can be scaled up, and what would be the relative ease or difficulty in the scale-up of different salts studied"), 168-69 (discussing how, the manufacturing route for pharmaceutical synthesis "usually is quite different" than that used by a discovery chemistry group).

99. Moriarty highlights the difficulties in adjusting a procedure based on general organic chemistry to a larger production scale for pharmaceutical manufacturing purposes. *See* EX1009, 3 (describing a synthesis of treprostinil that provided "low level of control of stereochemistry," which "led to significant separation problems in obtaining the final product and could not be used to fulfill our scale-up needs for development of UT-15"). As evidenced by Moriarty, pharmaceutical chemical production at-scale, especially for ultra-pure products at batch scale, is significantly different from chemistry on the benchtop, as would be performed by an organic or medicinal chemist.

100. Thus, in my opinion, an organic or medicinal chemist is not an appropriate definition for the person or ordinary skill in the art. Neither is a sophomore organic chemistry student or an individual with a bachelors with five years' experience in organic or medicinal chemistry. Rather, the POSA in the relevant field in December 2007 would have been an experienced process chemist

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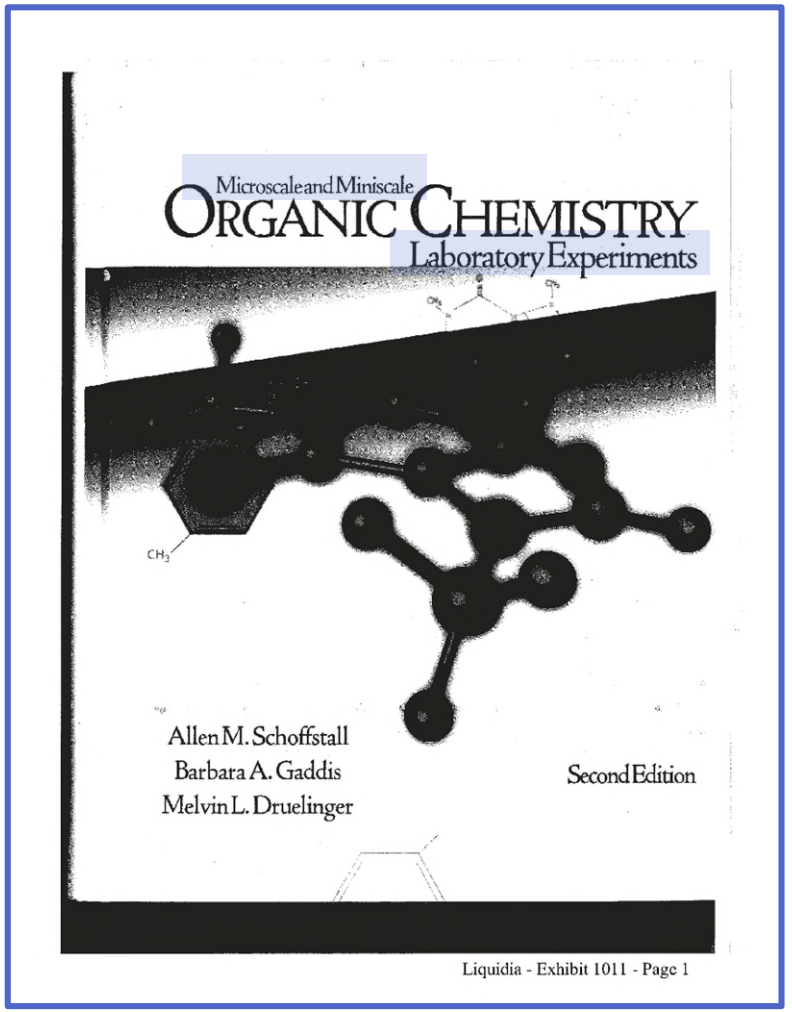
EX2002 (Pinal), ¶100; Paper 12 (POR), 22-27; Paper 25 (Sur-Reply), 13-16.

…DR. WINKLER'S OPINION LACKS SUPPORT

- Dr. Winkler does not cite a single piece of evidence (except for his own CV) in rendering his opinion on the level of ordinary skill in the art.

- Instead, he makes references elsewhere to undergraduate textbooks on micro and miniscale laboratory experiments and dismisses the technology of the '901 patent as "organic chemistry 101."



EX1002 (Winkler), ¶¶14-17 (POSA definition); *id.*, ¶¶5, 47 (organic chemistry 101); Paper 6 (POPR), 56-57; Paper 12 (POR), 22-27; EX2002 (Pinal), ¶¶21-27, 80, 84-85, 88, 90-101, 141, 202-07.

THE EXPERTS' CONTRASTING EXPERIENCE

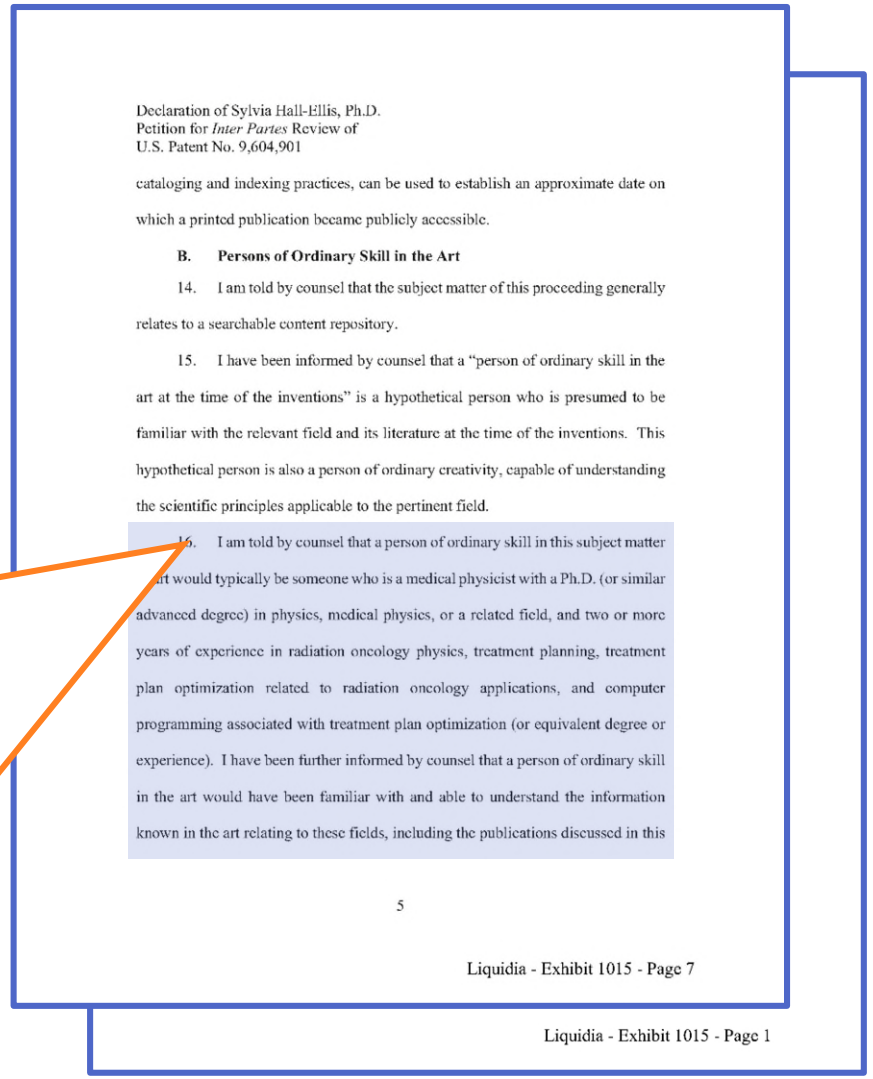
Dr. Rodolfo Pinal	Dr. Jeffrey Winkler
▪ **Ph.D. in Pharmaceutical Sciences** ▪ Associate Professor, Department of Industrial and Physical Pharmacy at Purdue University ▪ Director of Purdue's Center for Pharmaceutical Processing Research ▪ 30+ years studying formulation science ▪ **13+ years in pharmaceutical industry** – Research Associate + Senior Scientist in pre-formulation – Principal Scientist in sterile dosage forms – Principal Scientist + Research Leader in solid state pharmaceutics – Extensive work with process chemists in the chemical synthesis department's Kilo Lab.	▪ **Ph.D. in Chemistry** – 35+ years of experience in academia – Focuses on development of new synthetic organic methodology and natural product synthesis – "an expert in the field of organic chemistry" ▪ **Submitted unsworn "declaration" that merely copied the attorney argument in the Petition** – Testimony riddled with scientific errors and inaccuracies ▪ **Evasive and unresponsive at depositions**

Paper 12 (POR), 22-27; EX2002 (Pinal); EX2026 (Winkler Depo #1); 47:12-20; Paper 6 (POPR), 29-30.

DR. HALL-ELLIS'S BIZARRE POSA DEFINITION

A POSA "would typically be someone who is a **medical physicist** with a Ph.D. (or similar advanced degree) in **physics, medical physics**, or a related field, and two or more years of experience in **radiation oncology physics, treatment planning, treatment plan optimization related to radiation oncology applications, and computer programming associated with treatment plan optimization**."

- Dr. Hall Ellis



Declaration of Sylvia Hall-Ellis, Ph.D.
Petition for *Inter Partes* Review of
U.S. Patent No. 9,604,901

cataloging and indexing practices, can be used to establish an approximate date on which a printed publication became publicly accessible.

B. Persons of Ordinary Skill in the Art

14. I am told by counsel that the subject matter of this proceeding generally relates to a searchable content repository.

15. I have been informed by counsel that a "person of ordinary skill in the art at the time of the inventions" is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the inventions. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

16. I am told by counsel that a person of ordinary skill in this subject matter art would typically be someone who is a medical physicist with a Ph.D. (or similar advanced degree) in physics, medical physics, or a related field, and two or more years of experience in radiation oncology physics, treatment planning, treatment plan optimization related to radiation oncology applications, and computer programming associated with treatment plan optimization (or equivalent degree or experience). I have been further informed by counsel that a person of ordinary skill in the art would have been familiar with and able to understand the information known in the art relating to these fields, including the publications discussed in this

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Liquidia - Exhibit 1015 - Page 7

Liquidia - Exhibit 1015 - Page 1

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EX1015 (Hall-Ellis), ¶16; Paper 6 (POPR), 55; Paper 25 (Sur-Reply), 13-16.

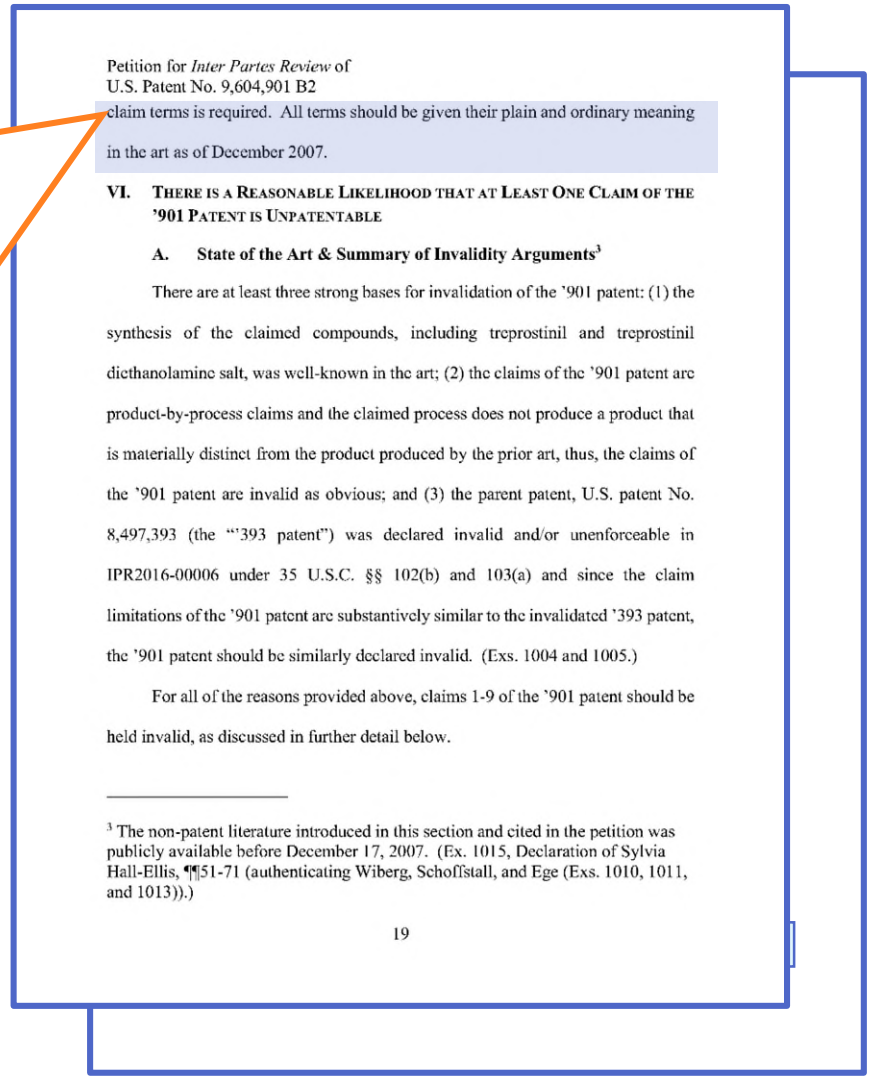
CLAIM CONSTRUCTION

LIQUIDIA OFFERED NO CONSTRUCTIONS

"The petition must set forth: … (3) **How the challenged claim is to be construed**."

- *37 C.F.R. §42.1-4(b)(3)*

"For purposes of resolving this IPR, **Petitioner does not believe construction of claim terms is required**." - Liquidia



Petition for *Inter Partes Review* of
U.S. Patent No. 9,604,901 B2

claim terms is required. All terms should be given their plain and ordinary meaning in the art as of December 2007.

VI. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '901 PATENT IS UNPATENTABLE

A. State of the Art & Summary of Invalidity Arguments[3]

There are at least three strong bases for invalidation of the '901 patent: (1) the synthesis of the claimed compounds, including treprostinil and treprostinil diethanolamine salt, was well-known in the art; (2) the claims of the '901 patent are product-by-process claims and the claimed process does not produce a product that is materially distinct from the product produced by the prior art, thus, the claims of the '901 patent are invalid as obvious; and (3) the parent patent, U.S. patent No. 8,497,393 (the "'393 patent") was declared invalid and/or unenforceable in IPR2016-00006 under 35 U.S.C. §§ 102(b) and 103(a) and since the claim limitations of the '901 patent are substantively similar to the invalidated '393 patent, the '901 patent should be similarly declared invalid. (Exs. 1004 and 1005.)

For all of the reasons provided above, claims 1-9 of the '901 patent should be held invalid, as discussed in further detail below.

[3] The non-patent literature introduced in this section and cited in the petition was publicly available before December 17, 2007. (Ex. 1015, Declaration of Sylvia Hall-Ellis, ¶¶51-71 (authenticating Wiberg, Schoffstall, and Ege (Exs. 1010, 1011, and 1013)).)

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Paper 1 (Petition), 18-19; Paper 6 (POPR), 7; Paper 12 (POR), 8.

LIQUIDIA'S EVER-CHANGING MOODS

Claim Term	Liquidia's IPR Construction	Liquidia's District Court Construction
▪ Pharmaceutical Batch (claims 1-4, 6, and 8)	▪ No construction required	▪ "Pharmaceutical batch made according to the process recited in steps (a) – (d) and optionally (e), wherein no purification steps appear between alkylation and salt formation"
▪ Contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil	▪ No construction required	▪ "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, wherein the salt is formed without isolation of treprostinil after alkylation and hydrolysis"
▪ Ambient temperature (claim 6)	▪ No construction required	▪ "Room temperature or, on average 25˚ C"
▪ Storing/Storage (claim 6)	▪ No construction required	▪ Indefinite

Paper 1 (Petition), 18-19; EX1053 (Markman Transcript); Paper 38 (Petitioner's Motion to Submit Supplemental Evidence), 6-8.

THE BOARD FOLLOWED UT'S CONSTRUCTION FOR FOUR TERMS

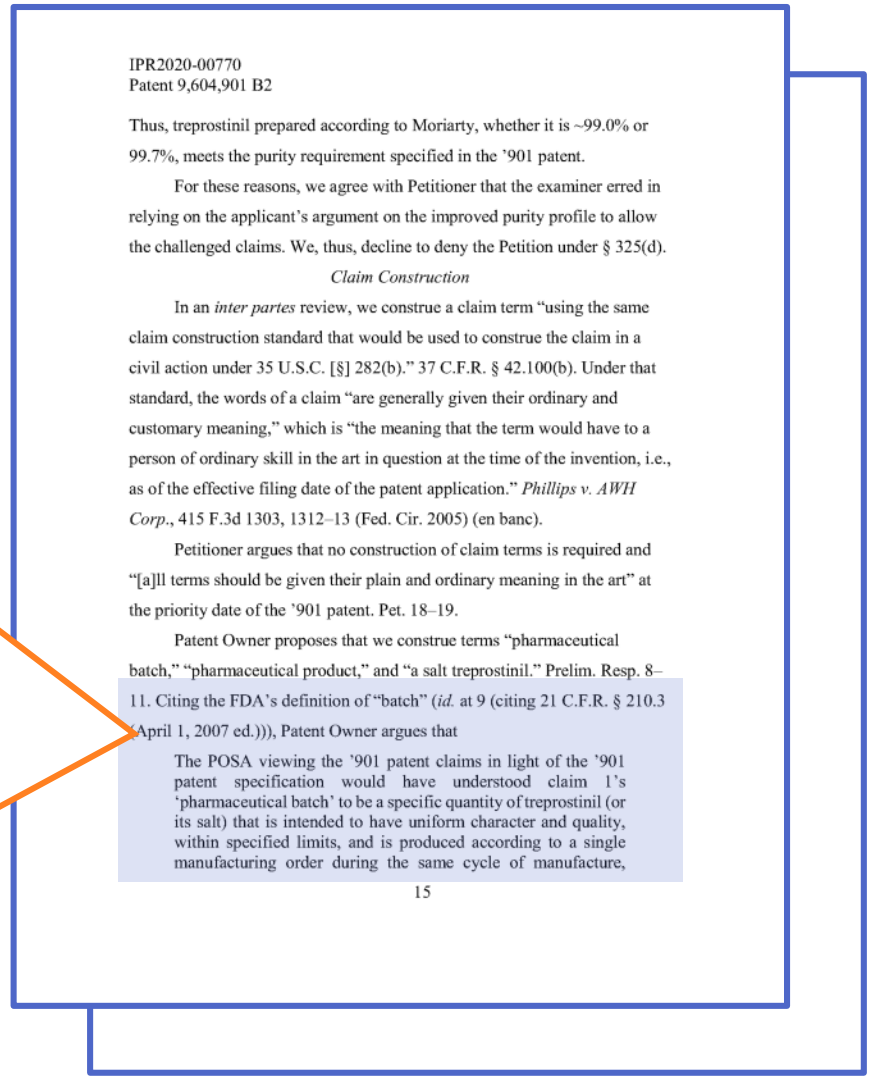
- Pharmaceutical Batch
- Pharmaceutical Product
- Storing/Storage
- A Salt Treprostinil

Paper 7 (Institution Decision), 15-17; Paper 6 (POPR), 6-11.

THE BOARD'S PHARMACEUTICAL BATCH CONSTRUCTION

"[A] specific quantity of treprostinil (or its salt) that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture, wherein the **uniform character and quality** is such that it still contains impurities resulting from the method by which it is produced."

- Institution Decision



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Thus, treprostinil prepared according to Moriarty, whether it is ~99.0% or 99.7%, meets the purity requirement specified in the '901 patent.

For these reasons, we agree with Petitioner that the examiner erred in relying on the applicant's argument on the improved purity profile to allow the challenged claims. We, thus, decline to deny the Petition under § 325(d).

Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Petitioner argues that no construction of claim terms is required and "[a]ll terms should be given their plain and ordinary meaning in the art" at the priority date of the '901 patent. Pet. 18–19.

Patent Owner proposes that we construe terms "pharmaceutical batch," "pharmaceutical product," and "a salt treprostinil." Prelim. Resp. 8–11. Citing the FDA's definition of "batch" (*id.* at 9 (citing 21 C.F.R. § 210.3 (April 1, 2007 ed.))), Patent Owner argues that

> The POSA viewing the '901 patent claims in light of the '901 patent specification would have understood claim 1's 'pharmaceutical batch' to be a specific quantity of treprostinil (or its salt) that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture,

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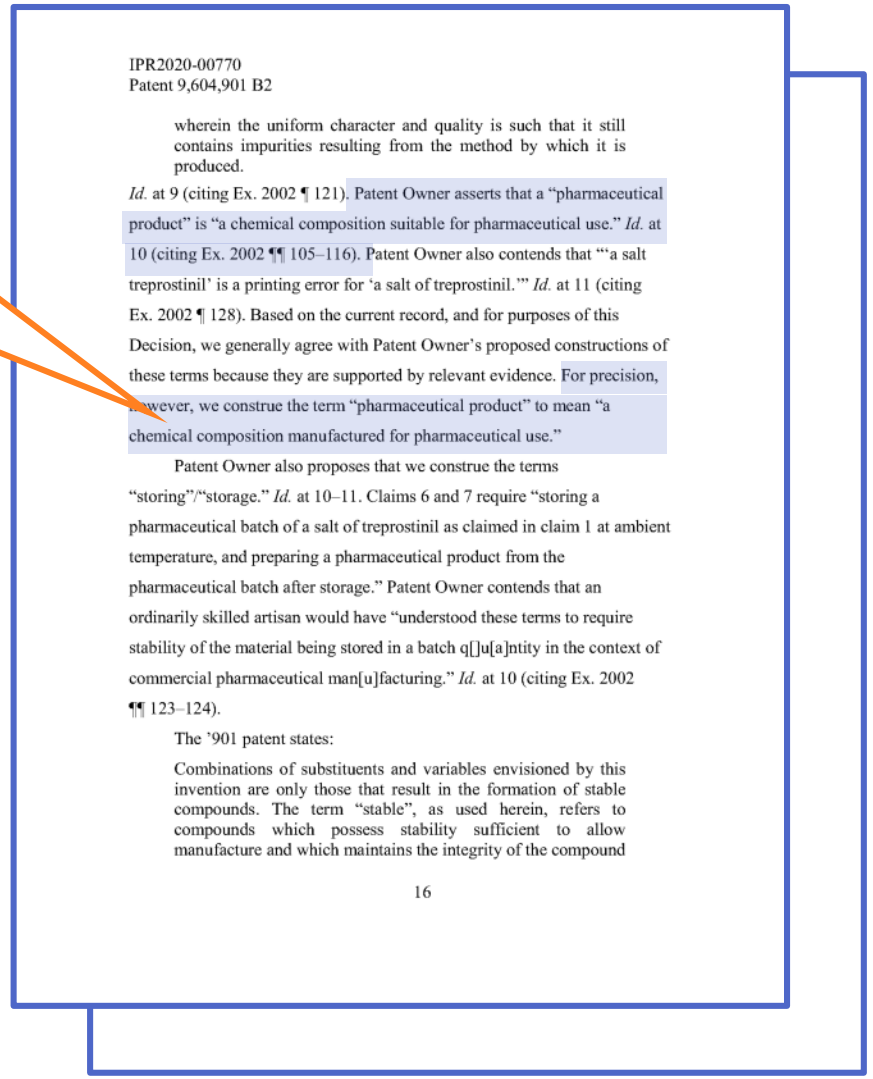
Paper 7 (Institution Decision), 15-16; Paper 12 (POR), 9-10; EX2025 (Pinal Response), ¶¶75-79.

THE BOARD'S PHARMACEUTICAL PRODUCT CONSTRUCTION

"[A] chemical composition manufactured for pharmaceutical use." - Institution Decision



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> wherein the uniform character and quality is such that it still contains impurities resulting from the method by which it is produced.

Id. at 9 (citing Ex. 2002 ¶ 121). Patent Owner asserts that a "pharmaceutical product" is "a chemical composition suitable for pharmaceutical use." *Id.* at 10 (citing Ex. 2002 ¶¶ 105–116). Patent Owner also contends that "'a salt treprostinil' is a printing error for 'a salt of treprostinil.'" *Id.* at 11 (citing Ex. 2002 ¶ 128). Based on the current record, and for purposes of this Decision, we generally agree with Patent Owner's proposed constructions of these terms because they are supported by relevant evidence. For precision, however, we construe the term "pharmaceutical product" to mean "a chemical composition manufactured for pharmaceutical use."

Patent Owner also proposes that we construe the terms "storing"/"storage." *Id.* at 10–11. Claims 6 and 7 require "storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage." Patent Owner contends that an ordinarily skilled artisan would have "understood these terms to require stability of the material being stored in a batch q[]u[a]ntity in the context of commercial pharmaceutical man[u]facturing." *Id.* at 10 (citing Ex. 2002 ¶¶ 123–124).

The '901 patent states:

> Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound

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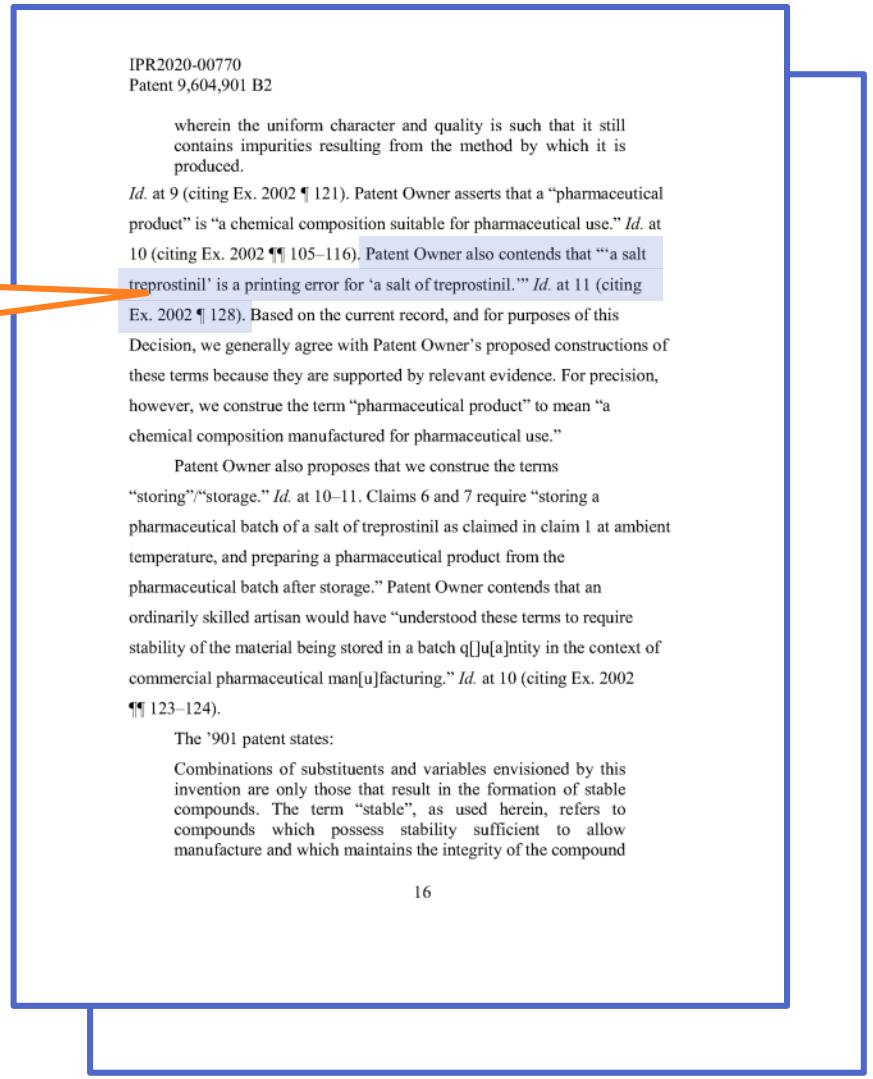
Paper 7 (Institution Decision), 15-16; Paper 6 (POPR), 9-10; Paper 12 (POR), 10-11; EX2025 (Pinal Response), ¶¶71-74.

THE BOARD'S A SALT TREPROSTINIL CONSTRUCTION

"[A] salt of treprostinil." - Institution Decision



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wherein the uniform character and quality is such that it still contains impurities resulting from the method by which it is produced.

Id. at 9 (citing Ex. 2002 ¶ 121). Patent Owner asserts that a "pharmaceutical product" is "a chemical composition suitable for pharmaceutical use." *Id.* at 10 (citing Ex. 2002 ¶¶ 105–116). Patent Owner also contends that "'a salt treprostinil' is a printing error for 'a salt of treprostinil.'" *Id.* at 11 (citing Ex. 2002 ¶ 128). Based on the current record, and for purposes of this Decision, we generally agree with Patent Owner's proposed constructions of these terms because they are supported by relevant evidence. For precision, however, we construe the term "pharmaceutical product" to mean "a chemical composition manufactured for pharmaceutical use."

Patent Owner also proposes that we construe the terms "storing"/"storage." *Id.* at 10–11. Claims 6 and 7 require "storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage." Patent Owner contends that an ordinarily skilled artisan would have "understood these terms to require stability of the material being stored in a batch q[]u[a]ntity in the context of commercial pharmaceutical man[u]facturing." *Id.* at 10 (citing Ex. 2002 ¶¶ 123–124).

The '901 patent states:

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound

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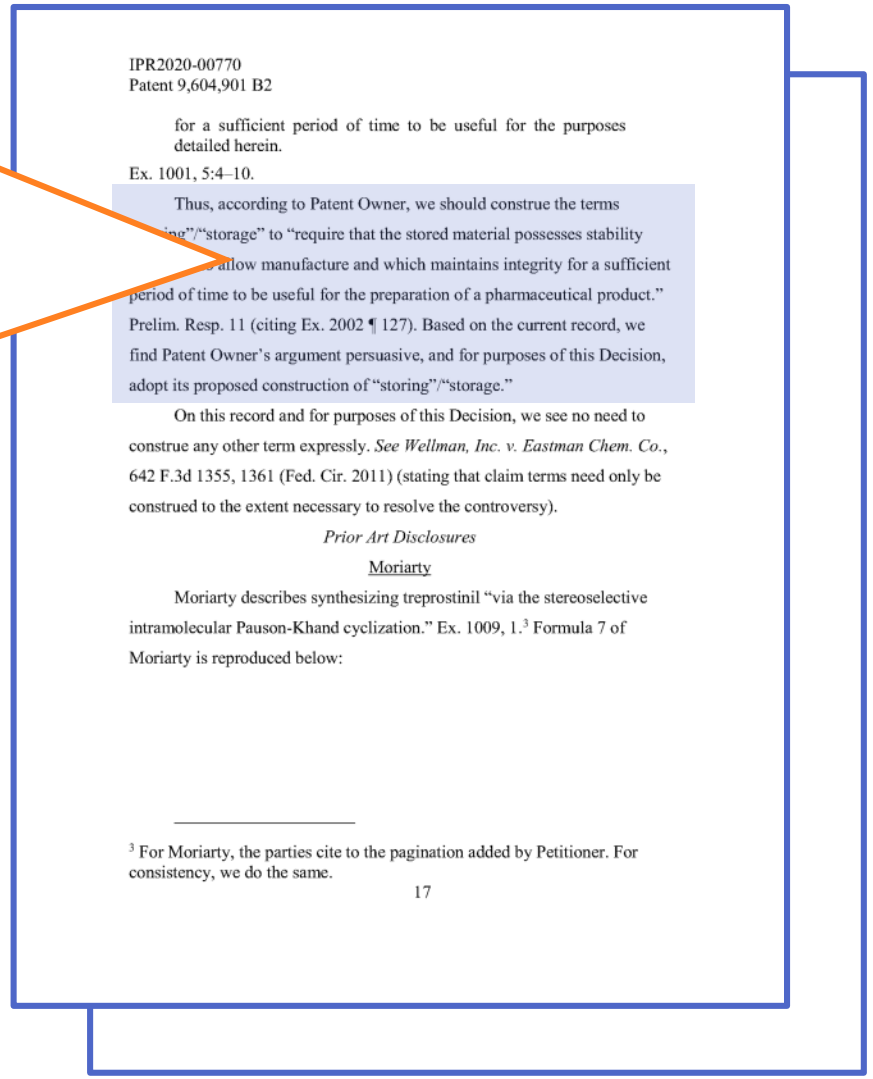
Paper 7 (Institution Decision), 15-16; Paper 12 (POR), 12; EX2025 (Pinal Response), ¶80.

THE BOARD'S STORING/STORAGE CONSTRUCTION

Requiring "stability of the material being stored in a batch quantity in the context of commercial pharmaceutical manufacturing" and "that the **stored material possesses stability** sufficient to allow manufacture and which maintains integrity for a sufficient period of time to be useful for the preparation of a pharmaceutical product."

- Institution Decision



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for a sufficient period of time to be useful for the purposes detailed herein.

Ex. 1001, 5:4–10.

Thus, according to Patent Owner, we should construe the terms "storing"/"storage" to "require that the stored material possesses stability sufficient to allow manufacture and which maintains integrity for a sufficient period of time to be useful for the preparation of a pharmaceutical product." Prelim. Resp. 11 (citing Ex. 2002 ¶ 127). Based on the current record, we find Patent Owner's argument persuasive, and for purposes of this Decision, adopt its proposed construction of "storing"/"storage."

On this record and for purposes of this Decision, we see no need to construe any other term expressly. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating that claim terms need only be construed to the extent necessary to resolve the controversy).

Prior Art Disclosures

Moriarty

Moriarty describes synthesizing treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1009, 1.[3] Formula 7 of Moriarty is reproduced below:

[3] For Moriarty, the parties cite to the pagination added by Petitioner. For consistency, we do the same.

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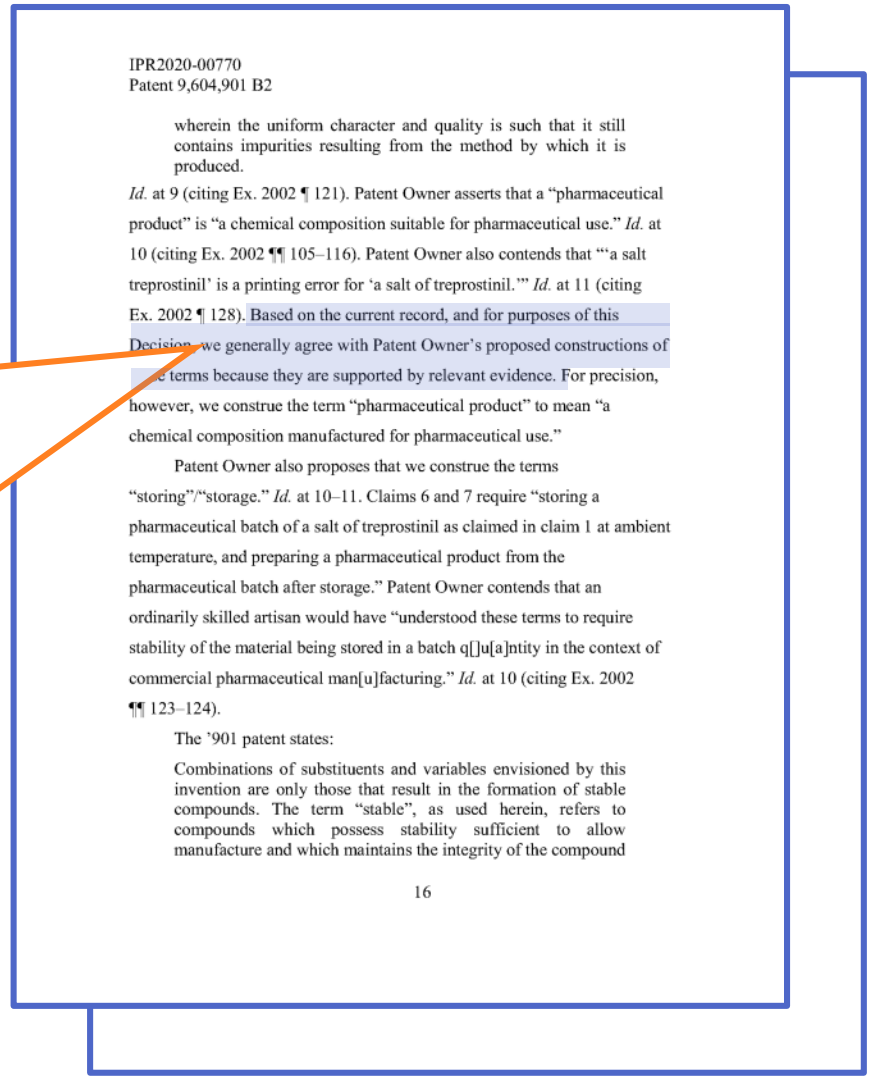
Paper 7 (Institution Decision), 16-17; Paper 12 (POR), 11-12; EX2025 (Pinal Response), ¶¶81-83.

RELEVANT EVIDENCE SUPPORTS UT'S POSITIONS

"Based on the current record, and for the purposes of this decision, we generally agree with Patent Owner's proposed constructions of these terms because **they are supported by relevant evidence**."

- Institution Decision



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wherein the uniform character and quality is such that it still contains impurities resulting from the method by which it is produced.

Id. at 9 (citing Ex. 2002 ¶ 121). Patent Owner asserts that a "pharmaceutical product" is "a chemical composition suitable for pharmaceutical use." *Id.* at 10 (citing Ex. 2002 ¶¶ 105–116). Patent Owner also contends that "'a salt treprostinil' is a printing error for 'a salt of treprostinil.'" *Id.* at 11 (citing Ex. 2002 ¶ 128). Based on the current record, and for purposes of this Decision, we generally agree with Patent Owner's proposed constructions of these terms because they are supported by relevant evidence. For precision, however, we construe the term "pharmaceutical product" to mean "a chemical composition manufactured for pharmaceutical use."

Patent Owner also proposes that we construe the terms "storing"/"storage." *Id.* at 10–11. Claims 6 and 7 require "storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage." Patent Owner contends that an ordinarily skilled artisan would have "understood these terms to require stability of the material being stored in a batch q[]u[a]ntity in the context of commercial pharmaceutical man[u]facturing." *Id.* at 10 (citing Ex. 2002 ¶¶ 123–124).

The '901 patent states:

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound

16

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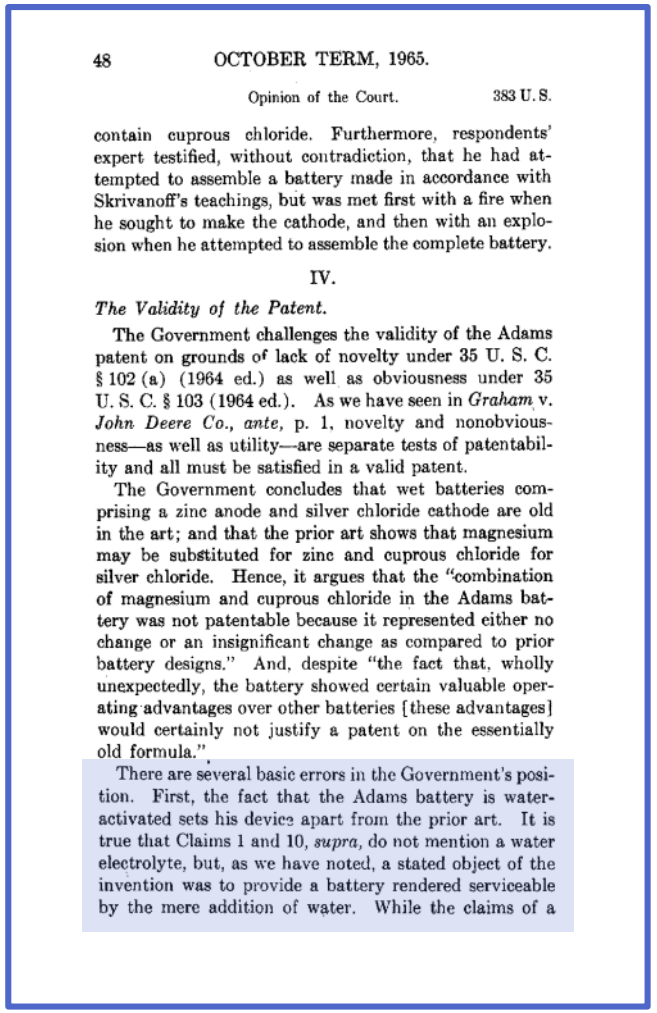
Paper 7 (Institution Decision), 15-16; Paper 12 (POR), 8-16; EX2025 (Pinal Response), ¶¶71-83.

UT'S CONSTRUCTIONS FOLLOW FROM THE SPECIFICATION

"[I]t is fundamental that **claims are to be construed in the light of the specifications**, and both are to be read with a view to ascertaining the invention."

- *United States v. Adams*, 383 U.S. 39, 48-49 (1966).



48 OCTOBER TERM, 1965.

Opinion of the Court. 383 U. S.

contain cuprous chloride. Furthermore, respondents' expert testified, without contradiction, that he had attempted to assemble a battery made in accordance with Skrivanoff's teachings, but was met first with a fire when he sought to make the cathode, and then with an explosion when he attempted to assemble the complete battery.

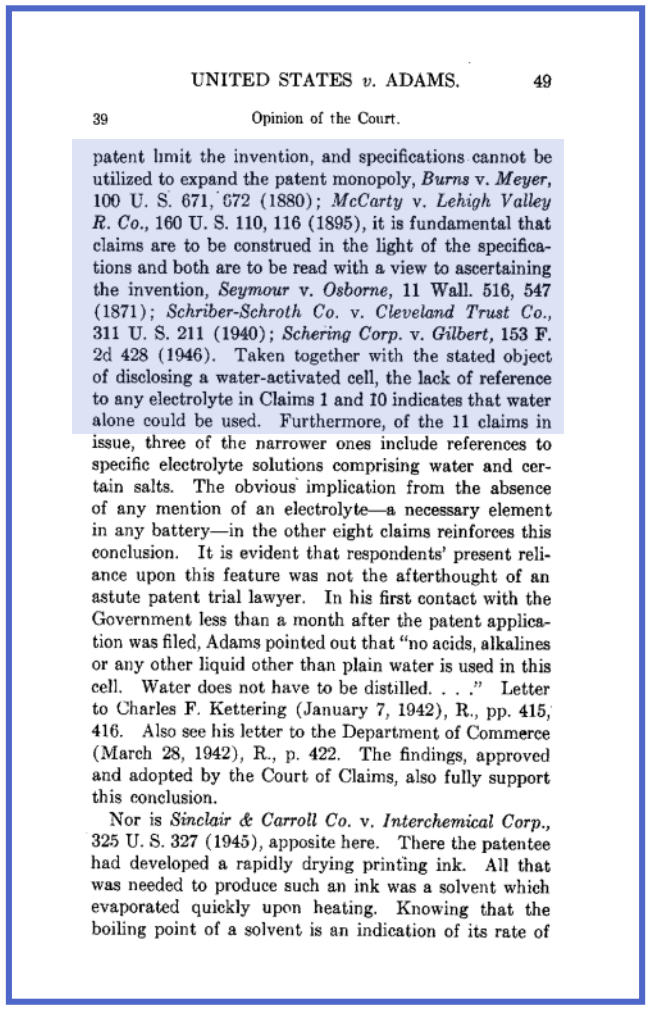
IV.

The Validity of the Patent.

The Government challenges the validity of the Adams patent on grounds of lack of novelty under 35 U. S. C. § 102 (a) (1964 ed.) as well as obviousness under 35 U. S. C. § 103 (1964 ed.). As we have seen in *Graham* v. *John Deere Co.*, *ante*, p. 1, novelty and nonobviousness—as well as utility—are separate tests of patentability and all must be satisfied in a valid patent.

The Government concludes that wet batteries comprising a zinc anode and silver chloride cathode are old in the art; and that the prior art shows that magnesium may be substituted for zinc and cuprous chloride for silver chloride. Hence, it argues that the "combination of magnesium and cuprous chloride in the Adams battery was not patentable because it represented either no change or an insignificant change as compared to prior battery designs." And, despite "the fact that, wholly unexpectedly, the battery showed certain valuable operating advantages over other batteries [these advantages] would certainly not justify a patent on the essentially old formula."

There are several basic errors in the Government's position. First, the fact that the Adams battery is water-activated sets his device apart from the prior art. It is true that Claims 1 and 10, *supra*, do not mention a water electrolyte, but, as we have noted, a stated object of the invention was to provide a battery rendered serviceable by the mere addition of water. While the claims of a



UNITED STATES *v.* ADAMS. 49

39 Opinion of the Court.

patent limit the invention, and specifications cannot be utilized to expand the patent monopoly, *Burns* v. *Meyer*, 100 U. S. 671, 672 (1880); *McCarty* v. *Lehigh Valley R. Co.*, 160 U. S. 110, 116 (1895), it is fundamental that claims are to be construed in the light of the specifications and both are to be read with a view to ascertaining the invention, *Seymour* v. *Osborne*, 11 Wall. 516, 547 (1871); *Schriber-Schroth Co.* v. *Cleveland Trust Co.*, 311 U. S. 211 (1940); *Schering Corp.* v. *Gilbert*, 153 F. 2d 428 (1946). Taken together with the stated object of disclosing a water-activated cell, the lack of reference to any electrolyte in Claims 1 and 10 indicates that water alone could be used. Furthermore, of the 11 claims in issue, three of the narrower ones include references to specific electrolyte solutions comprising water and certain salts. The obvious implication from the absence of any mention of an electrolyte—a necessary element in any battery—in the other eight claims reinforces this conclusion. It is evident that respondents' present reliance upon this feature was not the afterthought of an astute patent trial lawyer. In his first contact with the Government less than a month after the patent application was filed, Adams pointed out that "no acids, alkalines or any other liquid other than plain water is used in this cell. Water does not have to be distilled. . . ." Letter to Charles F. Kettering (January 7, 1942), R., pp. 415, 416. Also see his letter to the Department of Commerce (March 28, 1942), R., p. 422. The findings, approved and adopted by the Court of Claims, also fully support this conclusion.

Nor is *Sinclair & Carroll Co.* v. *Interchemical Corp.*, 325 U. S. 327 (1945), apposite here. There the patentee had developed a rapidly drying printing ink. All that was needed to produce such an ink was a solvent which evaporated quickly upon heating. Knowing that the boiling point of a solvent is an indication of its rate of

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Paper 6 (POPR), 6-7; Paper 12 (POR), 8.

LIQUIDIA TAKES SHORTCUTS USING THE ’393 IPR

LIQUIDIA DOES NOT ANALYZE THE CLAIMS AS A WHOLE

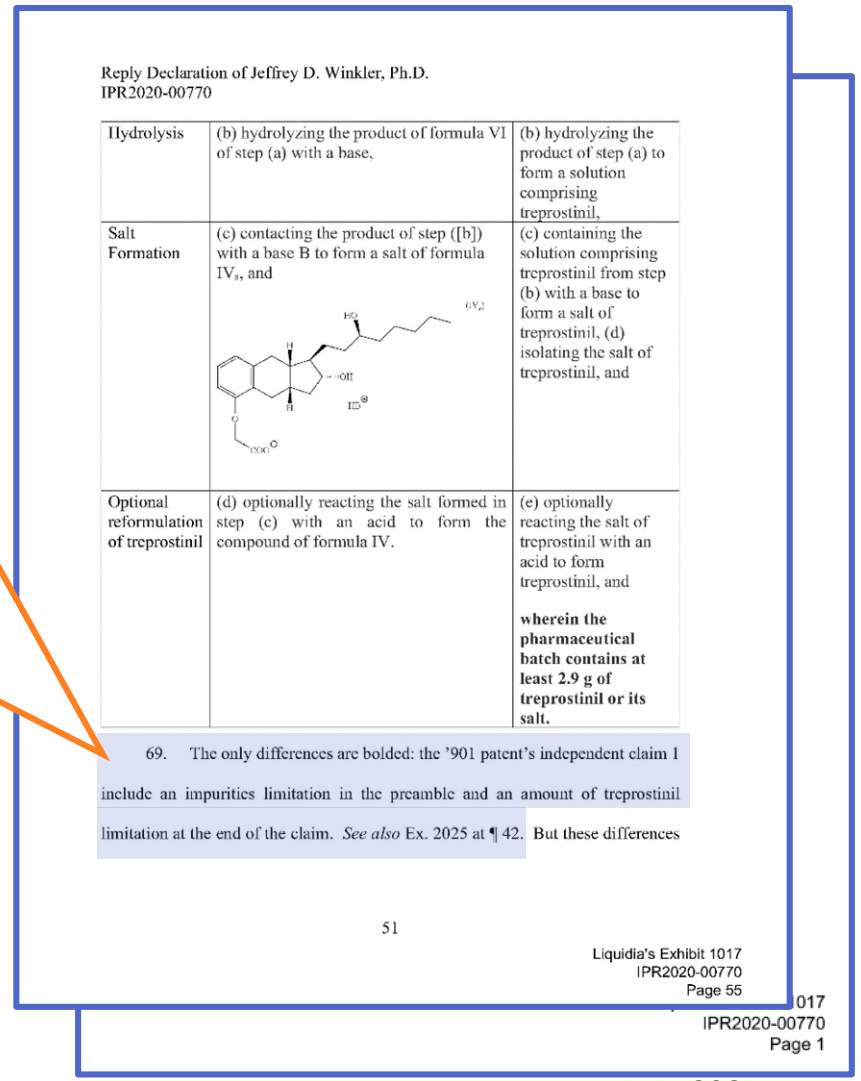
- Liquidia and Dr. Winkler identified and then considered only two differences from the ’393 patent claims.
- Liquidia and Dr. Winkler decided that those differences were “immaterial.”
- Therefore, they say, the ’393 patent IPR Final Written Decision controls.

Paper 25 (Sur-Reply), 4-5; *see* Paper 1 (Petition), 4-8, 19; EX1002 (Winkler), ¶¶36-37; Paper 15 (Reply), 1, 10-12; EX1017 (Winkler Reply), ¶¶24, 39-40, 64-73, 128.

LIQUIDIA + DR. WINKLER FOCUS ON "DIFFERENCES," NOT EACH CLAIM AS A WHOLE

"**The only differences are** bolded: the '901 patent's independent claim 1 includes **an impurities limitation** in the preamble **and an amount of treprostinil** limitation at the end of the claim."

- Dr. Winkler



Reply Declaration of Jeffrey D. Winkler, Ph.D.
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Hydrolysis	(b) hydrolyzing the product of formula VI of step (a) with a base,	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,
Salt Formation	(c) contacting the product of step ([b]) with a base B to form a salt of formula IV_a, and	(c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and
Optional reformulation of treprostinil	(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and **wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.**

69. The only differences are bolded: the '901 patent's independent claim 1 include an impurities limitation in the preamble and an amount of treprostinil limitation at the end of the claim. *See also* Ex. 2025 at ¶ 42. But these differences

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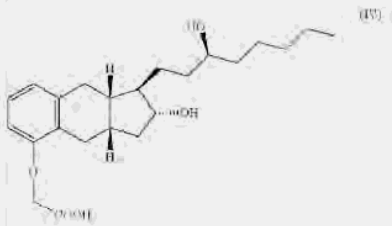
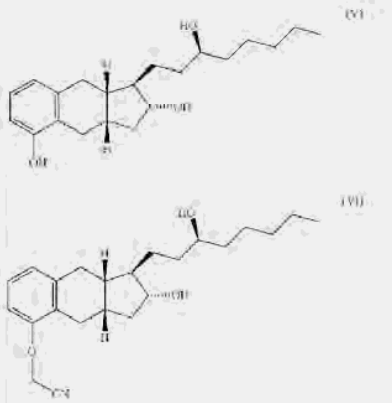
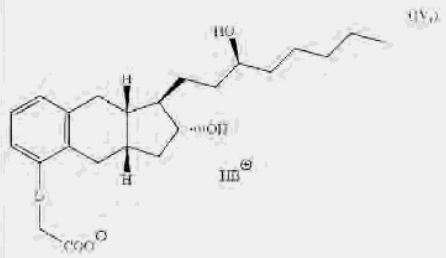
EX1017 (Winkler Reply), ¶69; Paper 15 (Reply), 11-12; Paper 25 (Sur-Reply), 4-5.

LIQUIDIA + DR. WINKLER FOCUS ON "DIFFERENCES," NOT EACH CLAIM AS A WHOLE

Limitation	'393 Patent Claim 9[6]	'901 Patent Claim 1
A product of treprostinil or a salt thereof	A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A pharmaceutical batch consisting of treprostinil or a salt thereof and **impurities resulting from**
Alkylation of benzindene triol	(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	(a) alkylating a benzindene triol,

Hydrolysis	(b) hydrolyzing the product of formula VI of step (a) with a base,	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,
Salt Formation	(c) contacting the product of step ([b]) with a base B to form a salt of formula IV_s, and 	(c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and
Optional reformulation of treprostinil	(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and **wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.**

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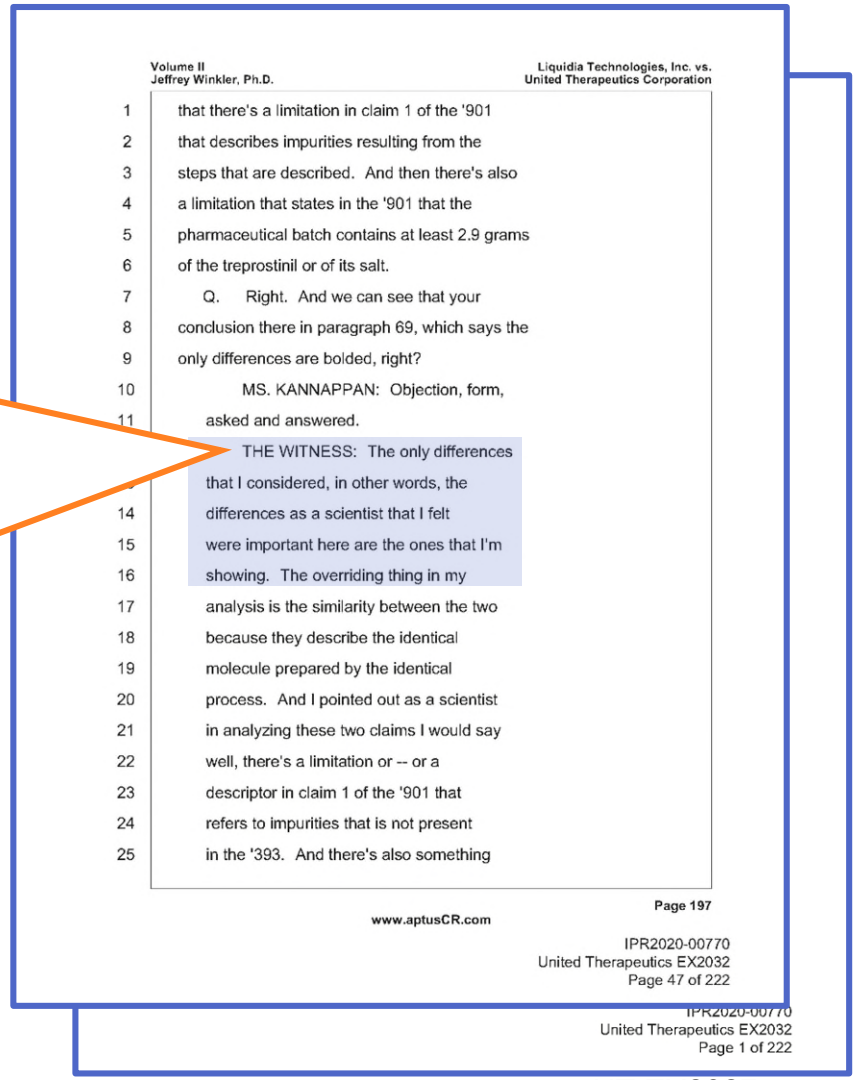
Paper 25 (Sur-Reply), 4-5; *see* Paper 15 (Reply), 11-12; EX1017 (Winkler Reply), ¶¶68-69.

DR. WINKLER ONLY CONSIDERS TWO CLAIM LIMITATIONS

"**The only differences that I considered**, in other words, the differences as a scientist that I felt were important here **are the ones that I'm showing**."

- Dr. Winkler



Volume II
Jeffrey Winkler, Ph.D.

Liquidia Technologies, Inc. vs.
United Therapeutics Corporation

that there's a limitation in claim 1 of the '901 that describes impurities resulting from the steps that are described. And then there's also a limitation that states in the '901 that the pharmaceutical batch contains at least 2.9 grams of the treprostinil or of its salt.

Q. Right. And we can see that your conclusion there in paragraph 69, which says the only differences are bolded, right?

MS. KANNAPPAN: Objection, form, asked and answered.

THE WITNESS: The only differences that I considered, in other words, the differences as a scientist that I felt were important here are the ones that I'm showing. The overriding thing in my analysis is the similarity between the two because they describe the identical molecule prepared by the identical process. And I pointed out as a scientist in analyzing these two claims I would say well, there's a limitation or -- or a descriptor in claim 1 of the '901 that refers to impurities that is not present in the '393. And there's also something

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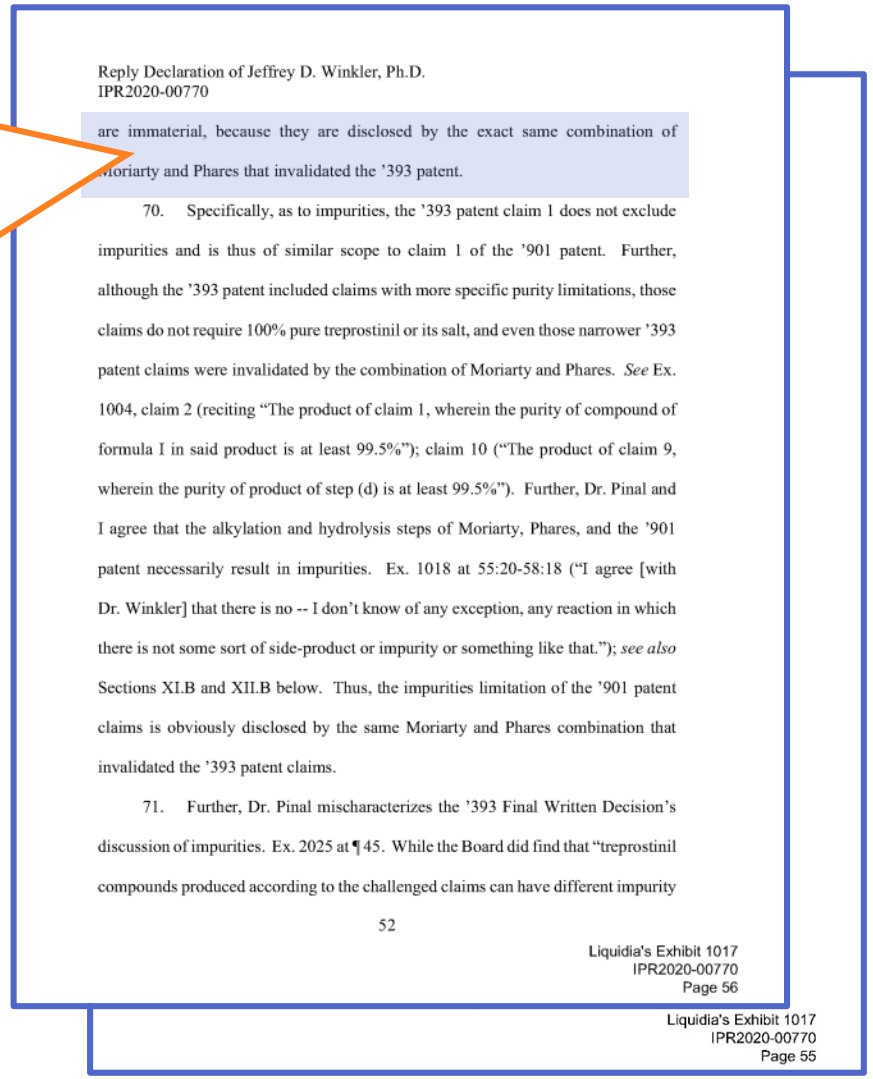
EX2032 (Winkler Depo #2), 194:20-198:4; Paper 25 (Sur-Reply), 4-5.

DR. WINKLER CONSIDERS EVEN THESE TWO LIMITATIONS "IMMATERIAL"

"[T]hese differences are immaterial, because they are disclosed by the exact same combination of Moriarty and Phares that invalidated the '393 patent."

- Dr. Winkler

...but a closer look shows even these limitations are not taught by the asserted art.



Reply Declaration of Jeffrey D. Winkler, Ph.D.
IPR2020-00770

are immaterial, because they are disclosed by the exact same combination of Moriarty and Phares that invalidated the '393 patent.

70. Specifically, as to impurities, the '393 patent claim 1 does not exclude impurities and is thus of similar scope to claim 1 of the '901 patent. Further, although the '393 patent included claims with more specific purity limitations, those claims do not require 100% pure treprostinil or its salt, and even those narrower '393 patent claims were invalidated by the combination of Moriarty and Phares. *See* Ex. 1004, claim 2 (reciting "The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%"); claim 10 ("The product of claim 9, wherein the purity of product of step (d) is at least 99.5%"). Further, Dr. Pinal and I agree that the alkylation and hydrolysis steps of Moriarty, Phares, and the '901 patent necessarily result in impurities. Ex. 1018 at 55:20-58:18 ("I agree [with Dr. Winkler] that there is no -- I don't know of any exception, any reaction in which there is not some sort of side-product or impurity or something like that."); *see also* Sections XI.B and XII.B below. Thus, the impurities limitation of the '901 patent claims is obviously disclosed by the same Moriarty and Phares combination that invalidated the '393 patent claims.

71. Further, Dr. Pinal mischaracterizes the '393 Final Written Decision's discussion of impurities. Ex. 2025 at ¶ 45. While the Board did find that "treprostinil compounds produced according to the challenged claims can have different impurity

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Liquidia's Exhibit 1017
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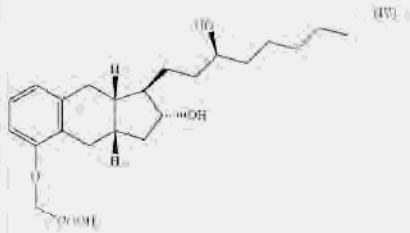
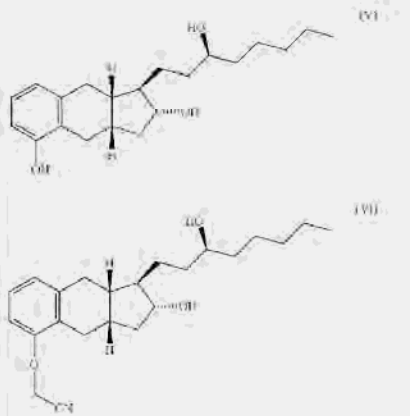
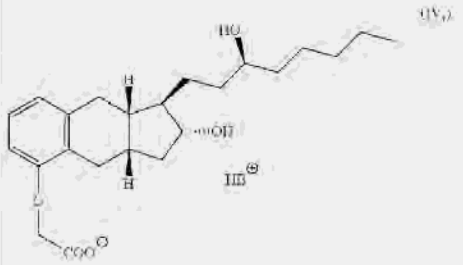
EX1017 (Winkler Reply), ¶69; Paper 15 (Reply), 11-12; Paper 25 (Sur-Reply), 4-5.

LIQUIDIA'S COMPARISON WITH THE '393 PATENT IS BOTH INACCURATE + MISLEADING

Limitation	'393 Patent Claim 9[6]	'901 Patent Claim 1
A product of treprostinil or a salt thereof	A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A pharmaceutical batch consisting of treprostinil or a salt thereof and **impurities resulting from**
Alkylation of benzindene triol	(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	(a) alkylating a benzindene triol,

Hydrolysis	(b) hydrolyzing the product of formula VI of step (a) with a base,	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,
Salt Formation	(c) contacting the product of step ([b]) with a base B to form a salt of formula IV_s, and 	(c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and
Optional reformulation of treprostinil	(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and **wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.**

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Paper 6 (POPR), 33-34, 43-50; Paper 12 (POR), 2-8, 14-16; EX2002 (Pinal), ¶¶72-83; EX2025 (Pinal Response), ¶43; *see* EX1017 (Winkler Reply), ¶¶68-69; Paper 15 (Reply), 11-12.

LIQUIDIA OVERLOOKS LACK OF OVERLAP OF DEPENDENT CLAIMS

’393 Patent	’901 Patent
▪ **Missing**	▪ 2. The **pharmaceutical batch** of claim 1, **which has been dried under vacuum**.
▪ **Missing**	▪ 3. A **pharmaceutical product** comprising a **therapeutically effective amount of treprostinil from a pharmaceutical batch** as claimed in claim 1.
▪ **Missing**	▪ 4. A **pharmaceutical product** comprising a **therapeutically effective amount of a salt [of] treprostinil from a pharmaceutical batch** as claimed in claim 1.
▪ **Missing**	▪ 6. A **method of preparing a pharmaceutical product from a pharmaceutical batch** as claimed in claim 1, comprising **storing a pharmaceutical batch of a salt of treprostinil** as claimed in claim 1 **at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage**.
▪ **Missing**	▪ 8. A **method of preparing a pharmaceutical batch**, as claimed in claim 1, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a **solution comprising treprostinil**, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) **isolating the salt of treprostinil**, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

UT EX2037

EX2025 (Pinal Response), ¶43; Paper 6 (POPR), 43-50; Paper 12 (POR), 2-8, 14-16.

GROUND 2: MORIARTY + PHARES

LIQUIDIA FAILED TO ESTABLISH MOTIVATION TO COMBINE

UT CAN ARGUE LACK OF MOTIVATION TO COMBINE

- **The ’901 and ’393 patent are directed to different inventions:**
  - Claim limitations are different
    - Pharmaceutical batch, impurities resulting from steps (a)-(d), at least 2.9 g, etc.
  - Claim scope is different
  - Claim construction is different
  - Level of ordinary skill in the art is different
  - Relevant field is different

Paper 6 (POPR), 62-64; Paper 12 (POR), 52-54.

UT CAN ARGUE LACK OF MOTIVATION TO COMBINE

- The Board must consider whether a POSA would have been motivated to combine the prior art in the way claimed **in the claims at issue** and had a reasonable expectation of success in doing so.
  - *PersonalWeb Techs. LLC v. Apple, Inc.*, 848 F.3d 987, 991 (Fed. Cir. 2017)

- **The issues decided in the 393 IPR are different and distinct from those at issue here.**

Issue preclusion requires that "an issue or fact or law is **actually litigated** and determined by a valid and final judgment, and the determination is essential to the judgment."

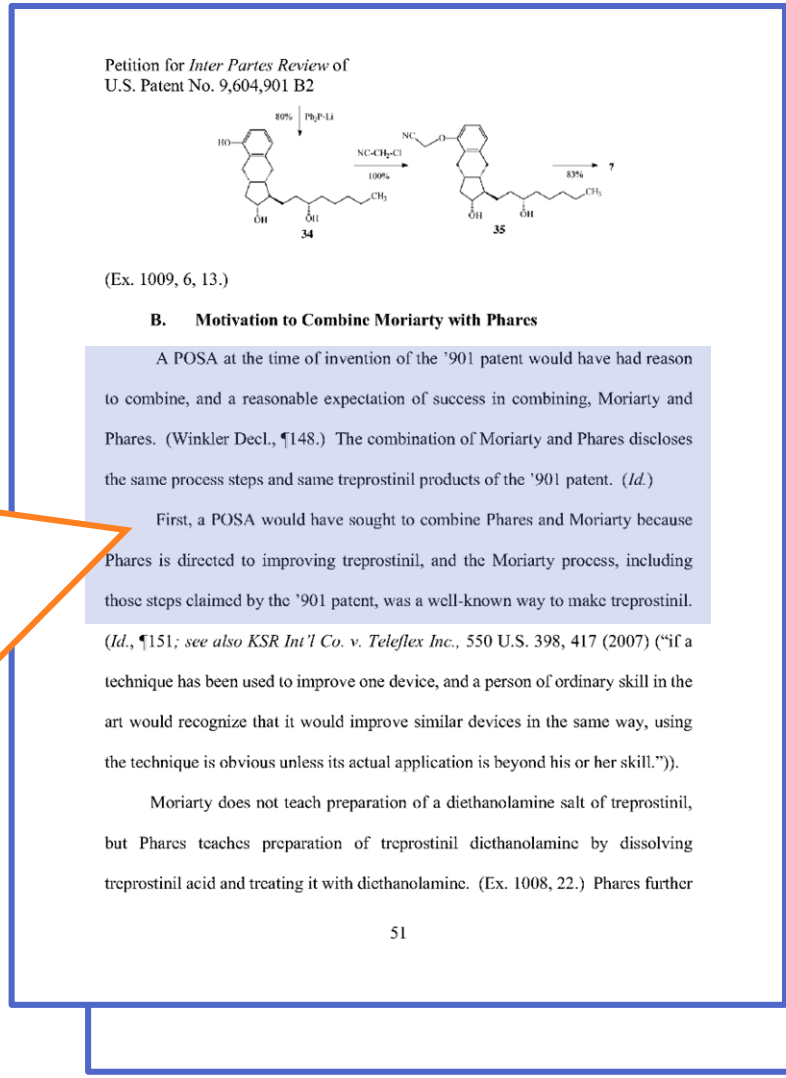
- *B & B Hardware, Inc. v. Hargis Indus., Inc.*, 135 U.S. 1293, 1303 (2015) (quoting Restatement (Second) of Judgements §27).

Paper 6 (POPR), 62-64; Paper 12 (POR), 52-54; Paper 7 (Institution Decision), 25, n.7 (encouraging parties to discuss whether issue preclusion applies in this proceeding).

LIQUIDIA'S MOTIVATION IMPROPERLY STARTS WITH THE '901 PATENT …

"A POSA at the time of invention of the '901 patent would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. **The combination of Moriarty and Phares discloses the same process steps and the same treprostinil product of the '901 patent**."

- Liquidia



Petition for *Inter Partes Review* of
U.S. Patent No. 9,604,901 B2

(Ex. 1009, 6, 13.)

B. Motivation to Combine Moriarty with Phares

A POSA at the time of invention of the '901 patent would have had reason to combine, and a reasonable expectation of success in combining, Moriarty and Phares. (Winkler Decl., ¶148.) The combination of Moriarty and Phares discloses the same process steps and same treprostinil products of the '901 patent. (*Id.*)

First, a POSA would have sought to combine Phares and Moriarty because Phares is directed to improving treprostinil, and the Moriarty process, including those steps claimed by the '901 patent, was a well-known way to make treprostinil. (*Id.*, ¶151; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) ("if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.")).

Moriarty does not teach preparation of a diethanolamine salt of treprostinil, but Phares teaches preparation of treprostinil diethanolamine by dissolving treprostinil acid and treating it with diethanolamine. (Ex. 1008, 22.) Phares further

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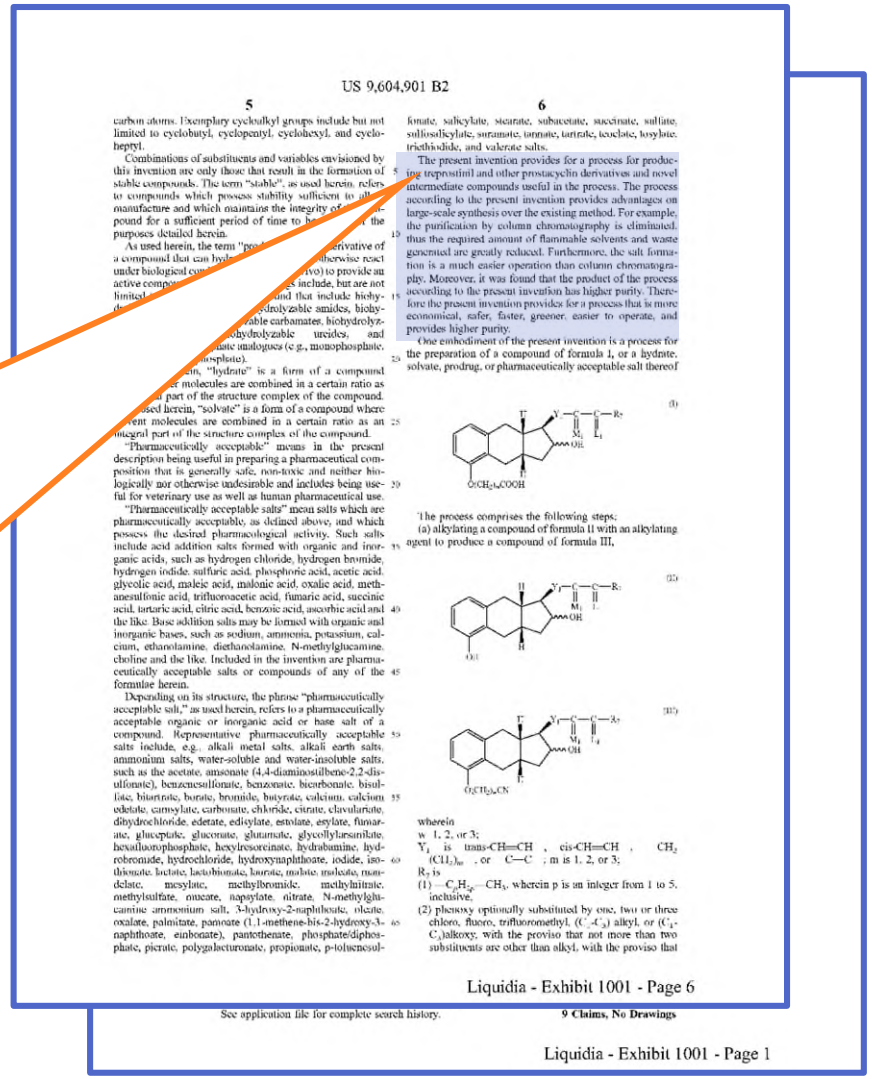
Paper 6 (POPR), 62-64; *see* Paper 1 (Petition), 51 (citation omitted).

…AND ENDS WITH THE ’901 PATENT

- Liquidia’s only other motivations—increasing synthetic efficiency and lowering production costs—come from the ’901 patent specification.

“[T]he present invention provides advantages [including that] the required amount of flammable solvents and waste generated are greatly reduced…**[T]he present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity**.”

- The ’901 Patent



US 9,604,901 B2

5 6

carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be [illegible] the purposes detailed herein.

As used herein, the term “pro[illegible]derivative of a compound that can hyd[illegible] otherwise react under biological con[illegible]tivo) to provide an active compo[illegible]s include, but are not limited[illegible]and that include biohydrolyzable amides, biohydrolyzable carbamates, biohydrolyzable ureides, and [illegible]ate analogues (e.g., monophosphate, bisphosphate).

As[illegible], “hydrate” is a form of a compound [illegible]er molecules are combined in a certain ratio as [illegible]al part of the structure complex of the compound. [illegible]sed herein, “solvate” is a form of a compound where [illegible]ent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

“Pharmaceutically acceptable” means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

“Pharmaceutically acceptable salts” mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase “pharmaceutically acceptable salt,” as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bisarbonate, bisulfite, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof

The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,

wherein

w is 1, 2, or 3;

Y_1 is trans-CH=CH, cis-CH=CH, CH_2, $(CH_2)_m$, or C≡C; m is 1, 2, or 3;

R_5 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that

Liquidia - Exhibit 1001 - Page 6

See application file for complete search history.

9 Claims, No Drawings

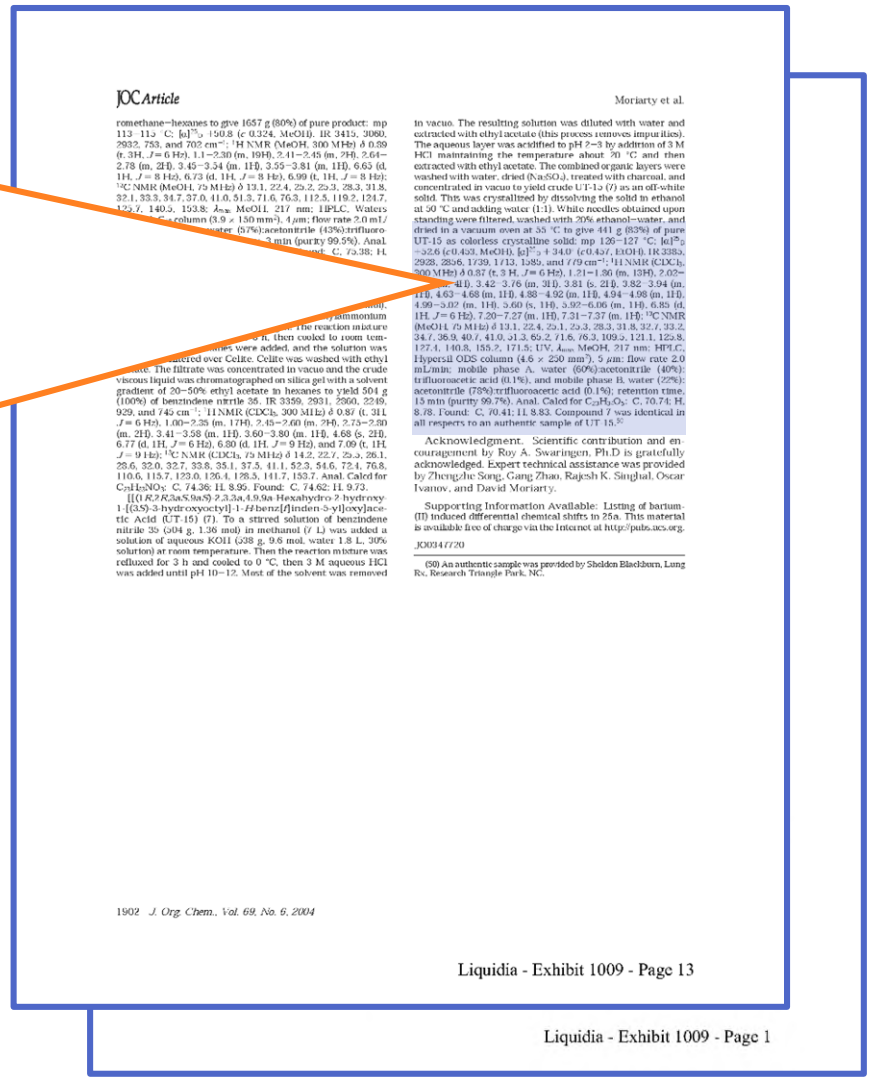
Liquidia - Exhibit 1001 - Page 1

UT EX2037

Paper 6 (POPR), 62-64; *see* Paper 1 (Petition), 51; EX1001 (901 Patent), 6:4-18.

WHY CHANGE MORIARTY?

at 50 °C and adding water (1:1). White needles obtained upon standing were filtered, washed with 20% ethanol–water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid; mp 126–127 °C; $[\alpha]^{25}_{D}$ +52.6 (*c* 0.453, MeOH), $[\alpha]^{25}_{D}$ + 34.0° (*c* 0.457, EtOH). IR 3385, 2928, 2856, 1739, 1713, 1585, and 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3 H, J = 6 Hz), 1.21–1.86 (m, 13H), 2.02–2.44 (m, 4H), 3.42–3.76 (m, 3H), 3.81 (s, 2H), 3.82–3.94 (m, 1H), 4.63–4.68 (m, 1H), 4.88–4.92 (m, 1H), 4.94–4.98 (m, 1H), 4.99–5.02 (m, 1H), 5.60 (s, 1H), 5.92–6.06 (m, 1H), 6.85 (d, 1H, J = 6 Hz), 7.20–7.27 (m, 1H), 7.31–7.37 (m, 1H); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.1, 25.3, 28.3, 31.8, 32.7, 33.2, 34.7, 36.9, 40.7, 41.0, 51.3, 65.2, 71.6, 76.3, 109.5, 121.1, 125.8, 127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH, 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm^2), 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%): trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H,



JOC Article

Moriarty et al.

romethane–hexanes to give 1657 g (80%) of pure product: mp 113–115 °C; $[\alpha]^{25}_{D}$ 150.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^{1}H NMR (MeOH, 300 MHz) δ 0.59 (t, 3H, J = 6 Hz), 1.1–2.30 (m, 19H), 2.41–2.45 (m, 2H), 2.64–2.78 (m, 2H), 3.45–3.54 (m, 1H), 3.55–3.81 (m, 11H), 6.65 (d, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8 Hz), 6.99 (t, 1H, J = 8 Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters [illegible] column (3.9 × 150 mm^2), 4 μm; flow rate 2.0 mL/ [illegible] water (57%):acetonitrile (43%):trifluoro- [illegible] 3 min (purity 99.5%). Anal. [illegible] C, 75.38; H,

[illegible] ammonium [illegible] The reaction mixture [illegible] were added, and the solution was [illegible] filtered over Celite. Celite was washed with ethyl [illegible]. The filtrate was concentrated in vacuo and the crude viscous liquid was chromatographed on silica gel with a solvent gradient of 20–50% ethyl acetate in hexanes to yield 504 g (100%) of benzindene nitrile 35. IR 3359, 2931, 2860, 2249, 929, and 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 6 Hz), 1.00–2.35 (m, 17H), 2.45–2.60 (m, 2H), 2.75–2.80 (m, 2H), 3.41–3.58 (m, 11H), 3.60–3.80 (m, 11H), 4.68 (s, 2H), 6.77 (d, 1H, J = 6 Hz), 6.80 (d, 1H, J = 9 Hz), and 7.09 (t, 1H, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

[[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1-*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (UT-15) (7). To a stirred solution of benzindene nitrile 35 (404 g, 1.26 mol) in methanol (7 L) was added a solution of aqueous KOH (338 g, 9.6 mol, water 1.8 L, 30% solution) at room temperature. Then the reaction mixture was refluxed for 3 h and cooled to 0 °C, then 3 M aqueous HCl was added until pH 10–12. Most of the solvent was removed in vacuo. The resulting solution was diluted with water and extracted with ethyl acetate (this process removes impurities). The aqueous layer was acidified to pH 2–3 by addition of 3 M HCl maintaining the temperature about 20 °C and then extracted with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), treated with charcoal, and concentrated in vacuo to yield crude UT-15 (7) as an off-white solid. This was crystallized by dissolving the solid in ethanol at 50 °C and adding water (1:1). White needles obtained upon standing were filtered, washed with 20% ethanol–water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid: mp 126–127 °C; $[\alpha]^{25}_{D}$ +52.6 (*c* 0.453, MeOH), $[\alpha]^{25}_{D}$ + 34.0 (*c* 0.457, EtOH). IR 3385, 2928, 2856, 1739, 1713, 1585, and 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3 H, J = 6 Hz), 1.21–1.86 (m, 13H), 2.02–[illegible] 41), 3.42–3.76 (m, 3H), 3.81 (s, 2H), 3.82–3.94 (m, 1H), 4.63–4.68 (m, 1H), 4.88–4.92 (m, 1H), 4.94–4.98 (m, 1H), 4.99–5.02 (m, 1H), 5.60 (s, 1H), 5.92–6.06 (m, 1H), 6.85 (d, 1H, J = 6 Hz), 7.20–7.27 (m, 1H), 7.31–7.37 (m, 1H); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.1, 25.3, 28.3, 31.8, 32.7, 33.2, 34.7, 36.9, 40.7, 41.0, 51.3, 65.2, 71.6, 76.3, 109.5, 121.1, 125.8, 127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH, 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm^2), 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%): trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.41; H, 8.83. Compound 7 was identical in all respects to an authentic sample of UT-15.[50]

Acknowledgment. Scientific contribution and encouragement by Roy A. Swaringen, Ph.D is gratefully acknowledged. Expert technical assistance was provided by Zhengzhe Song, Gang Zhao, Rajesh K. Singhal, Oscar Ivanov, and David Moriarty.

Supporting Information Available: Listing of barium-(II) induced differential chemical shifts in 25a. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034772O

(50) An authentic sample was provided by Sheldon Blackburn, Lung Rx, Research Triangle Park, NC.

EX1009 (Moriarty), 13; Paper 6 (POPR), 62-64; EX2002 (Pinal), ¶¶294, 297-300; *see* Paper 1 (Petition), 52, 56 (indicating the claimed invention may have worse purity than Moriarty); EX1002 (Winkler), ¶¶149, 151.

WHY CHANGE MORIARTY?

- Liquidia asserts a POSA would have combined Moriarty with Phares to "eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for the synthesis of treprostinil diethanolamine salt."
- **Neither Moriarty nor Phares notes an existing problem with synthetic efficacy or production costs of the Moriarty process.**
- **Phares does not teach that salt production increases synthetic efficiency or lowers production costs.**

Paper 6 (POPR), 62-64; EX2002 (Pinal), ¶¶294, 297-300; *see* EX1002 (Winkler), ¶¶149, 151; Paper 1 (Petition), 51-53.

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- **Adding Phares's salt formation adds steps, forms a new chemical entity, adds to the number of synthetic steps, increases complexity, imparts concerns over stability.**

Paper 6 (POPR), 62-64; EX2002 (Pinal), ¶¶294, 297-300; *see* EX1002 (Winkler), ¶¶149, 151; Paper 1 (Petition), 51-53.

THE WORKING EXAMPLE IS MORE COMPLEX THAN MORIARTY

Step No.	Steps	Former Process (Batch size: 500 g)	Moriarty (EX1009) (Batch size: ~500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
		Nitrile		
1	Triol weight	500 g	452 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	20 L	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	1145 g	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	133 g	2,270 g (2 eq)
5	Tetrabutylammonium bromide	42 g (0.08 eq)	39.94 g	145 g (0.03 eq)
6	Reactor size	72-Liter		50-gallon
7	Reflux time	8 hours	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	Yes, 10 L	No
9	Filter	Celite	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Ethyl Acetate	Acetone (50 L)
11	Evaporation	Yes	Yes	Yes
12	Purification	Silica gel column Dichloromethane: 0.5 L Ethyl acetate: 45 L Hexane: 60 L	Silica gel column Ethyl acetate: 20-50% Hexane: 80-50%	No column
13	Evaporation after column	Yes	Yes	No
14	Yield of nitrile	109-112%	100%	Not checked
		Treprostinil (intermediate)		
15	Methanol	7.6 L (50-L reactor)	7 L	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	538 g	3,375g (4 eq)
17	Water	2.2 L	1.8 L	17 L
18	% of KOH	30%	30%	20%
19	Reflux time	3-3.5 h	3 h	4-5 h
20	Acid used	2.6 L (3M)	3M HCl	12 L (3M)
21	Removal of impurities	3 x 3 L Ethyl acetate	Ethyl Acetate	2 x 20 L Ethyl acetate
22	Acidification	0.7 L	3 M HCl	6.5 L
23	Ethyl acetate extraction	5 x 17 L = 35 L	Yes	90 + 45 + 45 = 180 L
24	Water washing	2 x 8 L	Yes	3 x 40 L
25	Sodium bicarbonate washing	Not done	Not done	120 g in 30 L water + 15 L brine
26	Brine washing	Not done	Not done	1 x 40 L
27	Sodium sulfate	1 kg	Yes	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	Yes	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Yes	Pass hot solution (75° C.) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution

EX2025 (Pinal Response), ¶¶89-90 (annotating '901 patent Example 6); Paper 6 (POPR), 61-62; Paper 12 (POR), 63-64; EX2002 (Pinal), ¶¶133-34.

THE WORKING EXAMPLE IS MORE COMPLEX THAN MORIARTY

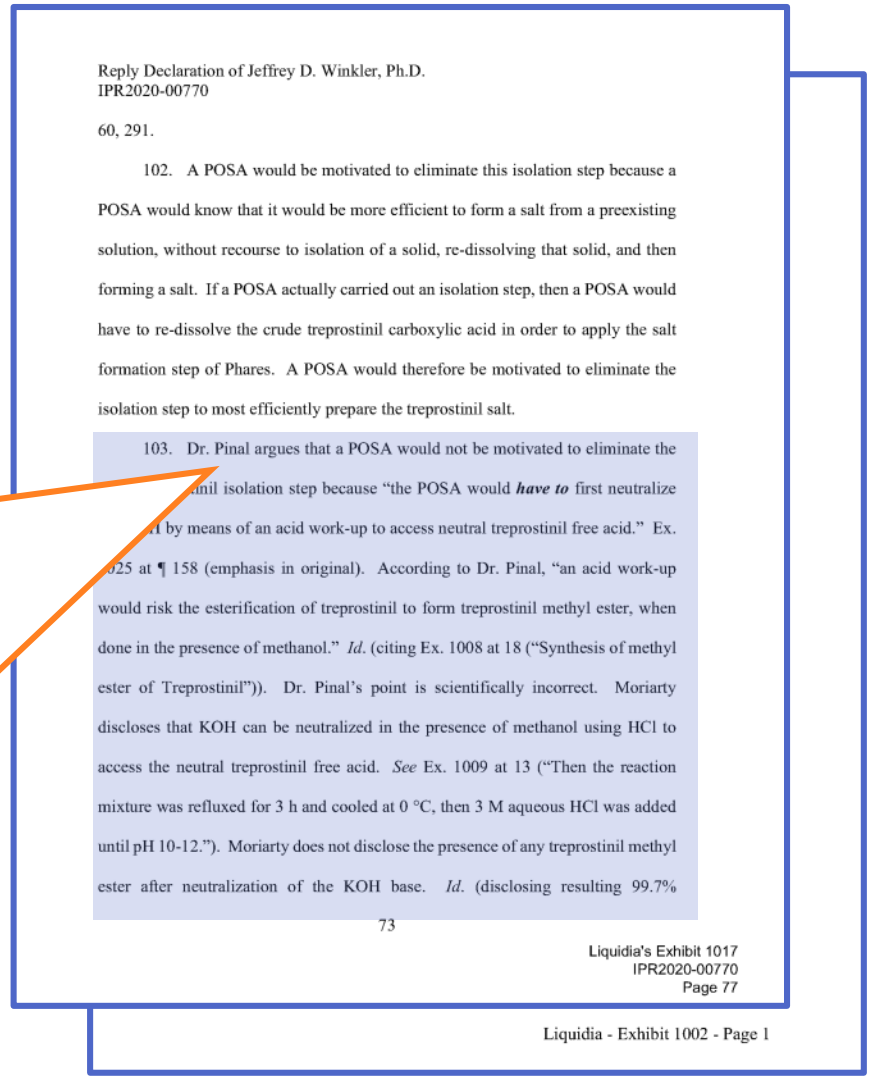
Step No.	Steps	Former Process (Batch size: 500 g)	present invention (Batch size: 5 kg)
	Nitrile		
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutyl-ammonium bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50-gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane: 0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112%	Not checked
	Treprostinil (intermediate)		
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L
18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3M)	12 L (3M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90 + 45 + 45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30 L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75° C.) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
	Treprostinil Diethanolamine Salt		
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75° C.
32	Cooling	N/A	To 20° C. over weekend; add 40 L ethyl acetate; cooled to 10° C.
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
	Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)		
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L
38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge −0° C. 24 h	50° C. to 0° C. ramp, 0° C. overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55° C.	6-15 hours, 55° C.
50	Vacuum	<–0.095 mPA	<5 Torr
51	UT-15 yield weight	~535 g	~1,100 g
52	% yield from triol)	~91%	~89%
53	Purity	~99.0%	99.9%

EX1001 (901 Patent), Example 6; Paper 6 (POPR), 61-62; EX2002 (Pinal), ¶¶133-34; Paper 12 (POR), 31-32; EX2025 (Pinal Response), ¶¶89-90.

DR. WINKLER'S CHEMICAL IMPOSSIBILITY

"**Dr. Pinal argues that a POSA would not be motivated to eliminate the crude treprostinil isolation step because 'the POSA would have to first neutralize the KOH by means of an acid work-up to access neutral treprostinil free acid'...Moriarty discloses that KOH can be neutralized** in the presence of methanol using HCl to access the neutral treprostinil free acid. *See* Ex. 1009 at 13 ('Then the reaction mixture was refluxed for 3 h and cooled at 0 ˚C, then 3 M aqueous HCl was added **until pH 10-12**.')."

- Dr. Winkler



Reply Declaration of Jeffrey D. Winkler, Ph.D.
IPR2020-00770

60, 291.

102. A POSA would be motivated to eliminate this isolation step because a POSA would know that it would be more efficient to form a salt from a preexisting solution, without recourse to isolation of a solid, re-dissolving that solid, and then forming a salt. If a POSA actually carried out an isolation step, then a POSA would have to re-dissolve the crude treprostinil carboxylic acid in order to apply the salt formation step of Phares. A POSA would therefore be motivated to eliminate the isolation step to most efficiently prepare the treprostinil salt.

103. Dr. Pinal argues that a POSA would not be motivated to eliminate the crude treprostinil isolation step because "the POSA would ***have to*** first neutralize the KOH by means of an acid work-up to access neutral treprostinil free acid." Ex. 2025 at ¶ 158 (emphasis in original). According to Dr. Pinal, "an acid work-up would risk the esterification of treprostinil to form treprostinil methyl ester, when done in the presence of methanol." *Id.* (citing Ex. 1008 at 18 ("Synthesis of methyl ester of Treprostinil")). Dr. Pinal's point is scientifically incorrect. Moriarty discloses that KOH can be neutralized in the presence of methanol using HCl to access the neutral treprostinil free acid. *See* Ex. 1009 at 13 ("Then the reaction mixture was refluxed for 3 h and cooled at 0 °C, then 3 M aqueous HCl was added until pH 10-12."). Moriarty does not disclose the presence of any treprostinil methyl ester after neutralization of the KOH base. *Id.* (disclosing resulting 99.7%

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Liquidia's Exhibit 1017
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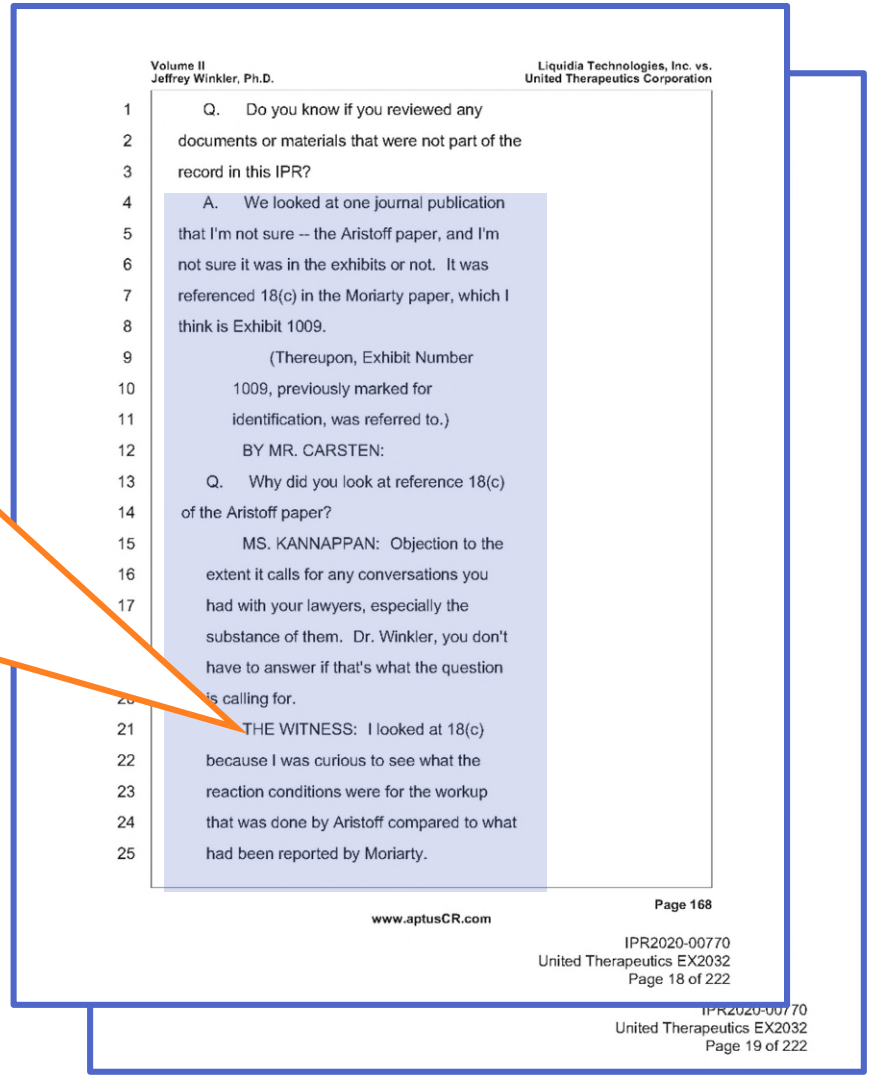
UT EX2037

EX1017 (Winkler Reply), ¶103; EX2025 (Pinal Response), ¶¶158, 185, 232; Paper 31 (MtE), 5-8; Paper 12 (POR), 29-34.

DR. WINKLER'S ARISTOFF HAIL MARY FAILS TO CONSIDER THE DIFFERENT PROCESSES

"**[T]he neutralization doesn't occur at pH 10 to 12**...I looked at footnote 18(c), I saw the paper by Aristoff…in 1985. And so I looked at that paper to see whether the workup procedure for the formation of the treprostinil free acid, how that compared to what was described in Moriarty…"

- Dr. Winkler



Volume II
Jeffrey Winkler, Ph.D.

Liquidia Technologies, Inc. vs.
United Therapeutics Corporation

Q. Do you know if you reviewed any documents or materials that were not part of the record in this IPR?

A. We looked at one journal publication that I'm not sure -- the Aristoff paper, and I'm not sure it was in the exhibits or not. It was referenced 18(c) in the Moriarty paper, which I think is Exhibit 1009.

(Thereupon, Exhibit Number 1009, previously marked for identification, was referred to.)

BY MR. CARSTEN:

Q. Why did you look at reference 18(c) of the Aristoff paper?

MS. KANNAPPAN: Objection to the extent it calls for any conversations you had with your lawyers, especially the substance of them. Dr. Winkler, you don't have to answer if that's what the question is calling for.

THE WITNESS: I looked at 18(c) because I was curious to see what the reaction conditions were for the workup that was done by Aristoff compared to what had been reported by Moriarty.

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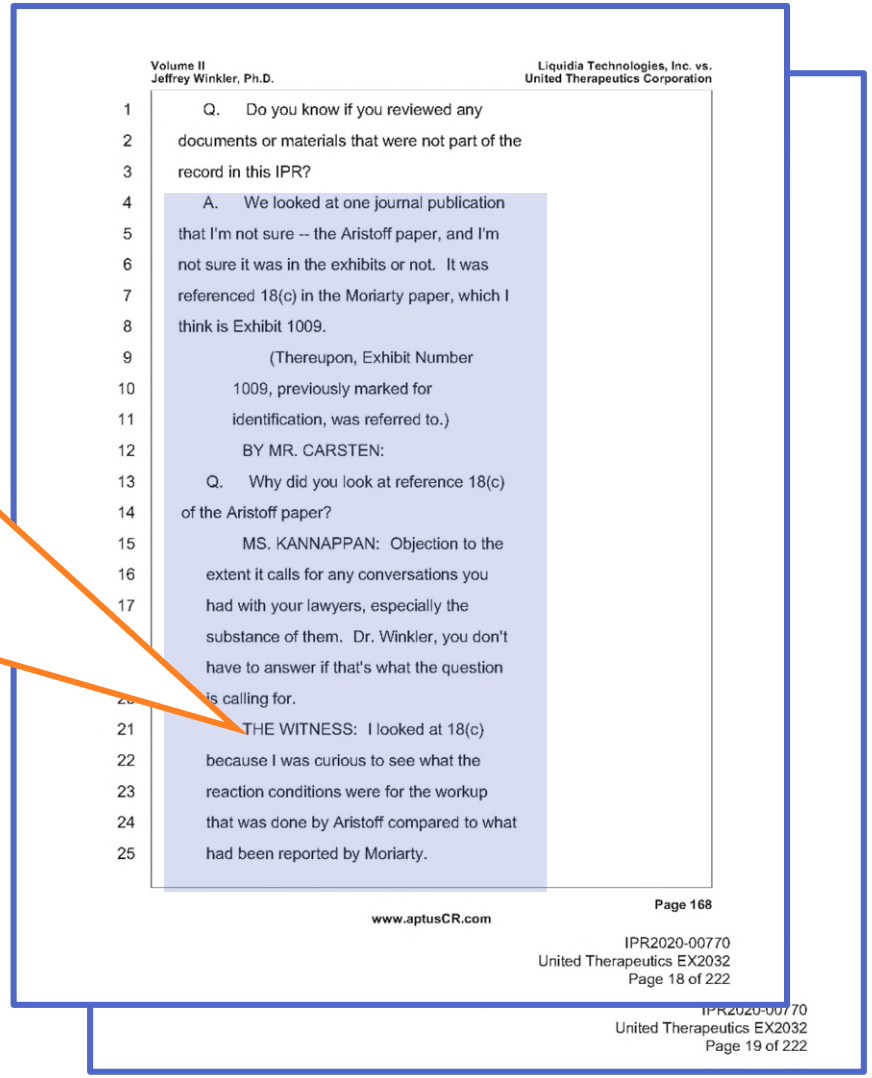
EX2032 (Winkler Depo #2), 168:1-177:12; Paper 31 (MtE), 5-8.

WHAT HAPPENED TO DR. WINKLER'S RATIONALE?

"**[T]he neutralization doesn't occur at pH 10 to 12**…[M]ost of the solvent was removed in vacuo. The resulting solution was diluted with water and extracted in ethyl acetate…The aqueous layer was acidified to pH 2 to 3 by addition of 3 molar HCl…**and then extracted with ethyl acetate.**

- Dr. Winkler

- **Dr. Winkler backtracks to agree Moriarty's full work-up needs to be performed before salt form can be pursued.**



Volume II
Jeffrey Winkler, Ph.D.

Liquidia Technologies, Inc. vs.
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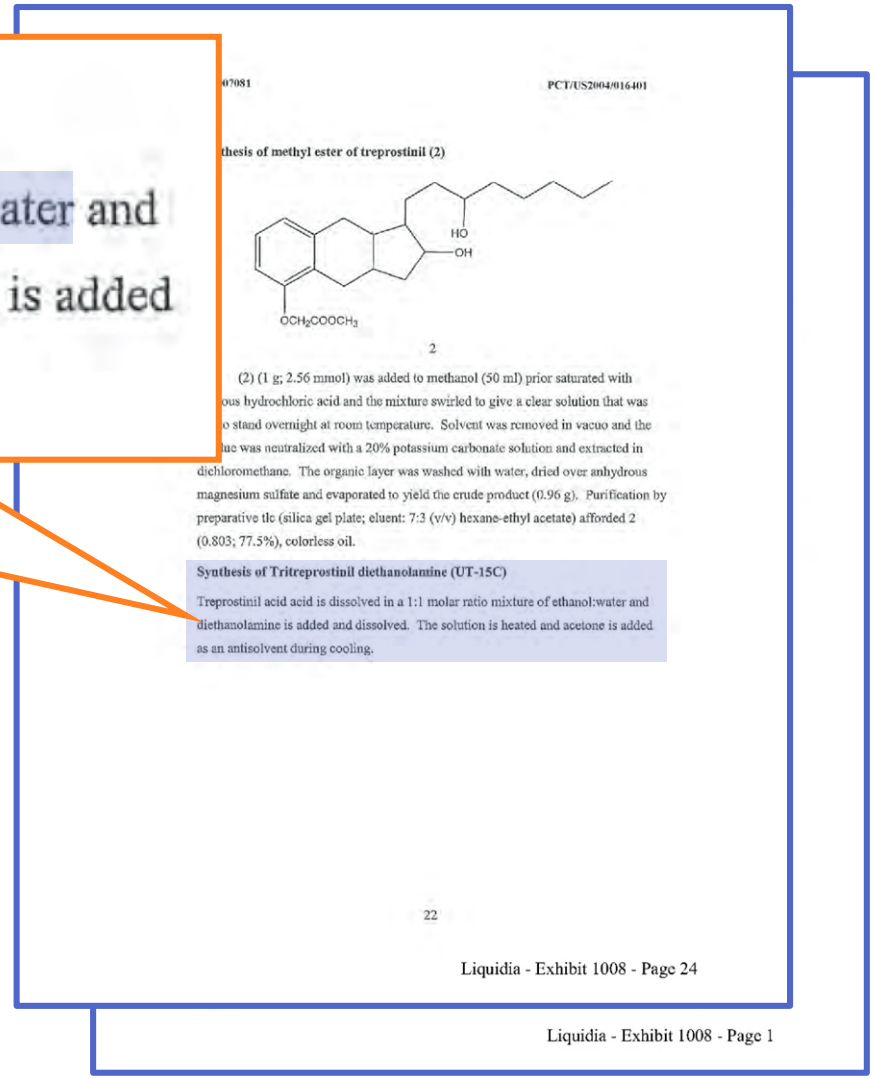
EX2032 (Winkler Depo #2), 168:1-177:12; Paper 31 (MtE), 5-8; Paper 25 (Sur-Reply), 1-2, 20-24; Paper 12 (POR), 29-34; Paper 1 (Petition), 38 (asserting a POSA could skip Moriarty's isolation to be "faster, more efficient, and more economical"); EX2025 (Pinal Response), ¶¶158-63.

DR. WINKLER'S BACKTRACK UNDERMINES ANY MOTIVATION

Synthesis of Tritreprostinil diethanolamine (UT-15C)

Treprostinil acid acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.



07081 PCT/US2004/016401

thesis of methyl ester of treprostinil (2)

2

(2) (1 g; 2.56 mmol) was added to methanol (50 ml) prior saturated with ous hydrochloric acid and the mixture swirled to give a clear solution that was o stand overnight at room temperature. Solvent was removed in vacuo and the due was neutralized with a 20% potassium carbonate solution and extracted in dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield the crude product (0.96 g). Purification by preparative tlc (silica gel plate; eluent: 7:3 (v/v) hexane-ethyl acetate) afforded 2 (0.803; 77.5%), colorless oil.

Synthesis of Tritreprostinil diethanolamine (UT-15C)

Treprostinil acid acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

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Liquidia - Exhibit 1008 - Page 24

Liquidia - Exhibit 1008 - Page 1

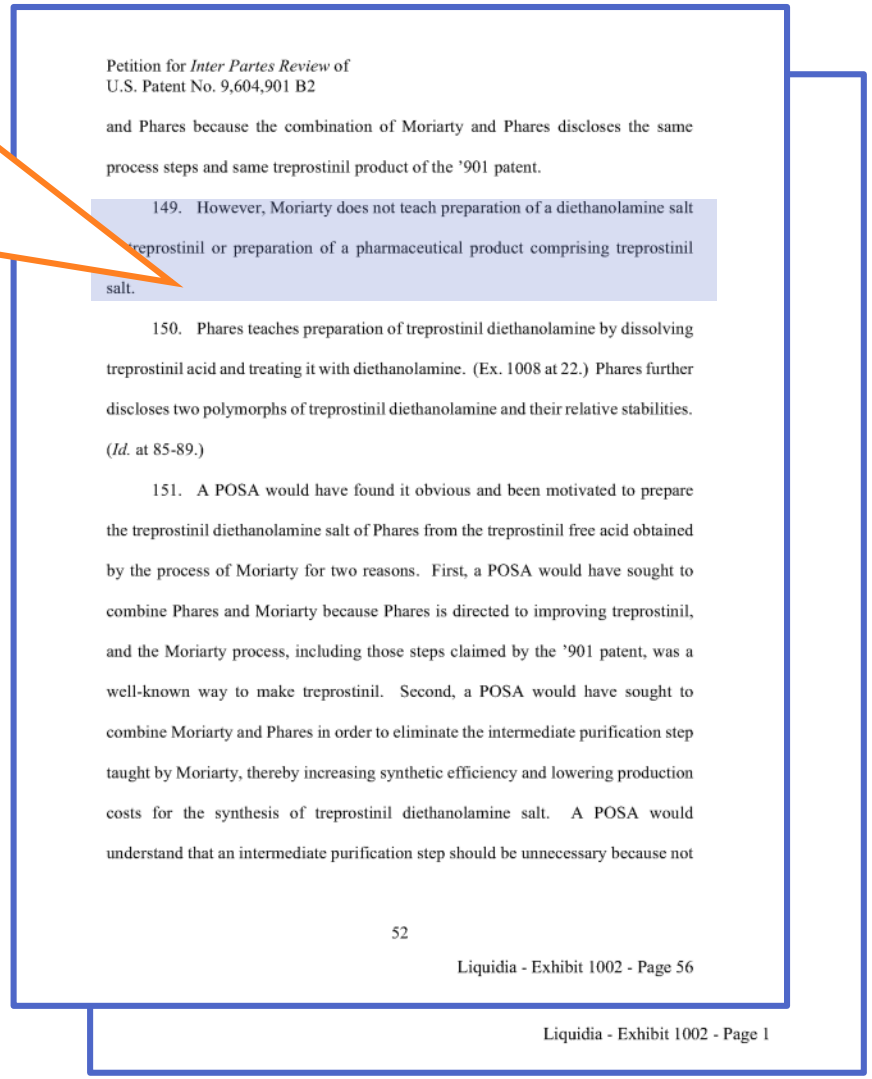
UT EX2037

EX1008 (Phares), 22; Paper 6 (POPR), 51; EX2025 (Pinal Response), ¶¶158-63, 237; Paper 12 (POR), 30-32.

WHY CHANGE MORIARTY?

"Moriarty **does not teach preparation of a diethanolamine salt** of treprostinil **or preparation of a pharmaceutical product** comprising treprostinil salt."

- Dr. Winkler



Petition for *Inter Partes Review* of
U.S. Patent No. 9,604,901 B2

and Phares because the combination of Moriarty and Phares discloses the same process steps and same treprostinil product of the '901 patent.

149. However, Moriarty does not teach preparation of a diethanolamine salt treprostinil or preparation of a pharmaceutical product comprising treprostinil salt.

150. Phares teaches preparation of treprostinil diethanolamine by dissolving treprostinil acid and treating it with diethanolamine. (Ex. 1008 at 22.) Phares further discloses two polymorphs of treprostinil diethanolamine and their relative stabilities. (*Id.* at 85-89.)

151. A POSA would have found it obvious and been motivated to prepare the treprostinil diethanolamine salt of Phares from the treprostinil free acid obtained by the process of Moriarty for two reasons. First, a POSA would have sought to combine Phares and Moriarty because Phares is directed to improving treprostinil, and the Moriarty process, including those steps claimed by the '901 patent, was a well-known way to make treprostinil. Second, a POSA would have sought to combine Moriarty and Phares in order to eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for the synthesis of treprostinil diethanolamine salt. A POSA would understand that an intermediate purification step should be unnecessary because not

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Liquidia - Exhibit 1002 - Page 56

Liquidia - Exhibit 1002 - Page 1

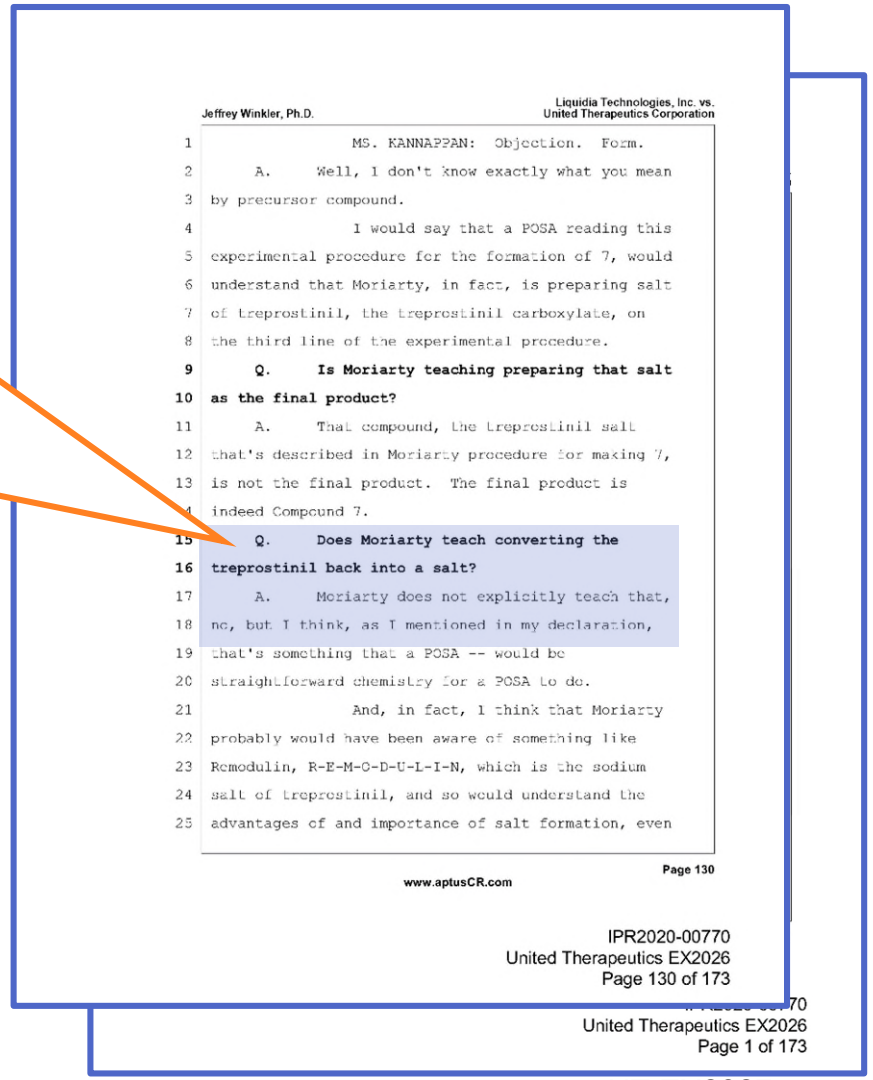
UT EX2037

EX1002 (Winkler), ¶149; Paper 6 (POPR), 62-64; EX2002 (Pinal), ¶¶294, 297-300; Paper 12 (POR), 60-62.

WHY CHANGE MORIARTY?

Q: "Does Moriarty teach converting the treprostinil back into a salt?"

Dr. Winkler: "**Moriarty does not explicitly teach that, no**."



Jeffrey Winkler, Ph.D. — Liquidia Technologies, Inc. vs. United Therapeutics Corporation

MS. KANNAPPAN: Objection. Form.

A. Well, I don't know exactly what you mean by precursor compound.

I would say that a POSA reading this experimental procedure for the formation of 7, would understand that Moriarty, in fact, is preparing salt of treprostinil, the treprostinil carboxylate, on the third line of the experimental procedure.

Q. Is Moriarty teaching preparing that salt as the final product?

A. That compound, the treprostinil salt that's described in Moriarty procedure for making 7, is not the final product. The final product is indeed Compound 7.

Q. Does Moriarty teach converting the treprostinil back into a salt?

A. Moriarty does not explicitly teach that, no, but I think, as I mentioned in my declaration, that's something that a POSA -- would be straightforward chemistry for a POSA to do.

And, in fact, I think that Moriarty probably would have been aware of something like Remodulin, R-E-M-O-D-U-L-I-N, which is the sodium salt of treprostinil, and so would understand the advantages of and importance of salt formation, even

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EX2025 (Winkler Depo #1), 130:15-18; Paper 6 (POPR), 62-64; EX2002 (Pinal), ¶¶294, 297-300; Paper 12 (POR), 60-62.

DR. WINKLER ADMITS MORIARTY DOES NOT TEACH AT LEAST:

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and
wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim **1**, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim **1**.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim **1**.

5. The product of claim **4**, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim **1**, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim **1** at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim **6**, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim **1**, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim **8**, wherein the salt of treprostinil is a diethanolamine salt.

EX1002 (Winkler), ¶149; EX2025 (Winkler Depo #1), 130:15-18; Paper 6 (POPR), 62-64; Paper 12 (POR), 60-62; EX1001 (901 Patent), 17:24-18:29.

NO ESTABLISHED MOTIVATION TO COMBINE

- Moriarty and Phares teach different compounds and have different focuses and aims.

- The mere fact that a modification *could* be made falls well short of a motivation such that the POSA would have made the modification.

"**[I]t is not enough** to show that 'a skilled artisan, once presented with the two references, would have understood that they could be combined.'"

- *Johns Manville Corp. v. Knauf Insulation, Inc.*, IPR2018-00827, Paper 9, 10-11 (2018) (informative) (*citing Personal Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017)).

Paper 6 (POPR), 64; Paper 12 (POR), 54-56; EX2025 (Pinal Response), ¶¶110-13, 161-62, 250, 260-64.

MORIARTY + PHARES ARE DIRECTED TO DIFFERENT PROBLEMS

- Moriarty only addresses improving the **synthesis** of treprostinil.
  - Does not address or contemplate salts, prodrugs, or enantiomers thereof.
  - Does not identify anything wrong, inefficient, or undesirable about its synthesis or treprostinil product.
  - Teaches treprostinil for subcutaneous injection.

- Phares contemplates chemical modifications to treprostinil, focusing on prodrugs and their enantiomers, to yield an oral, topical, or transdermal drug.
  - Teaches treprostinil's absolute oral bioavailability is less than 10%.
  - Teaches treprostinil is irritating on skin contact, while prodrugs are not.
  - Does not teach scalability or purity.
  - Notes treprostinil diethanolamine is hygroscopic and polymorphic.

Paper 6 (POPR), 50-51, 64; Paper 12 (POR), 54-56; EX2025 (Pinal Response), ¶¶110-13, 161-62, 250, 260-64

LIQUIDIA'S BELATED MOTIVATION ARGUMENTS

LIQUIDIA IMPROPERLY EXPANDS ON PETITION IN REPLY

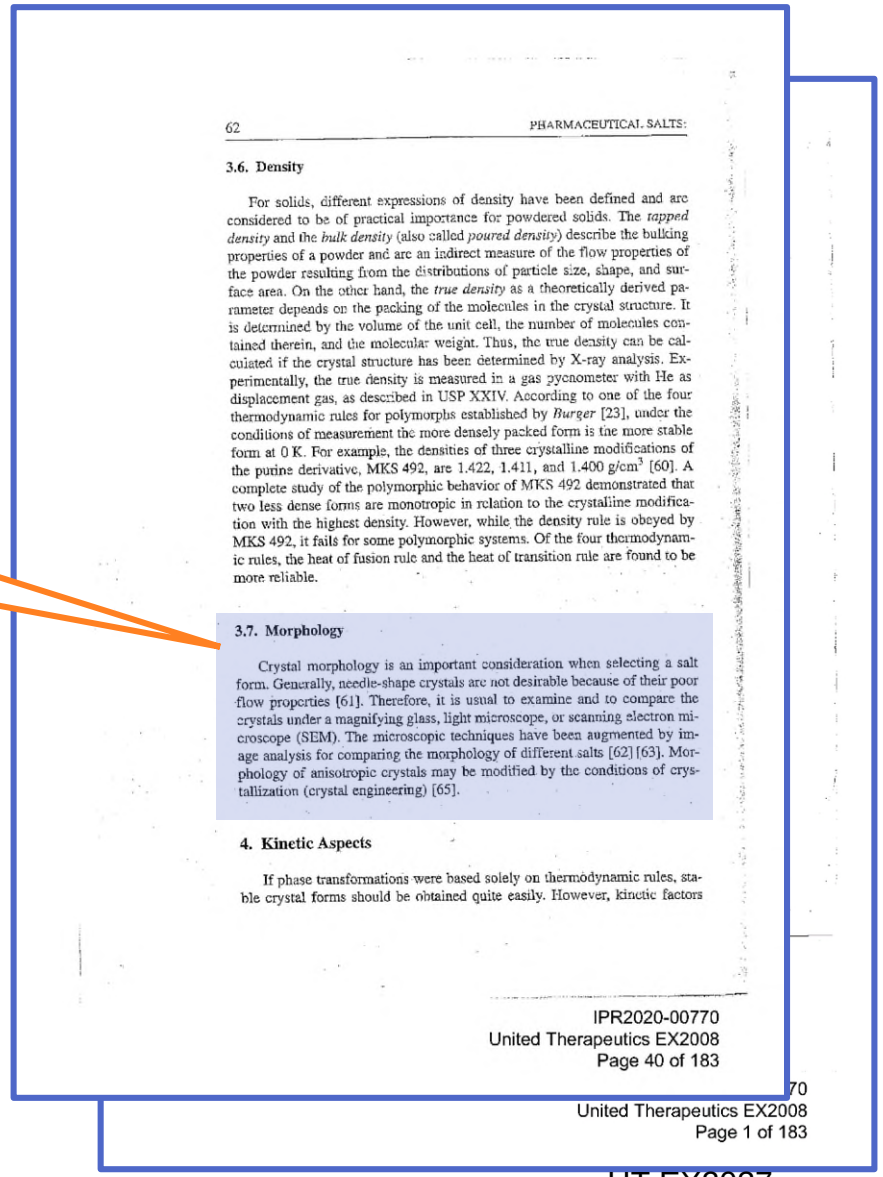
- **Argues new motivations to combine Moriarty with Phares including:**
  - Crystal morphology
  - Safety
  - Improved bioavailability

Paper 25 (Sur-Reply), 1-2; *see* Paper 15 (Reply), 13-16; EX2032 (Winkler Depo #2), 287:6-296:19 (clinical safety), 250:11-252:16 (bioavailability), 321:1-322:9 (crystal morphology).

A PROPERLY CREDENTIALED POSA UNDERSTANDS THAT CRYSTAL MORPHOLOGY IS IMPORTANT

"Crystal morphology is an important consideration when selecting a salt form."

- Stahl



62 PHARMACEUTICAL SALTS:

3.6. Density

For solids, different expressions of density have been defined and are considered to be of practical importance for powdered solids. The *tapped density* and the *bulk density* (also called *poured density*) describe the bulking properties of a powder and are an indirect measure of the flow properties of the powder resulting from the distributions of particle size, shape, and surface area. On the other hand, the *true density* as a theoretically derived parameter depends on the packing of the molecules in the crystal structure. It is determined by the volume of the unit cell, the number of molecules contained therein, and the molecular weight. Thus, the true density can be calculated if the crystal structure has been determined by X-ray analysis. Experimentally, the true density is measured in a gas pycnometer with He as displacement gas, as described in USP XXIV. According to one of the four thermodynamic rules for polymorphs established by *Burger* [23], under the conditions of measurement the more densely packed form is the more stable form at 0 K. For example, the densities of three crystalline modifications of the purine derivative, MKS 492, are 1.422, 1.411, and 1.400 g/cm^3 [60]. A complete study of the polymorphic behavior of MKS 492 demonstrated that two less dense forms are monotropic in relation to the crystalline modification with the highest density. However, while the density rule is obeyed by MKS 492, it fails for some polymorphic systems. Of the four thermodynamic rules, the heat of fusion rule and the heat of transition rule are found to be more reliable.

3.7. Morphology

Crystal morphology is an important consideration when selecting a salt form. Generally, needle-shape crystals are not desirable because of their poor flow properties [61]. Therefore, it is usual to examine and to compare the crystals under a magnifying glass, light microscope, or scanning electron microscope (SEM). The microscopic techniques have been augmented by image analysis for comparing the morphology of different salts [62] [63]. Morphology of anisotropic crystals may be modified by the conditions of crystallization (crystal engineering) [65].

4. Kinetic Aspects

If phase transformations were based solely on thermodynamic rules, stable crystal forms should be obtained quite easily. However, kinetic factors

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EX2008 (Stahl), 62; Paper 6 (POPR), 66-67; EX2002 (Pinal), ¶258; Paper 12 (POR), 7, 32, 36-37; EX2025 (Pinal Response), ¶¶267-68.

MORIARTY DISCLOSES NEEDLE-SHAPED CRYSTALS

extracted with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), treated with charcoal, and concentrated in vacuo to yield crude UT-15 (7) as an off-white solid. This was crystallized by dissolving the solid in ethanol at 50 °C and adding water (1:1). White needles obtained upon standing were filtered, washed with 20% ethanol–water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid; mp 126–127 °C; $[\alpha]^{25}_D$

EX1009 (Moriarty), 13; Paper 6 (POPR), 66-67; EX2002 (Pinal), ¶¶301-02; Paper 25 (Sur-Reply), 1-2; EX2025 (Pinal Response), ¶¶267-68; *see* EX2026 (Winkler Depo #1), 134:22-135:17.

LIQUIDIA OFFERS NO ARGUMENT + DR. WINKLER OFFERS NO OPINION ON CRYSTAL MORPHOLOGY

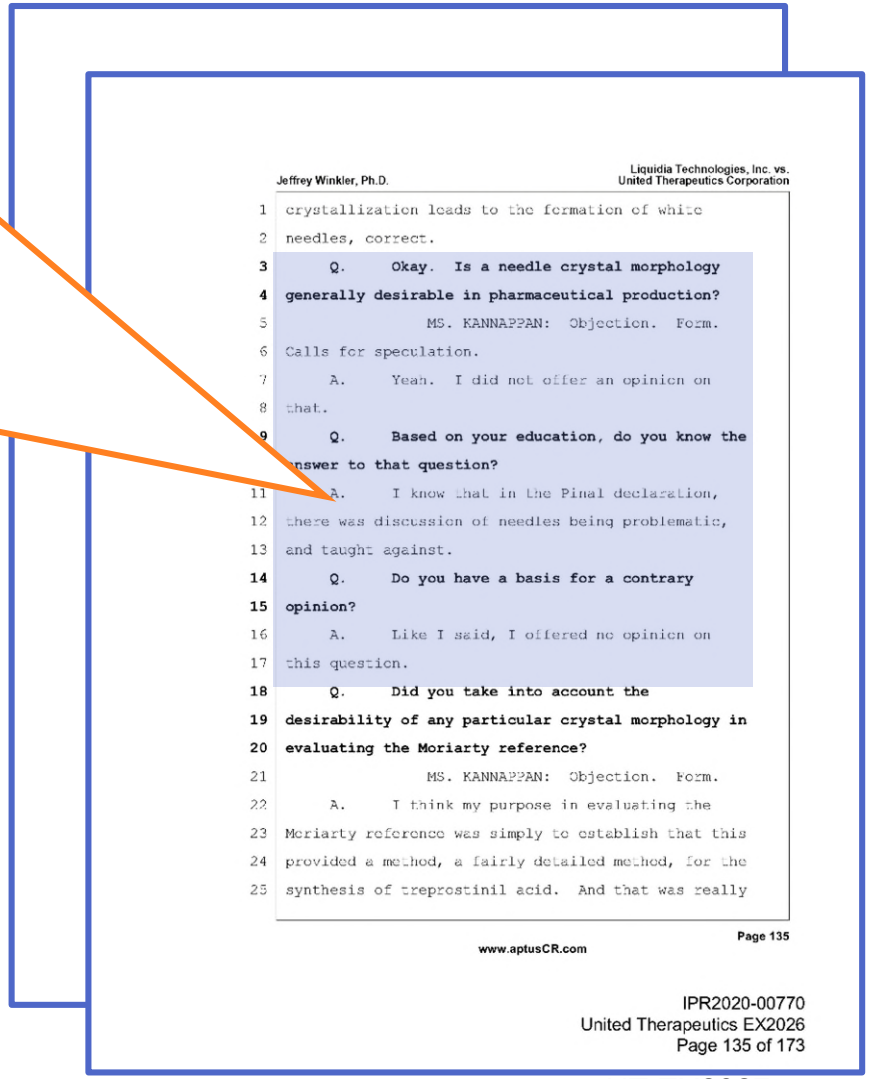
Q: "Is a needle crystal morphology generally desirable in pharmaceutical production?"

***

Dr. Winkler: "**I did not offer an opinion on that**…I know that **in the Pinal declaration there was discussion of needles being problematic, and taught against**."

Q: "Do you have a basis for a contrary opinion?"

Dr. Winkler: "Like I said, **I offered no opinion on this question**."



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crystallization leads to the formation of white needles, correct.

Q. Okay. Is a needle crystal morphology generally desirable in pharmaceutical production?

MS. KANNAPPAN: Objection. Form. Calls for speculation.

A. Yeah. I did not offer an opinion on that.

Q. Based on your education, do you know the answer to that question?

A. I know that in the Pinal declaration, there was discussion of needles being problematic, and taught against.

Q. Do you have a basis for a contrary opinion?

A. Like I said, I offered no opinion on this question.

Q. Did you take into account the desirability of any particular crystal morphology in evaluating the Moriarty reference?

MS. KANNAPPAN: Objection. Form.

A. I think my purpose in evaluating the Moriarty reference was simply to establish that this provided a method, a fairly detailed method, for the synthesis of treprostinil acid. And that was really

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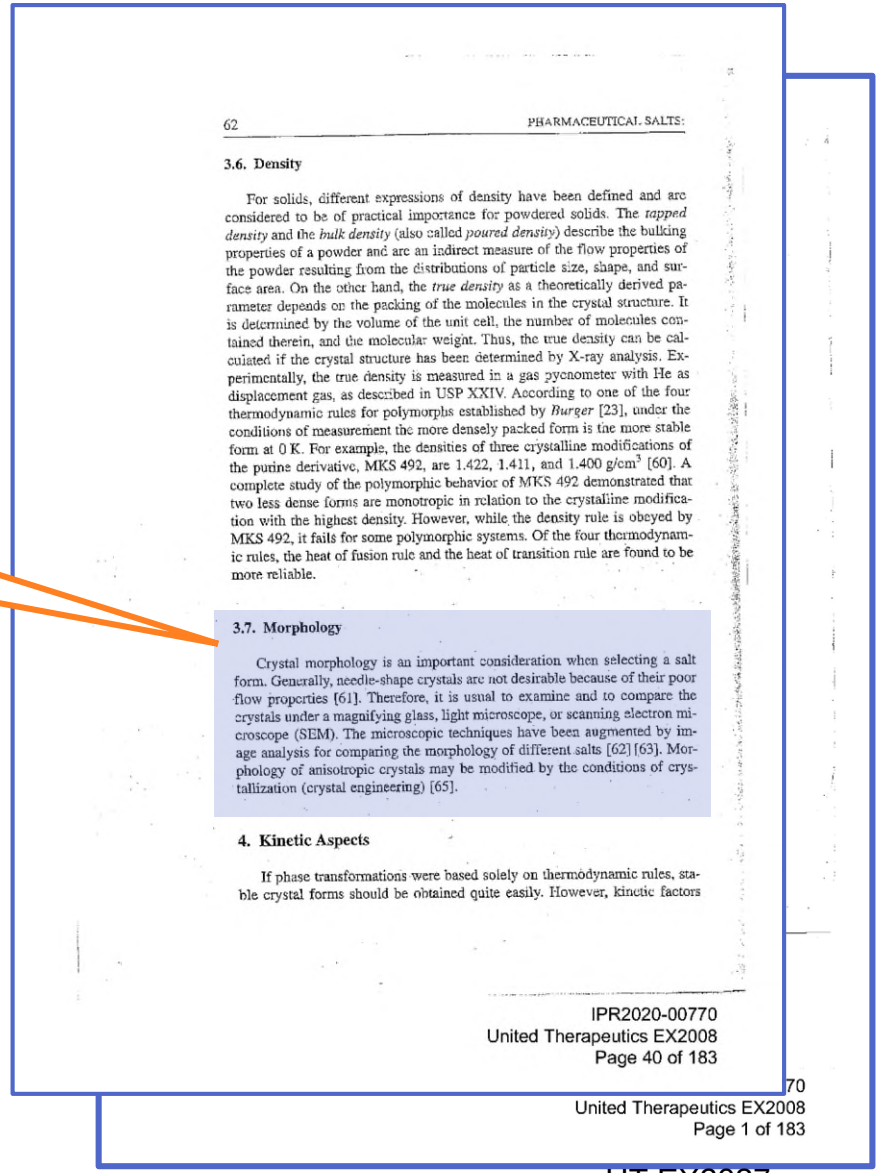
EX2026 (Winkler Depo #1), 134:22-135:17; Paper 6 (POPR), 66-67; EX2002 (Pinal), ¶¶301-02; Paper 12 (POR), 38, 62; EX2025 (Pinal Response), ¶¶267-68.

THE PRIOR ART CONFIRMS MORIARTY'S NEEDLES WOULD HAVE BEEN UNDESIRABLE

"Generally, **needle-shaped crystals are not desirable** because of their poor flow properties."

- Stahl



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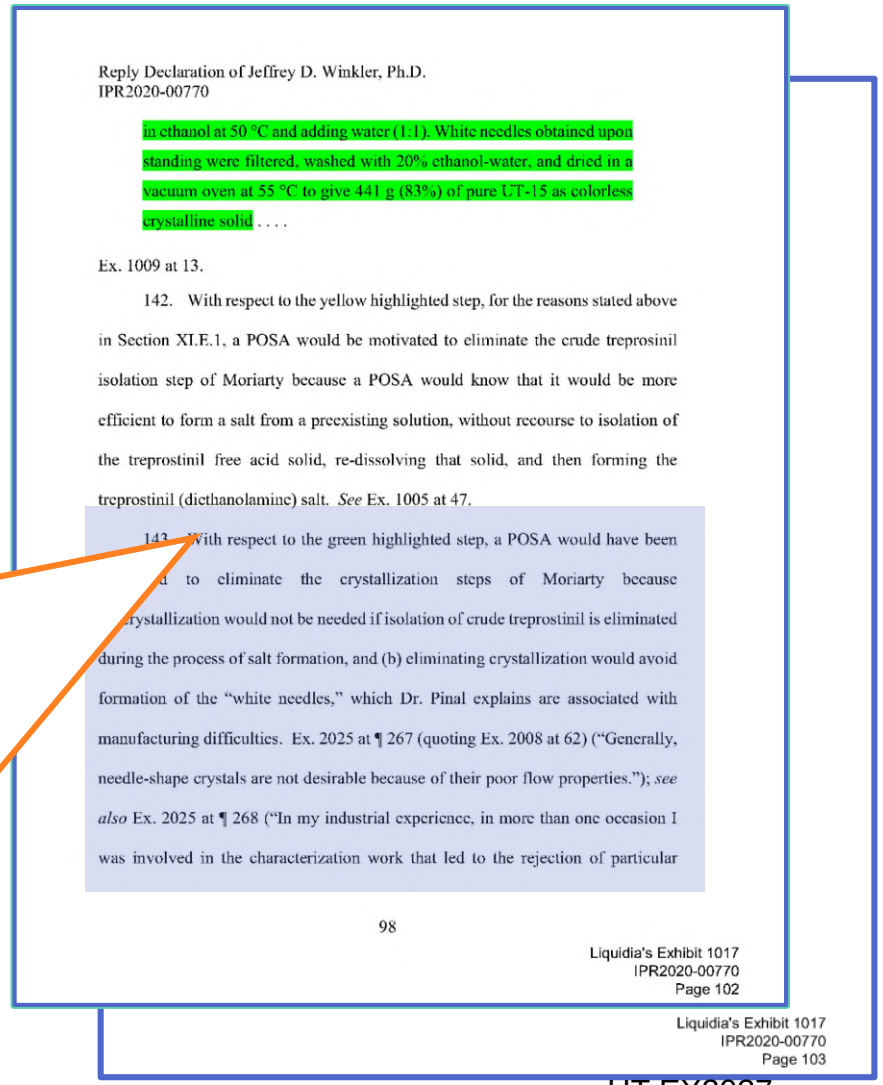
EX2008 (Stahl), 62; ; Paper 6 (POPR), 66-67; EX2002 (Pinal), ¶¶301-02.

…ONLY AT THE REPLY STAGE DID DR. WINKLER DEVELOP A THEORY BASED ON PINAL'S TESTIMONY

"[A] POSA would have been motivated to eliminate the crystallization steps of Moriarty [to]…**avoid formation of the 'white needles,' which Dr. Pinal explains are associated with manufacturing difficulties**…and directly form the treprostinil salt of Phares from the treprostinil solution of Moriarty."

- Dr. Winkler



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in ethanol at 50 °C and adding water (1:1). White needles obtained upon standing were filtered, washed with 20% ethanol-water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid . . . .

Ex. 1009 at 13.

142. With respect to the yellow highlighted step, for the reasons stated above in Section XI.E.1, a POSA would be motivated to eliminate the crude treprosinil isolation step of Moriarty because a POSA would know that it would be more efficient to form a salt from a preexisting solution, without recourse to isolation of the treprostinil free acid solid, re-dissolving that solid, and then forming the treprostinil (diethanolamine) salt. *See* Ex. 1005 at 47.

143. With respect to the green highlighted step, a POSA would have been motivated to eliminate the crystallization steps of Moriarty because (a) crystallization would not be needed if isolation of crude treprostinil is eliminated during the process of salt formation, and (b) eliminating crystallization would avoid formation of the "white needles," which Dr. Pinal explains are associated with manufacturing difficulties. Ex. 2025 at ¶ 267 (quoting Ex. 2008 at 62) ("Generally, needle-shape crystals are not desirable because of their poor flow properties."); *see also* Ex. 2025 at ¶ 268 ("In my industrial experience, in more than one occasion I was involved in the characterization work that led to the rejection of particular

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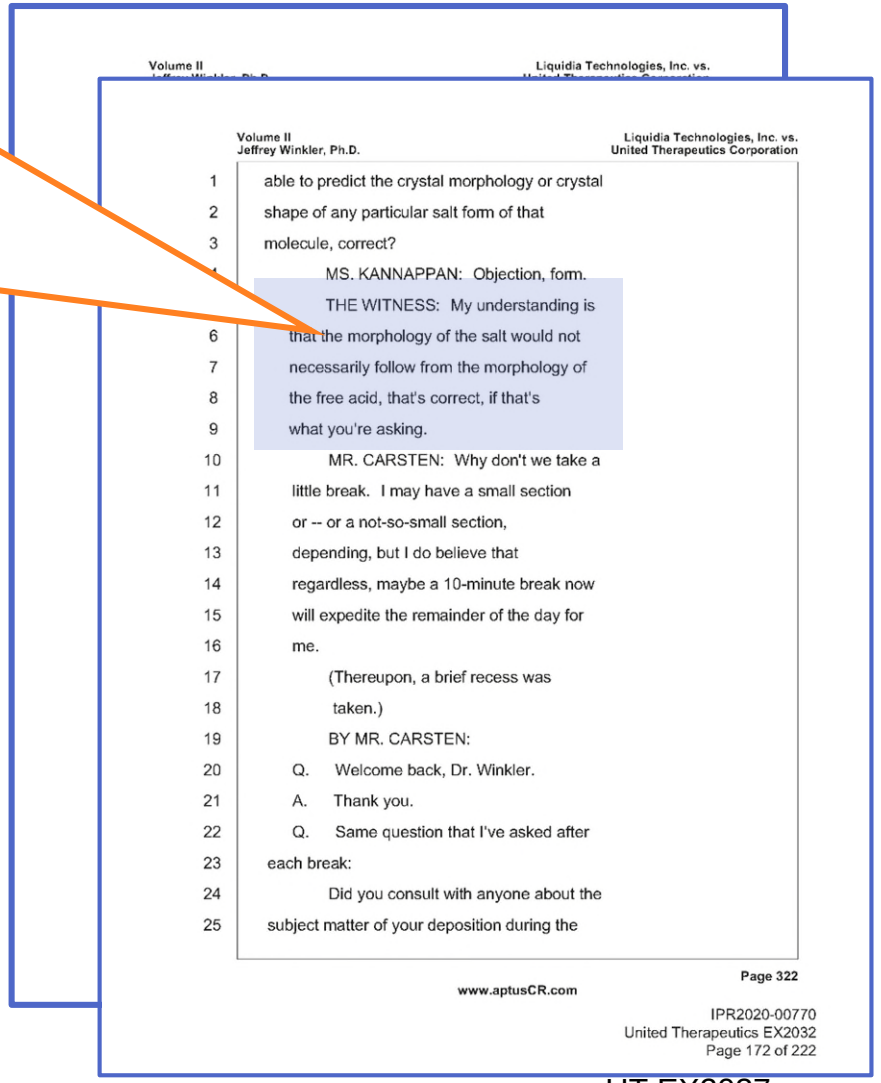
EX1017 (Winkler Reply), ¶143; Paper 25 (Sur-Reply), 1; EX2025 (Pinal Response), ¶268.

BUT EVEN DR. WINKLER AGREES MORPHOLOGY WOULD STILL BE UNPREDICTABLE

"My understanding is that the **morphology of the salt would not necessarily follow from the morphology of the free acid**, that's correct, if that's what you're asking."

- Dr. Winkler



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able to predict the crystal morphology or crystal shape of any particular salt form of that molecule, correct?

MS. KANNAPPAN: Objection, form.

THE WITNESS: My understanding is that the morphology of the salt would not necessarily follow from the morphology of the free acid, that's correct, if that's what you're asking.

MR. CARSTEN: Why don't we take a little break. I may have a small section or -- or a not-so-small section, depending, but I do believe that regardless, maybe a 10-minute break now will expedite the remainder of the day for me.

(Thereupon, a brief recess was taken.)

BY MR. CARSTEN:

Q. Welcome back, Dr. Winkler.

A. Thank you.

Q. Same question that I've asked after each break:

Did you consult with anyone about the subject matter of your deposition during the

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EX2032 (Winkler Depo #2), 321:1-322:9; Paper 25 (Sur-Reply), 1; EX2025 (Pinal Response), ¶268.

BATRA CONFIRMS CRYSTAL MORPHOLOGY CHALLENGES

"The synthesis of UT-15C (3), **faced a number of challenges** during the early development of the final crystallization step. The **first problem to overcome was the tendency of the compound to oil-out** (formation of a gummy mass). The **second obstacle was designing a crystallization process that produced the desired form (Form B) consistently**." - Batra

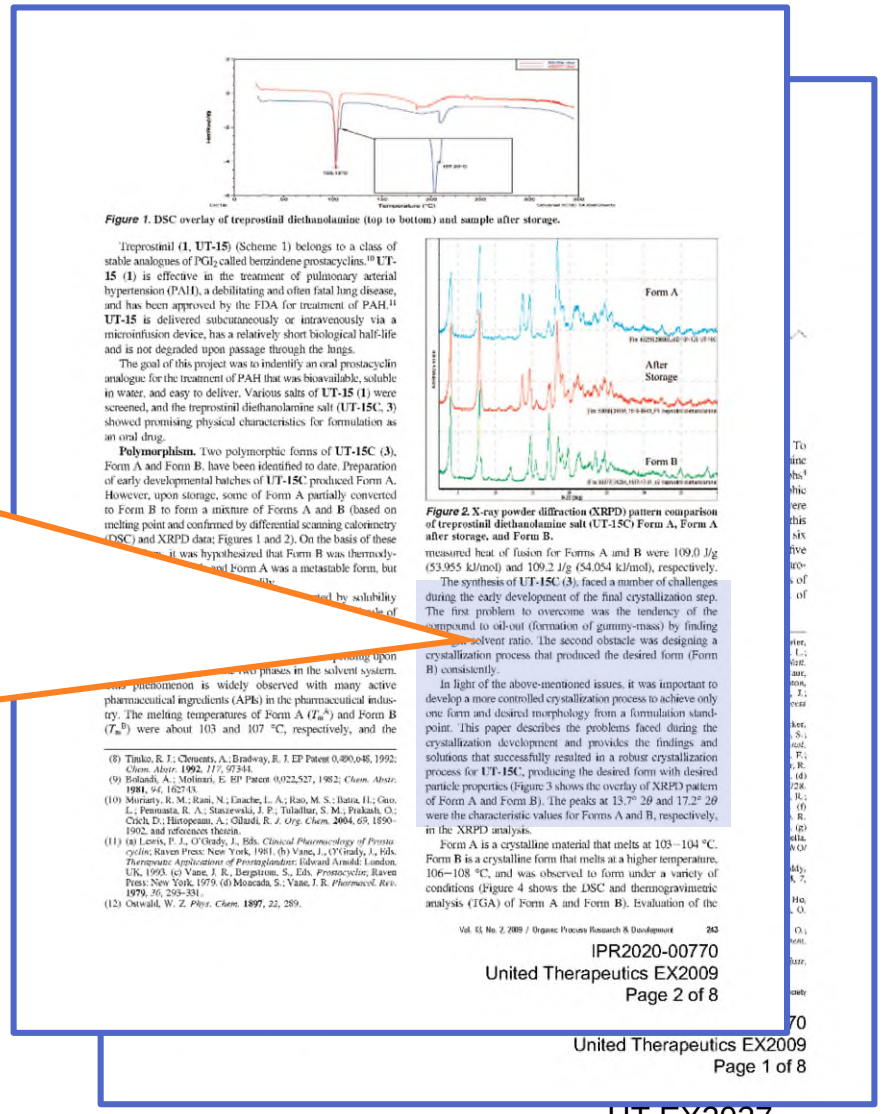

Figure 1. DSC overlay of treprostinil diethanolamine (top to bottom) and sample after storage.

Treprostinil (**1**, **UT-15**) (Scheme 1) belongs to a class of stable analogues of PGI_2 called benzindene prostacyclins.[10] **UT-15** (**1**) is effective in the treatment of pulmonary arterial hypertension (PAH), a debilitating and often fatal lung disease, and has been approved by the FDA for treatment of PAH.[11] **UT-15** is delivered subcutaneously or intravenously via a microinfusion device, has a relatively short biological half-life and is not degraded upon passage through the lungs.

The goal of this project was to indentify an oral prostacyclin analogue for the treatment of PAH that was bioavailable, soluble in water, and easy to deliver. Various salts of **UT-15** (**1**) were screened, and the treprostinil diethanolamine salt (**UT-15C**, **3**) showed promising physical characteristics for formulation as an oral drug.

Polymorphism. Two polymorphic forms of **UT-15C** (**3**), Form A and Form B, have been identified to date. Preparation of early developmental batches of **UT-15C** produced Form A. However, upon storage, some of Form A partially converted to Form B to form a mixture of Forms A and B (based on melting point and confirmed by differential scanning calorimetry (DSC) and XRPD data; Figures 1 and 2). On the basis of these [illegible] it was hypothesized that Form B was thermodynamically [illegible] and Form A was a metastable form, but [illegible] by solubility [illegible] phenomenon is widely observed with many active pharmaceutical ingredients (APIs) in the pharmaceutical industry. The melting temperatures of Form A (T_m^A) and Form B (T_m^B) were about 103 and 107 °C, respectively, and the [illegible] phases in the solvent system. [illegible] upon

(8) Tinuke, R. T.; Clements, A.; Bradway, R. J. EP Patent 0,400,048, 1992; *Chem. Abstr.* **1992**, *117*, 97344.
(9) Bolandi, A.; Molinari, E. EP Patent 0,022,527, 1982; *Chem. Abstr.* **1981**, *94*, 162743.
(10) Moriarty, R. M.; Rani, N.; Enache, L. A.; Rao, M. S.; Batra, H.; Guo, L.; Penmasta, R. A.; Staszewski, J. P.; Tuladhar, S. M.; Prakash, O.; Crich, D.; Hirtopanm, A.; Ciliardi, R. *J. Org. Chem.* **2004**, *69*, 1890–1902, and references therein.
(11) (a) Lewis, P. J., O'Grady, J., Eds. *Clinical Pharmacology of Prostacyclin*; Raven Press: New York, 1981. (b) Vane, J., O'Grady, J., Eds. *Therapeutic Applications of Prostaglandins*; Edward Arnold: London, UK, 1993. (c) Vane, J. R., Bergstrom, S., Eds. *Prostacyclin*; Raven Press: New York, 1979. (d) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293–331.
(12) Ostwald, W. *Z. Phys. Chem.* **1897**, *22*, 289.

Figure 2. X-ray powder diffraction (XRPD) pattern comparison of treprostinil diethanolamine salt (UT-15C) Form A, Form A after storage, and Form B.

measured heat of fusion for Forms A and B were 109.0 J/g (53.955 kJ/mol) and 109.2 J/g (54.054 kJ/mol), respectively.

The synthesis of **UT-15C** (**3**), faced a number of challenges during the early development of the final crystallization step. The first problem to overcome was the tendency of the compound to oil-out (formation of gummy-mass) by finding [illegible] solvent ratio. The second obstacle was designing a crystallization process that produced the desired form (Form B) consistently.

In light of the above-mentioned issues, it was important to develop a more controlled crystallization process to achieve only one form and desired morphology from a formulation standpoint. This paper describes the problems faced during the crystallization development and provides the findings and solutions that successfully resulted in a robust crystallization process for **UT-15C**, producing the desired form with desired particle properties (Figure 3 shows the overlay of XRPD pattern of Form A and Form B). The peaks at 13.7° 2θ and 17.2° 2θ were the characteristic values for Forms A and B, respectively, in the XRPD analysis.

Form A is a crystalline material that melts at 103−104 °C. Form B is a crystalline form that melts at a higher temperature, 106−108 °C, and was observed to form under a variety of conditions (Figure 4 shows the DSC and thermogravimetric analysis (TGA) of Form A and Form B). Evaluation of the

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EX2009 (Batra), 243; Paper 6 (POPR), 53; Paper 12 (POR), 24-25, 38; EX2002 (Pinal), ¶¶231-34, 259, 302; EX2025 (Pinal Response), ¶¶213-16, 268.

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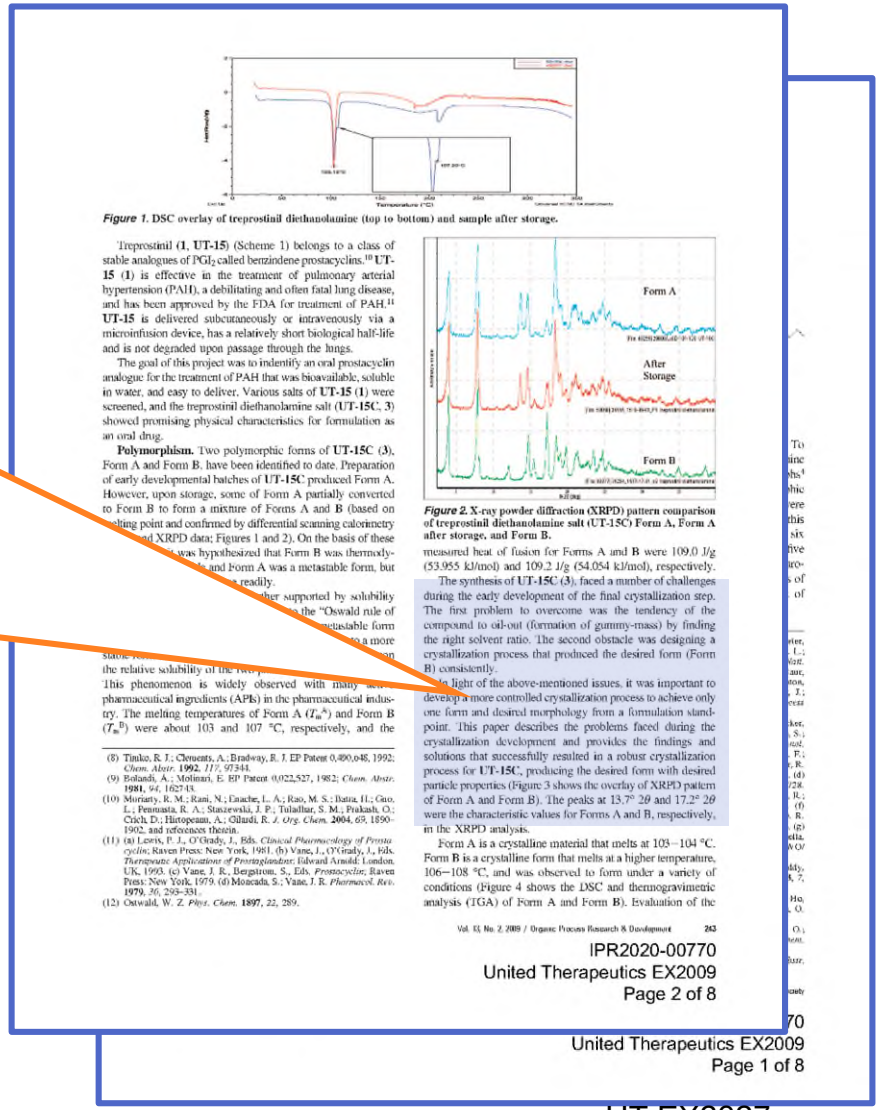

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[illegible] supported by solubility [illegible] the "Oswald rule of [illegible] metastable form [illegible] a more stable [illegible] the relative solubility of the two [illegible]. This phenomenon is widely observed with many active pharmaceutical ingredients (APIs) in the pharmaceutical industry. The melting temperatures of Form A (T_m^A) and Form B (T_m^B) were about 103 and 107 °C, respectively, and the

(8) Tinkle, R. T.; Clements, A.; Bradway, R. J. EP Patent 0,400,048, 1992; *Chem. Abstr.* **1992**, *117*, 97344.
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(10) Moriarty, R. M.; Rani, N.; Enache, L. A.; Rao, M. S.; Batra, H.; Guo, L.; Penmasta, R. A.; Staszewski, J. P.; Tuladhar, S. M.; Prakash, O.; Crich, D.; Hirtopanni, A.; Ciliardi, R. *J. Org. Chem.* **2004**, *69*, 1890–1902, and references therein.
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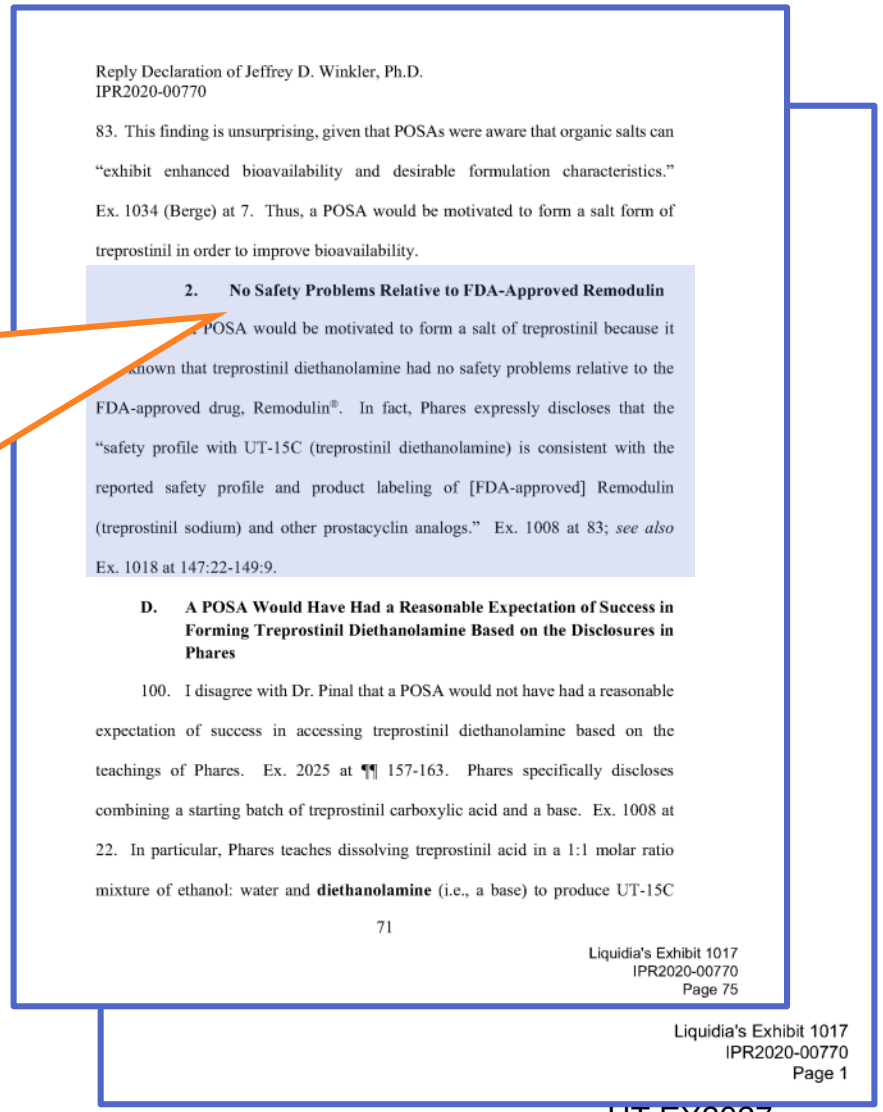
EX2009 (Batra), 243; Paper 6 (POPR), 53; EX2002 (Pinal), ¶¶231-34, 259, 302.

NEW SAFETY MOTIVATION INTRODUCED IN REPLY

"A POSA would be motivated to form a salt of treprostinil because it was known that treprostinil diethanolamine had no safety problems relative to the FDA-approved drug, Remodulin."

- Dr. Winkler



Reply Declaration of Jeffrey D. Winkler, Ph.D.
IPR2020-00770

83. This finding is unsurprising, given that POSAs were aware that organic salts can "exhibit enhanced bioavailability and desirable formulation characteristics." Ex. 1034 (Berge) at 7. Thus, a POSA would be motivated to form a salt form of treprostinil in order to improve bioavailability.

2. No Safety Problems Relative to FDA-Approved Remodulin

A POSA would be motivated to form a salt of treprostinil because it was known that treprostinil diethanolamine had no safety problems relative to the FDA-approved drug, Remodulin®. In fact, Phares expressly discloses that the "safety profile with UT-15C (treprostinil diethanolamine) is consistent with the reported safety profile and product labeling of [FDA-approved] Remodulin (treprostinil sodium) and other prostacyclin analogs." Ex. 1008 at 83; *see also* Ex. 1018 at 147:22-149:9.

D. A POSA Would Have Had a Reasonable Expectation of Success in Forming Treprostinil Diethanolamine Based on the Disclosures in Phares

100. I disagree with Dr. Pinal that a POSA would not have had a reasonable expectation of success in accessing treprostinil diethanolamine based on the teachings of Phares. Ex. 2025 at ¶¶ 157-163. Phares specifically discloses combining a starting batch of treprostinil carboxylic acid and a base. Ex. 1008 at 22. In particular, Phares teaches dissolving treprostinil acid in a 1:1 molar ratio mixture of ethanol: water and **diethanolamine** (i.e., a base) to produce UT-15C

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Liquidia's Exhibit 1017
IPR2020-00770
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Liquidia's Exhibit 1017
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Page 1

UT EX2037

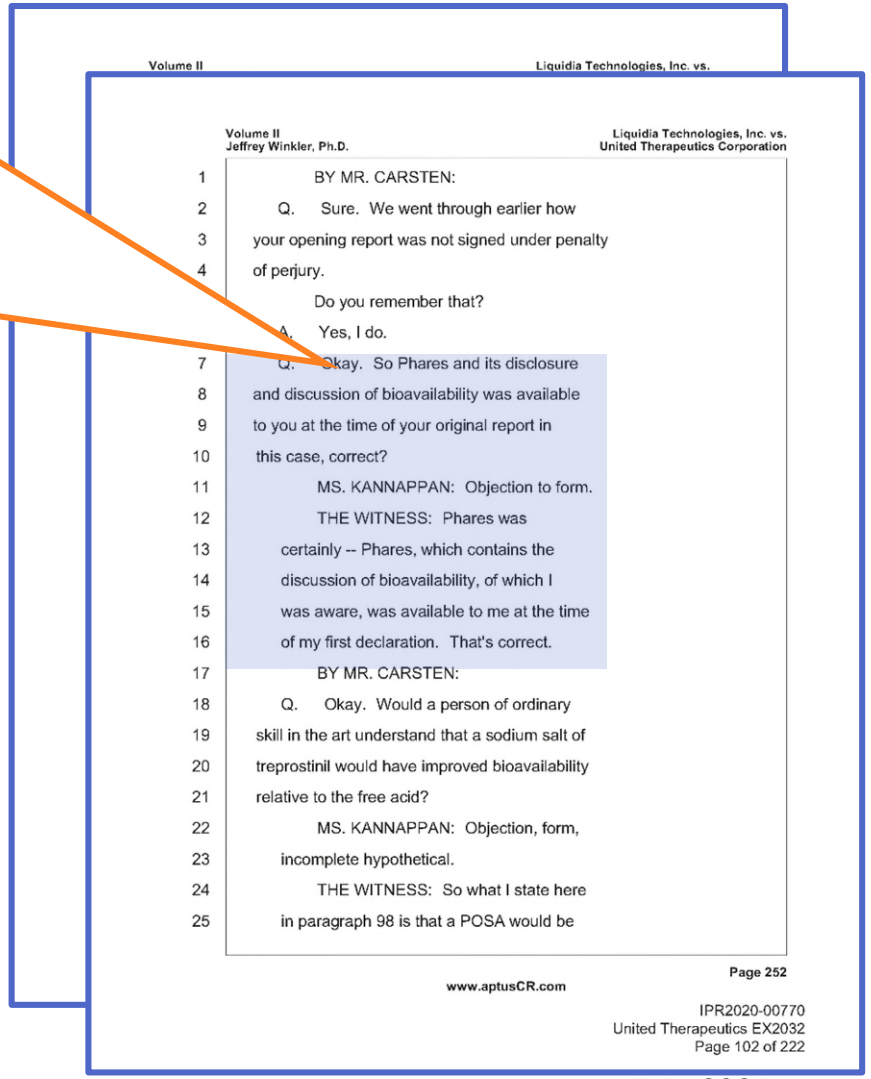
EX1017 (Winkler Reply), ¶99; Paper 25 (Sur-Reply), 2; *see* Paper 15 (Reply), 13-16; EX2032 (Winkler Depo #2), 287:6-296:19.

NEW BIOAVAILABILITY MOTIVATION INTRODUCED IN REPLY

Q: "Phares and its disclosure and discussion of bioavailability was available to you at the time of your original report in this case, correct?

***

Dr. Winkler: "**Phares, which contains the discussion of bioavailability, of which I was aware, was available to me at the time of my first declaration.** That is correct."



Volume II
Jeffrey Winkler, Ph.D.
Liquidia Technologies, Inc. vs.
United Therapeutics Corporation

BY MR. CARSTEN:
Q. Sure. We went through earlier how your opening report was not signed under penalty of perjury.
Do you remember that?
A. Yes, I do.
Q. Okay. So Phares and its disclosure and discussion of bioavailability was available to you at the time of your original report in this case, correct?
MS. KANNAPPAN: Objection to form.
THE WITNESS: Phares was certainly -- Phares, which contains the discussion of bioavailability, of which I was aware, was available to me at the time of my first declaration. That's correct.
BY MR. CARSTEN:
Q. Okay. Would a person of ordinary skill in the art understand that a sodium salt of treprostinil would have improved bioavailability relative to the free acid?
MS. KANNAPPAN: Objection, form, incomplete hypothetical.
THE WITNESS: So what I state here in paragraph 98 is that a POSA would be

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United Therapeutics EX2032
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UT EX2037

EX2032 (Winkler Depo #2), 250:11-252:16; Paper 25 (Sur-Reply), 2; *see* Paper 15 (Reply), 13-16; EX1017 (Winkler Reply), ¶98.

LIQUIDIA FAILED TO ESTABLISH REASONABLE EXPECTATION OF SUCCESS

LIQUIDIA FAILS TO ANALYZE THE CLAIMS AS A WHOLE

- Liquidia argues that "Phares successfully performed" the step of reacting treprostinil with diethanolamine to form a treprostinil diethanolamine salt.
- But that's not relevant to the dispute.
- And none of the claims are directed solely to reacting treprostinil with diethanolamine.

Criticizing piecemeal analysis of both the claims and the prior art that "**selected bits and pieces** from prior art patents that might be modified to fit its **legally incorrect** interpretation of each claim as consisting of one word."

- *KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007); accord Panduit Corp. v. Dennison Mfg. Co., 810* F.2d 1561, 1577-78 (Fed. Cir. 1987)

Paper 6 (POPR), 66.

LIQUIDIA'S EXPECTATION OF SUCCESS ARGUMENT IS ALL CONCLUSION + NO SUBSTANCE

- Dr. Winkler provides no support for his conclusions that a POSA would have had a reasonable expectation of success in achieving what Liquidia suggests.

- Expert testimony without basis is entitled to little or no weight.
  - 37 C.F.R. §42.65(a)

"It is well established that **conclusory statements** of counsel or a witness that a patent is invalid **do not raise a genuine issue of fact.**"

- *Biotec Biologische Naturverpackungen v. Biocorp., Inc.*.
249 F.3d 1341, 1353 (Fed. Cir. 2001)

Paper 6 (POPR), 65-67; EX2002 (Pinal), ¶¶294-308.

THE ART TEACHES CHALLENGES, NOT SUCCESSES

- Moriarty teaches difficulties associated with treprostinil's synthesis, purification, and scale up.

- Phares teaches complicating polymorphic forms and hygroscopicity of treprostinil diethanolamine.

- **A POSA would have been disincentivized to work on a challenging synthesis that yields multiple polymorphic forms of expected hygroscopic material.**

Paper 6 (POPR), 65-67; EX2002 (Pinal), ¶¶294-308; Paper 12 (POR), 24-25, 37-38.

LIQUIDIA'S OWN ART HIGHLIGHTS UNPREDICTABILITY

"Choosing the appropriate salt, however, **can be a very difficult task**, since each salt imparts unique properties to the parent compound…Unfortunately, there is **no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound**. Furthermore, even after many salts of the same basic agent have been prepared, **no efficient screening techniques exist** to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation properties." - Berge

Journal of Pharmaceutical Sciences

JANUARY 1977

VOLUME 66 NUMBER 1

REVIEW ARTICLE

Pharmaceutical Salts

STEPHEN M. BERGE *‡, LYLE D. BIGHLEY *, and DONALD C. MONKHOUSE *

Keyphrases □ Pharmaceutical salts—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Salts, pharmaceutical—general pharmacy, physicochemical properties, bioavailability, pharmaceutical properties, toxicology, review □ Physicochemical properties—dissolution, solubility, stability, and organoleptic properties of pharmaceutical salts, review □ Bioavailability—formulation effects, absorption alteration and pharmacokinetics of pharmaceutical salts, review □ Toxicology—pharmaceutical salts, review

CONTENTS

The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form. Choosing the appropriate salt, however, can be a very difficult task, since each salt imparts unique properties to the parent compound.

Salt-forming agents are often chosen empirically. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis: cost of raw materials, ease of crystallization, and percent yield. Other basic considerations include stability, hygroscopicity, and flowability of the resulting bulk drug. Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.

Some decision-making models have, however, been developed to help predict salt performance. For example, Walkling and Appino (1) described two techniques, "decision analysis" and "potential problem analysis," and applied them to the selection of the most suitable derivative of an organic acid for development as a tablet. The derivatives considered were the free acid and the potassium, sodium, and calcium salts. Both techniques are based on the chemical, physical, and biological properties of these specific derivatives and offer a promising avenue for developing optimal salt forms.

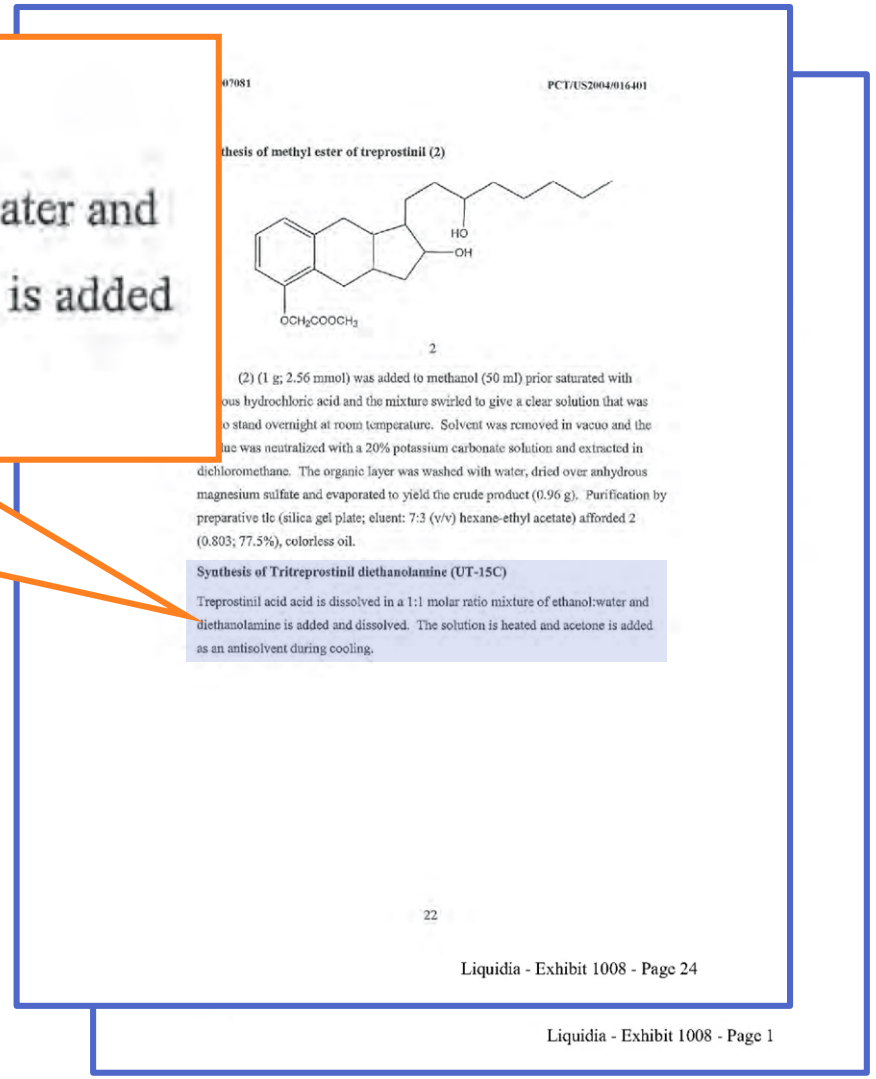
Information on salts is widely dispersed throughout the pharmaceutical literature, much of which addresses the use of salt formation to prolong the release of the active component, thereby eliminating various undesirable drug properties (2–6). This review surveys literature of the last 25 years, emphasizing comparisons between the properties of different salt forms of the same compound. Included also is a discussion of potentially useful salt forms. Our purpose is twofold: to present an overview of the many different salts from which new drug candidates can be chosen and

EX1034 (Berge), 1; Paper 25 (Sur-Reply), 1-2.

PHARES DOES NOT TEACH USEFUL SYNTHESES OF A PHARMACEUTICAL BATCH OF TREPROSTINIL OR TREPROSTINIL DIETHANOLAMINE

Synthesis of Tritreprostinil diethanolamine (UT-15C)

Treprostinil acid acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.



07081 PCT/US2004/016401

thesis of methyl ester of treprostinil (2)

2

(2) (1 g; 2.56 mmol) was added to methanol (50 ml) prior saturated with ous hydrochloric acid and the mixture swirled to give a clear solution that was o stand overnight at room temperature. Solvent was removed in vacuo and the ue was neutralized with a 20% potassium carbonate solution and extracted in dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield the crude product (0.96 g). Purification by preparative tlc (silica gel plate; eluent: 7:3 (v/v) hexane-ethyl acetate) afforded 2 (0.803; 77.5%), colorless oil.

Synthesis of Tritreprostinil diethanolamine (UT-15C)

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Liquidia - Exhibit 1008 - Page 24

Liquidia - Exhibit 1008 - Page 1

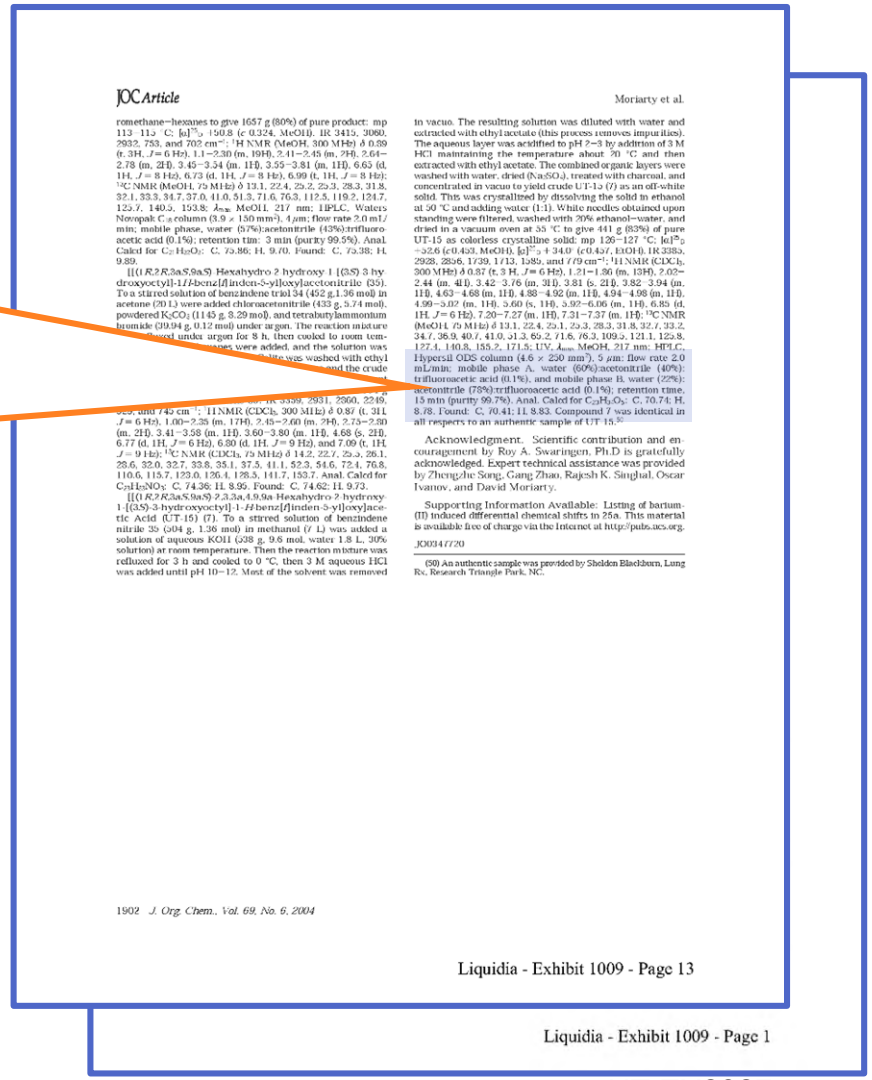
UT EX2037

EX1008 (Phares), 22; Paper 6 (POPR), 51; EX2025 (Pinal Response), ¶¶115-17; Paper 12 (POR), 30.

LIQUIDIA FAILED TO MEET ITS BURDEN ON IMPURITIES

MORIARTY DOES NOT TEACH SPECIFIC IMPURITIES

127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH, 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm^2), 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%): trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.41; H, 8.83. Compound 7 was identical in all respects to an authentic sample of UT-15.[50]



JOC Article

Moriarty et al.

...romethane–hexanes to give 1657 g (80%) of pure product: mp 113–115 °C; $[\alpha]^{25}_D$ 150.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^{1}H NMR (MeOH, 300 MHz) δ 0.59 (t, 3H, *J* = 6 Hz), 1.1–2.30 (m, 19H), 2.41–2.45 (m, 2H), 2.64–2.78 (m, 2H), 3.45–3.54 (m, 1H), 3.55–3.81 (m, 11H), 6.65 (d, 1H, *J* = 8 Hz), 6.73 (d, 1H, *J* = 8 Hz), 6.99 (t, 1H, *J* = 8 Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters Novapak C$_{18}$ column (3.9 × 150 mm^2), 4 μm; flow rate 2.0 mL/min; mobile phase, water (57%):acetonitrile (43%):trifluoroacetic acid (0.1%); retention time 3 min (purity 99.5%). Anal. Calcd for $C_{21}H_{28}O_3$: C, 75.86; H, 9.70. Found: C, 75.38; H, 9.89.

[[(1*R*,2*R*,3a*S*,9a*S*)-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (35). To a stirred solution of benzindene triol 34 (452 g, 1.36 mol) in acetone (20 L) were added chloroacetonitrile (433 g, 5.74 mol), powdered K_2CO_3 (1145 g, 8.29 mol), and tetrabutylammonium bromide (39.94 g, 0.12 mol) under argon. The reaction mixture ...stirred under argon for 8 h, then cooled to room tem... were added, and the solution was ...was washed with ethyl ... and the crude ... IR 3539, 2931, 2860, 2249, ... and 745 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.87 (t, 3H, *J* = 6 Hz), 1.00–2.35 (m, 17H), 2.45–2.60 (m, 2H), 2.75–2.80 (m, 2H), 3.41–3.58 (m, 1H), 3.60–3.80 (m, 1H), 4.68 (s, 2H), 6.77 (d, 1H, *J* = 6 Hz), 6.80 (d, 1H, *J* = 9 Hz), and 7.09 (t, 1H, *J* = 9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

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JO034772O

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UT EX2037

EX1009 (Moriarty), 13; Paper 6 (POPR), 67-69; EX2002 (Pinal), ¶¶300-02; Paper 12 (POR), 52, 56-57, 62-64.

MORIARTY DOES NOT TEACH SPECIFIC IMPURITIES

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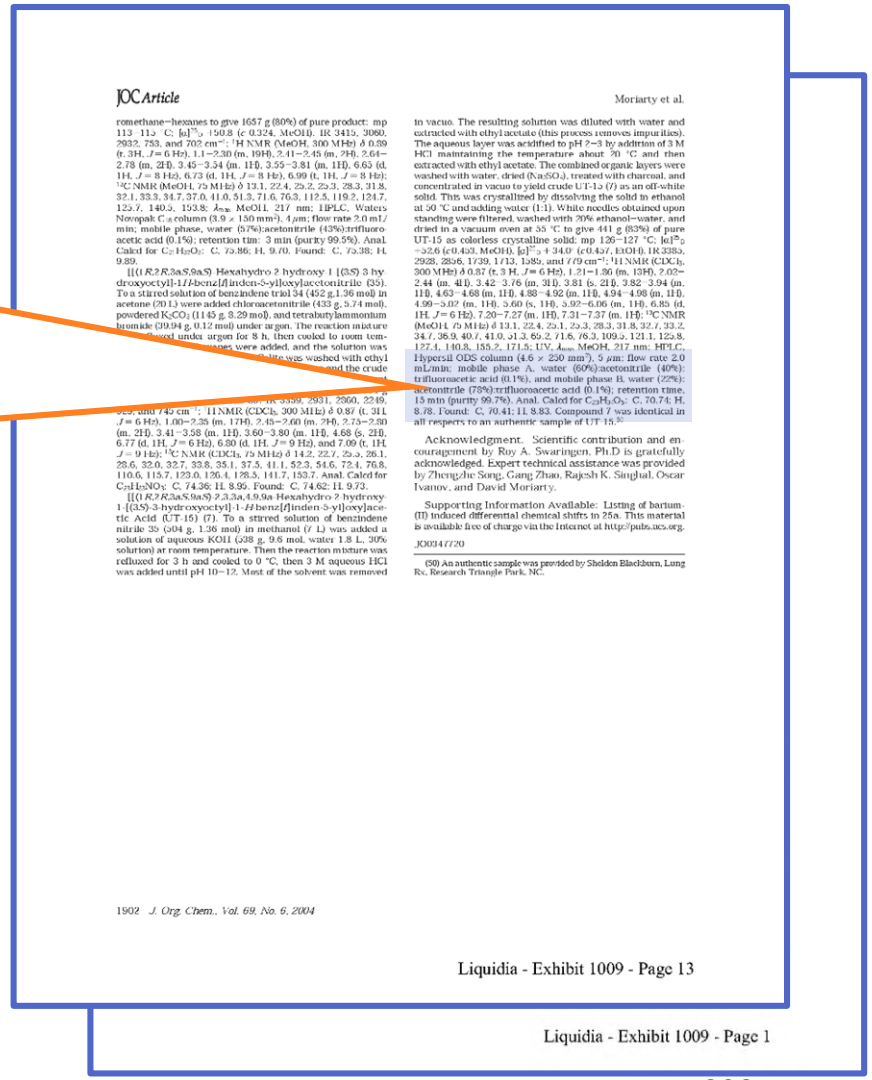
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Liquidia - Exhibit 1009 - Page 1

- Liquidia has not proven that impurities are inherently the result of the claimed process steps as claim 1 requires.
  - Liquidia's burden to demonstrate the 0.3% impurities met the limits of the claim.
  - Undisputed that Moriarty does not teach at least steps (c)-(d) of claim 1.

UT EX2037

EX1009 (Moriarty), 13; Paper 6 (POPR), 67-69; EX2002 (Pinal), ¶¶300-02; Paper 12 (POR), 52, 56-57, 62-64.

LIQUIDIA FAILED TO MEET ITS BURDEN ON 2.9 G SCALE

MORIARTY DOES NOT TEACH THE CLAIMED PHARMACEUTICAL BATCH AT A 2.9 GRAM SCALE

- The parties agree that Moriarty does not teach steps (c)-(e), and thus, does not teach a pharmaceutical batch prepared from a process that includes steps (c)-(e) at a 2.9 gram scale.

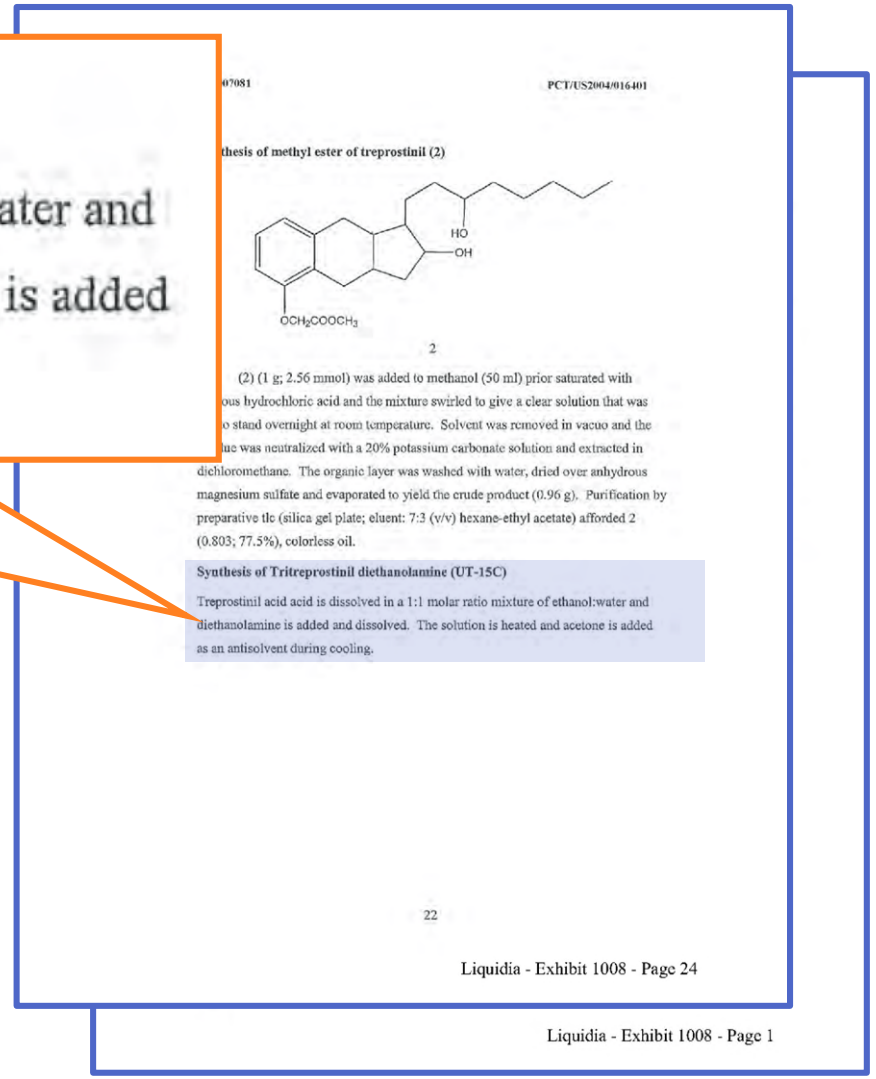
- Liquidia only provides an unsupported argument that the claimed 2.9 gram amount "would be possible."

Paper 6 (POPR), 68; EX2002 (Pinal), ¶¶304-08; Paper 12 (POR), 43-44; *see* Paper 1 (Petition), 63-64 (citing EX1002 (Winkler), ¶189).

PHARES DOES NOT TEACH ANY PARTICULAR AMOUNT OF TREPROSTINIL DIETHANOLAMINE

Synthesis of Tritreprostinil diethanolamine (UT-15C)

Treprostinil acid acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.



07081 PCT/US2004/016401

thesis of methyl ester of treprostinil (2)

2

(2) (1 g; 2.56 mmol) was added to methanol (50 ml) prior saturated with ous hydrochloric acid and the mixture swirled to give a clear solution that was o stand overnight at room temperature. Solvent was removed in vacuo and the lue was neutralized with a 20% potassium carbonate solution and extracted in dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield the crude product (0.96 g). Purification by preparative tlc (silica gel plate; eluent: 7:3 (v/v) hexane-ethyl acetate) afforded 2 (0.803; 77.5%), colorless oil.

Synthesis of Tritreprostinil diethanolamine (UT-15C)

Treprostinil acid acid is dissolved in a 1:1 molar ratio mixture of ethanol:water and diethanolamine is added and dissolved. The solution is heated and acetone is added as an antisolvent during cooling.

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Paper 6 (POPR), 51; EX2025 (Pinal Response), ¶¶102, 165-71, 270-74; Paper 12 (POR), 43-44.

PHARES DOES NOT TEACH 2.9 G OF ANYTHING

- Liquidia asserts “Phares teaches a reaction of ~1 g-scale quantities.”

- Only one reaction is ~1 gram scale—a reaction to form treprostinil methyl ester, which is irrelevant to treprostinil diethanolamine.
  - Uses 1.087 g treprostinil as a starting material to yield crude treprostinil methyl ester.
  - Acidification and purification yields 0.803 grams of purified methyl ester.
  - The methyl ester was not merely a final product, rather it was used as an intermediate to make other prodrugs.

Paper 6 (POPR), 60; EX2002 (Pinal), ¶¶220, 279-83; Paper 12 (POR), 43-44; EX2025 (Pinal Response), ¶¶102, 165-71, 270-74; Paper 1 (Petition), 39; EX1002 (Winkler), ¶102; EX1008 (Phares), 18-19, 22.

THE SCALE IN QUESTION IS PRODUCT, NOT STARTING MATERIAL

- Dr. Winkler cites his own experience in asserting reactions can be scaled up "by a factor of 3" with a reasonable expectation of success.
  - Scaling up an irrelevant synthesis of treprostinil methyl ester by a factor of 3 does not inform scale-up of a treprostinil salt.

- Dr. Winkler repeatedly confuses the amount of starting materials and the amount of product a synthesis yields.
  - Cites, *e.g.*, EX1031 to support contention that benchtop scale-type work in a lab includes working on over 2.9 grams, but EX1021 results in just 5 mg of end product.

Paper 6 (POPR), 60; Paper 25 (Sur-Reply), 15-16; EX2002 (Pinal), ¶¶220, 279-83; EX2025 (Pinal Response), ¶¶102, 165-71, 270-74, 293-94, 297; *see* EX2032 (Winkler Depo #2), 306:6-307:11.

LIQUIDIA FAILED TO MEET ITS BURDEN ON STORAGE IN CLAIMS 6 AND 7

CLAIMS 6 + 7 REQUIRE STABILITY AT AMBIENT TEMPERATURE FOR STORAGE

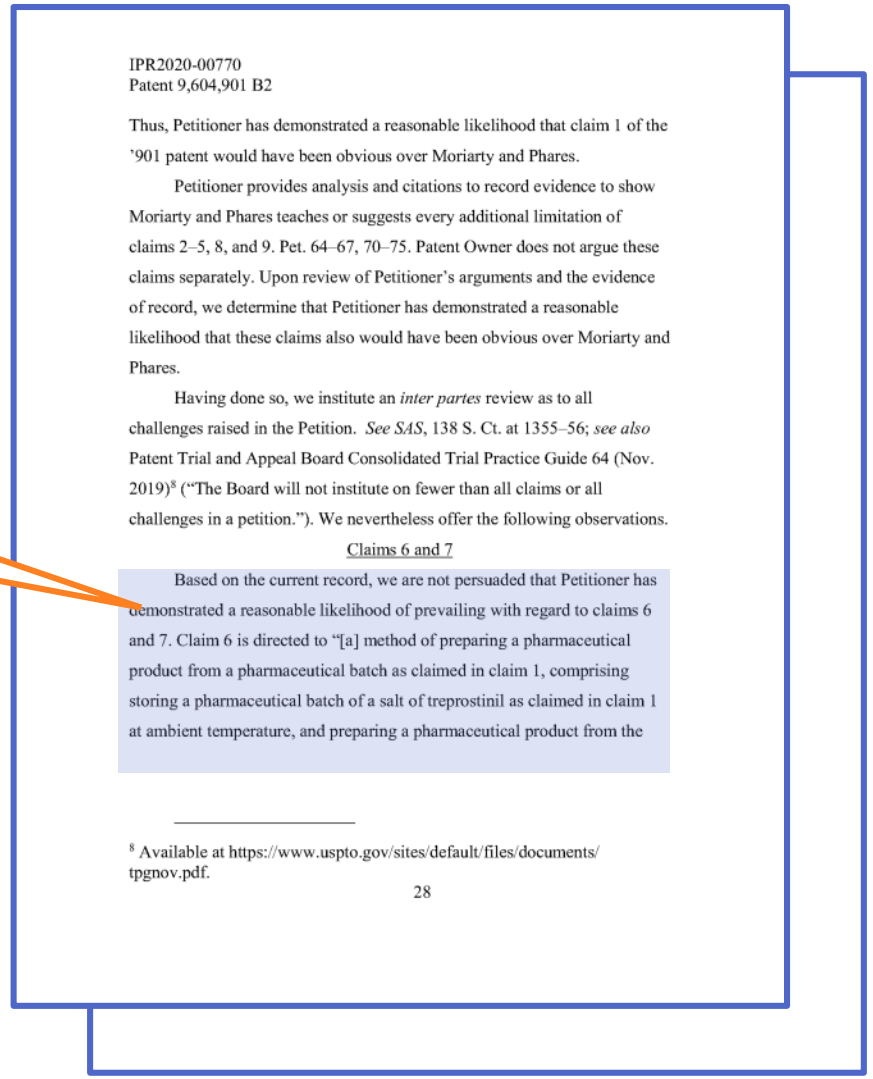
6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim **1**, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim **1** at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim **6**, wherein the salt of treprostinil is a diethanolamine salt.

EX1001 (901 Patent), claims 6-7; Paper 6 (POPR), 52; Paper 12 (POR), 50-51, 65-66; Paper 25 (Sur-Reply), 10-11.

BOARD NOT PERSUADED ON CLAIMS 6 + 7

"Based on the current record, we are not persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing with regard to claims 6 and 7." - Institution Decision



IPR2020-00770
Patent 9,604,901 B2

Thus, Petitioner has demonstrated a reasonable likelihood that claim 1 of the '901 patent would have been obvious over Moriarty and Phares.

Petitioner provides analysis and citations to record evidence to show Moriarty and Phares teaches or suggests every additional limitation of claims 2–5, 8, and 9. Pet. 64–67, 70–75. Patent Owner does not argue these claims separately. Upon review of Petitioner's arguments and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood that these claims also would have been obvious over Moriarty and Phares.

Having done so, we institute an *inter partes* review as to all challenges raised in the Petition. *See SAS*, 138 S. Ct. at 1355–56; *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide 64 (Nov. 2019)[8] ("The Board will not institute on fewer than all claims or all challenges in a petition."). We nevertheless offer the following observations.

Claims 6 and 7

Based on the current record, we are not persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing with regard to claims 6 and 7. Claim 6 is directed to "[a] method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the

[8] Available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

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Paper 7 (Institution Decision), 15-16; Paper 12 (POR), 9-10; EX2025, ¶91.

LIQUIDIA'S HASTY RETREAT

- Liquidia has not added any further evidence pertaining to storage or stability
- If anything, Liquidia and its expert have backtracked from the its initial positions regarding stability and storage.
  - Dr. Winkler's retraction of the polymorph stability arguments

Paper 37 (UT's Reply iso MtE), 3-4; Paper 25 (Sur-Reply), 16-19, 24-25.

NEITHER MORIARTY NOR PHARES TEACHES ANYTHING ABOUT STORAGE

- Moriarty does not mention or suggest storage or storage conditions
- Phares does not mention or suggest storage or storage conditions
- **Liquidia fails to explain why a POSA would have undertaken storage at ambient temperature, when treprostinil was known to be unstable and degrade under such conditions.**

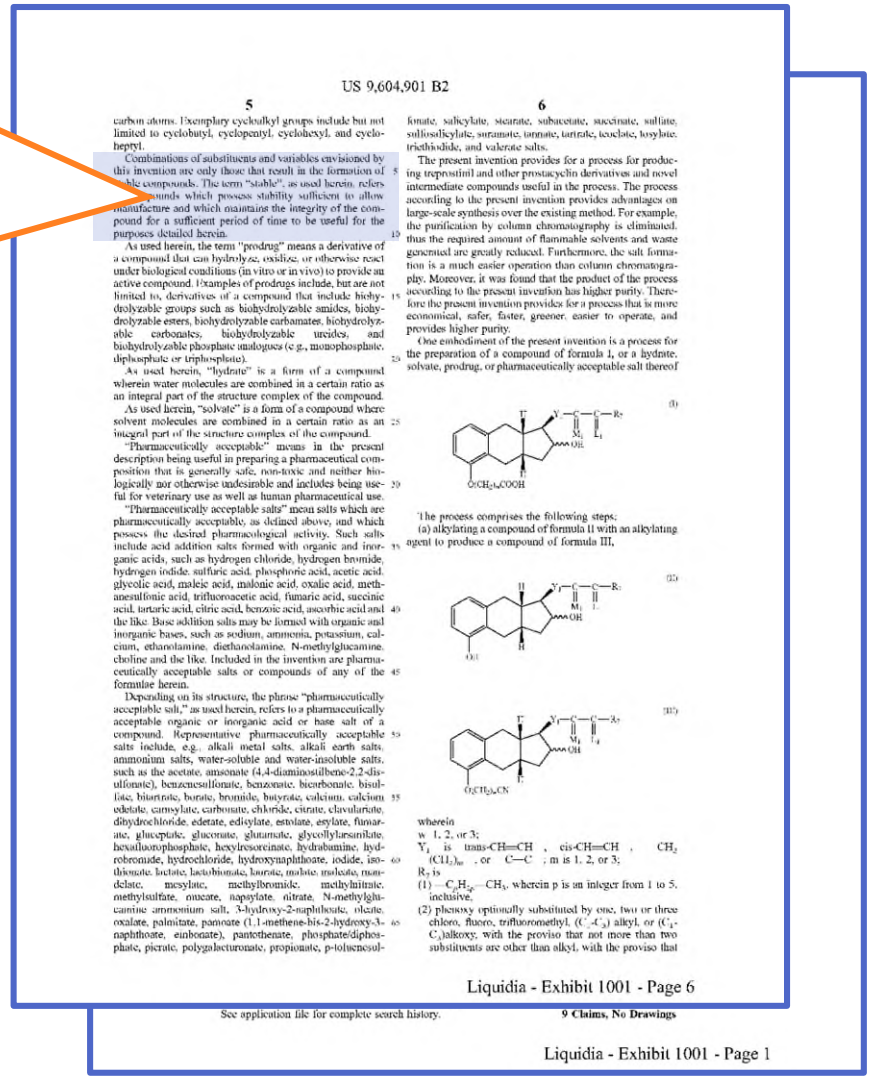
Paper 25 (Sur-Reply), 24-25; Paper 12 (POR), 50-51, 65-66.

LIQUIDIA FAILED TO MEET ITS BURDEN ON PHARMACEUTICAL BATCH

THE ’901 PATENT CLAIMS REQUIRE STABILITY

“…compounds which possess stability sufficient to allow manufacture and which **maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed** herein.”

- The ’901 Patent



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5 6

carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

As used herein, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound. Examples of prodrugs include, but are not limited to, derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (e.g., monophosphate, diphosphate or triphosphate).

As used herein, “hydrate” is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

As used herein, “solvate” is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

“Pharmaceutically acceptable” means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

“Pharmaceutically acceptable salts” mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase “pharmaceutically acceptable salt,” as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfite, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, embonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof

(I)

The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,

(II)

(III)

wherein

w 1, 2, or 3;

Y_1 is trans-CH=CH , cis-CH=CH , CH_2 $(CH_2)_m$, or C—C ; m is 1, 2, or 3;

R_5 is

(1) $—C_pH_{2p}—CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_5) alkyl, or (C_1-C_5)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that

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See application file for complete search history.

9 Claims, No Drawings

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EX1001 (901 Patent), 5:4-10; Paper 6 (POPR), 51-52; Paper 12 (POR), 9-10, 43, 51-52; Paper 25 (Sur-Reply), 10-11; EX2025 (Pinal Response), ¶¶78, 91.

THE CLAIMED PHARMACEUTICAL BATCHES AND PRODUCTS ALL REQUIRE STABILITY

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and
wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim **1**, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim **1**.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim **1**.

5. The product of claim **4**, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim **1**, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim **1** at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim **6**, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim **1**, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim **8**, wherein the salt of treprostinil is a diethanolamine salt.

EX1001, claims 1-9; Paper 6 (POPR), 51-55; Paper 12 (POR), 9-10, 43, 51-52; EX2025 (Pinal Response), ¶¶78, 91.

THE CLAIMED PHARMACEUTICAL BATCHES AND PRODUCTS ALL REQUIRE STABILITY

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wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim **1**, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim **1**.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim **1**.

5. The product of claim **4**, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim **1**, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim **1** at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim **6**, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim **1**, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim **8**, wherein the salt of treprostinil is a diethanolamine salt.

EX1001, claims 1-9; Paper 6 (POPR), 51-55; Paper 12 (POR), 9-10, 43, 51-52; EX2025 (Pinal Response), ¶¶78, 91.

TREPROSTINIL'S POLYMORPHIC NATURE THREATENS STABILITY

- Polymorphs are chemically identical solids crystalized in physically different crystalline lattice structures.
- Polymorphs are a nightmare for the pharmaceutical industry, and require an immense amount of work to evaluate, manufacture, and store reliably.
- Treprostinil diethanolamine has an inherent "tendency…to oil-out (formation of gummy mass)."

Paper 6 (POPR), 52-55; EX2002 (Pinal), ¶¶221-41; EX2009 (Batra), 242 (polymorph incidents have "serious implications" for market and patients; "project was suspended until a modified procedure was found"), 243 (26,000+ crystallizations for a study on polymorphs).

THE POLYMORPH INTERCONVERSION DATA IS NOT REPRESENTATIVE OF STORAGE CONDITIONS

Interconversion Studies of Treprostinil Diethanolamine

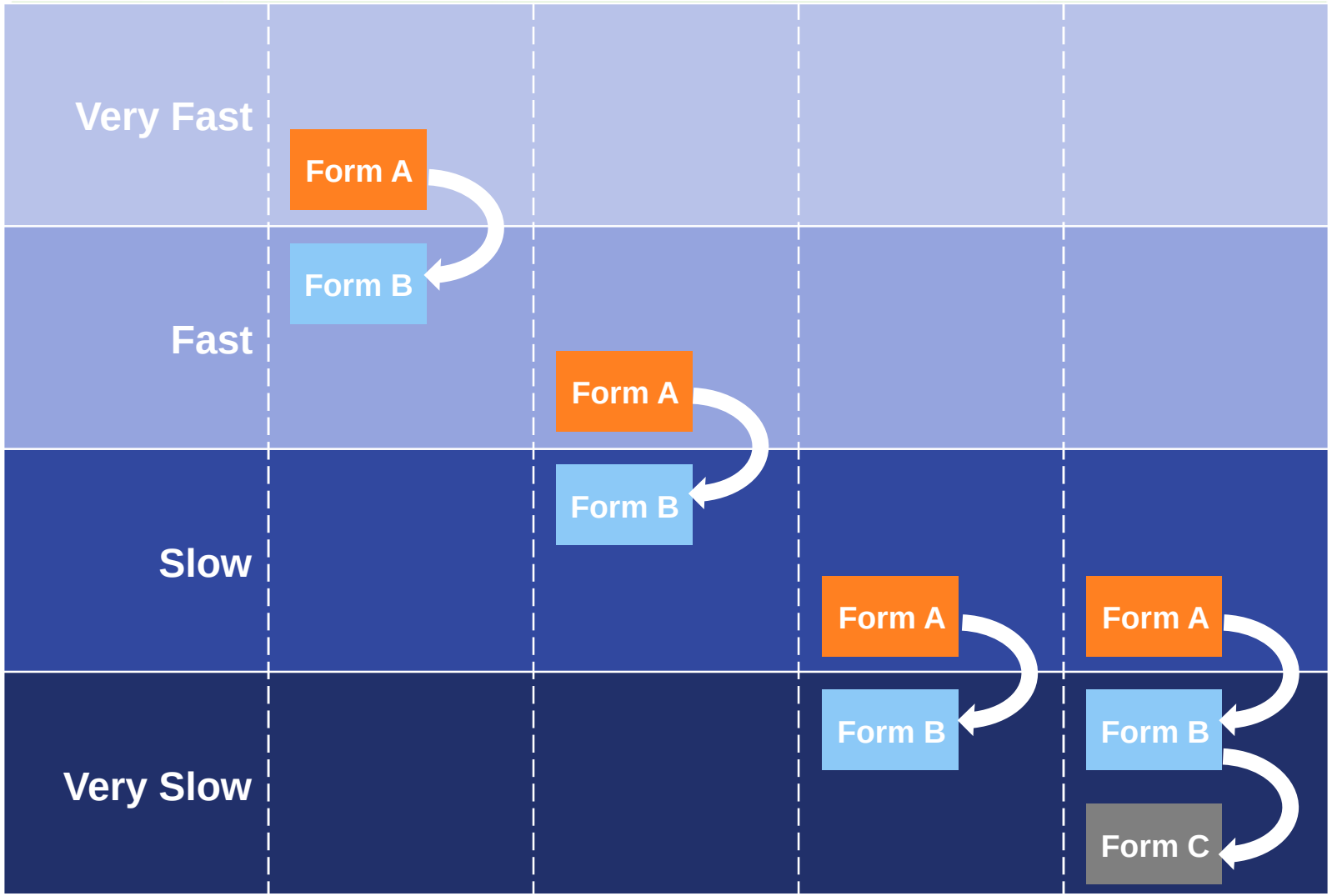
Sample No.	Forms	Solvent	Experiment/ Starting Materials	Temperature	Time
1557-22-01	A vs. B	isopropanol	solid mixture # 1557-20-01[a]	ambient	7 days
1557-47-02	A vs. B		solid mixture # 1557-35-01[d]	15 °C	11 days
1557-33-02	A vs. B		solid mixture # 1557-35-01[d]	30°C	1 day
1557-21-02[c]	A vs. B		solid mixture # 1557-20-01[b]	50°C	-
1557-20-03	A vs. B	tetrahydrofuran	solid mixture # 1557-20-01[c]	ambient	7 days
1557-47-01	A vs. B		solid mixture # 1557-35-01[d]	15°C	11 days
1557-33-01	A vs. B		solid mixture # 1557-35-01[d]	30°C	1 day
1557-21-01[c]	A vs. B		solid mixture # 1557-20-01[c]	50°C	-

a. saturated solution Sample ID 1557-21-03
b. saturated solution Sample ID 1519-96-03
c. saturated solution Sample ID 1519-96-02
d. saturated solution prepared just prior to addition of solids

UT EX2037

EX1008 (Phares), 89, Table 17; Paper 6 (POPR), 40-41; EX2002 (Pinal), ¶¶221-40; *see* EX1002 (Winkler), ¶¶114, 203.

RELATIVE POLYMORPH STABILITY DOES NOT EQUATE TO STORAGE STABILITY



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EX2002 (Pinal), ¶227; *id.*, ¶¶221-40; Paper 6 (POPR), 40-41; *see* EX1002 (Winkler), ¶¶114, 203.

PHARES DOES NOT TEACH STABILITY; SUGGESTS INSTABILITY

- General nature of polymorphs and salts suggest instability.

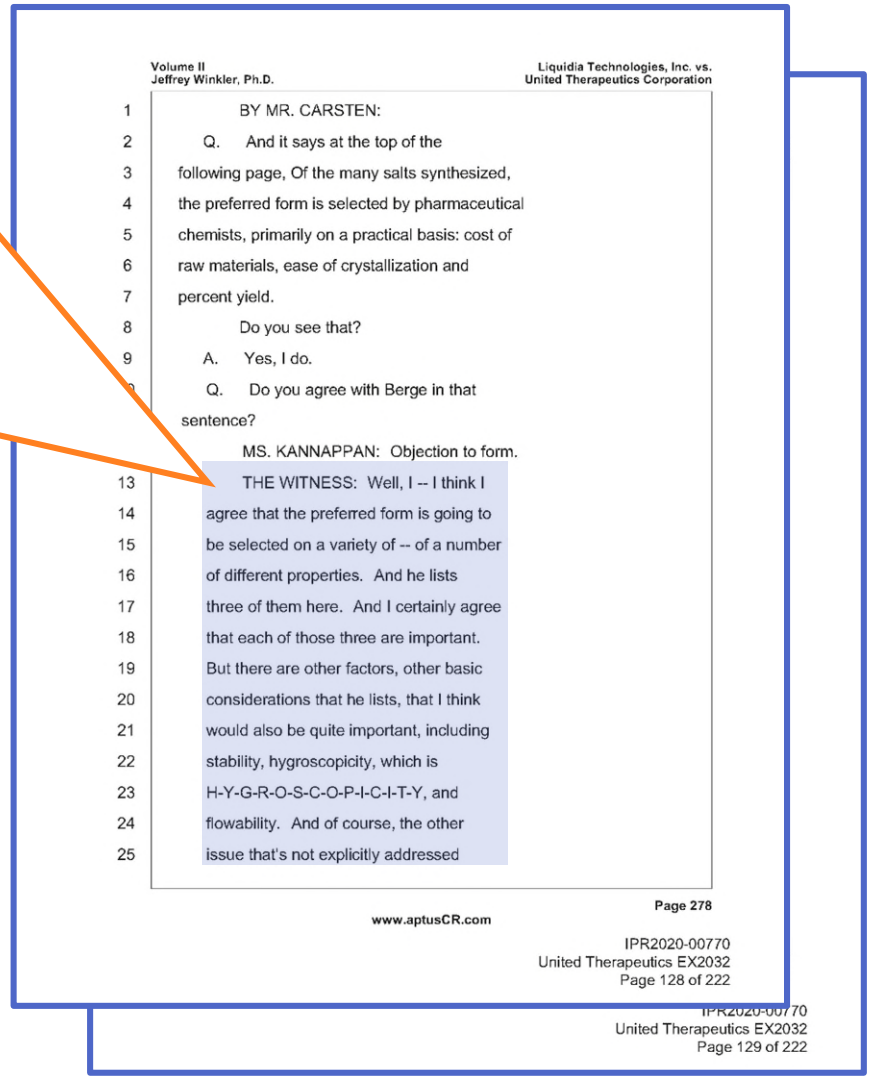
- In addition, Phares teaches treprostinil is notably hygroscopic.
  - Polymorph Form A gains “4.9% and 28% weight after 23 days in the ~52% RH and 68% RH chambers, respectively.”
  - Polymorph Form B gains 49% water at 95% relative humidity.

Paper 6 (POPR), 52-55; EX2002 (Pinal), ¶¶221-41; EX1008 (Phares), 87-88, Figs. 19, 22.

DR. WINKLER AGREES STABILITY + HYGROSCOPICITY ARE IMPORTANT, "BASIC" CONSIDERATIONS IN SALT SELECTION

"I agree that the preferred form [of salt] is going to be selected on a variety of—of a number of different properties. And [Berge] lists three of them here. And I certainly agree that each of those three are important. But **there are other factors, other basic considerations that he lists that I think would also be quite important, including stability, hygroscopicity, and flowability**."

- Dr. Winkler



Volume II
Jeffrey Winkler, Ph.D.

Liquidia Technologies, Inc. vs.
United Therapeutics Corporation

BY MR. CARSTEN:

Q. And it says at the top of the following page, Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists, primarily on a practical basis: cost of raw materials, ease of crystallization and percent yield.

Do you see that?

A. Yes, I do.

Q. Do you agree with Berge in that sentence?

MS. KANNAPPAN: Objection to form.

THE WITNESS: Well, I -- I think I agree that the preferred form is going to be selected on a variety of -- of a number of different properties. And he lists three of them here. And I certainly agree that each of those three are important. But there are other factors, other basic considerations that he lists, that I think would also be quite important, including stability, hygroscopicity, which is H-Y-G-R-O-S-C-O-P-I-C-I-T-Y, and flowability. And of course, the other issue that's not explicitly addressed

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EX2032, 278:2-279:12; Paper 25 (Sur-Reply), 18-22.

GROUND 1: PHARES

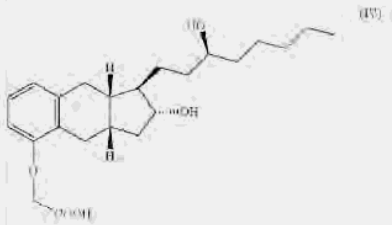
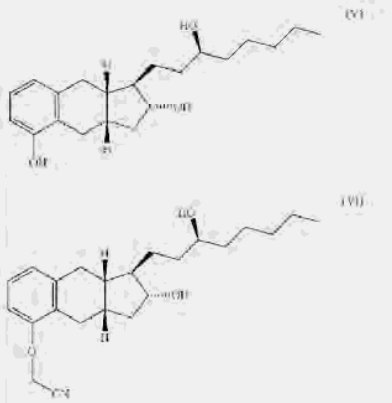
PHARES NEITHER TEACHES NOR SUGGESTS ALL OF THE CONTESTED CLAIM LIMITATIONS

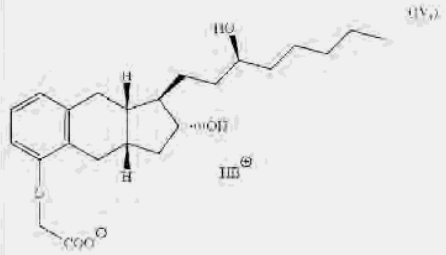
1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and

wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

EX1001 (901 Patent), claim 1; Paper 6 (POPR), 37-42, 50-55, 57-61; Paper 7 (Institution Decision), 31; Paper 12 (POR), 27-51; Paper 25 (Sur-Reply), 16-24.

LIQUIDIA DOES NOT ANALYZE THE CLAIMS AS A WHOLE

Limitation	'393 Patent Claim 9[6]	'901 Patent Claim 1
A product of treprostinil or a salt thereof	A product comprising a compound having formula IV  or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising	A pharmaceutical batch consisting of treprostinil or a salt thereof and **impurities resulting from**
Alkylation of benzindene triol	(a) alkylating a compound of formula V with an alkylating agent to produce a compound of formula VI, 	(a) alkylating a benzindene triol,

Hydrolysis	(b) hydrolyzing the product of formula VI of step (a) with a base,	(b) hydrolyzing the product of step (a) to form a solution comprising treprostinil,
Salt Formation	(c) contacting the product of step ([b]) with a base B to form a salt of formula IV_s, and 	(c) containing the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and
Optional reformulation of treprostinil	(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.	(e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and **wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.**

UT EX2037

Paper 25 (Sur-Reply), 4-5; *see* Paper 15 (Reply), 11; EX1017 (Winkler Reply), ¶¶68-69.

LIQUIDIA'S ARGUMENTS REST ON INHERENCY

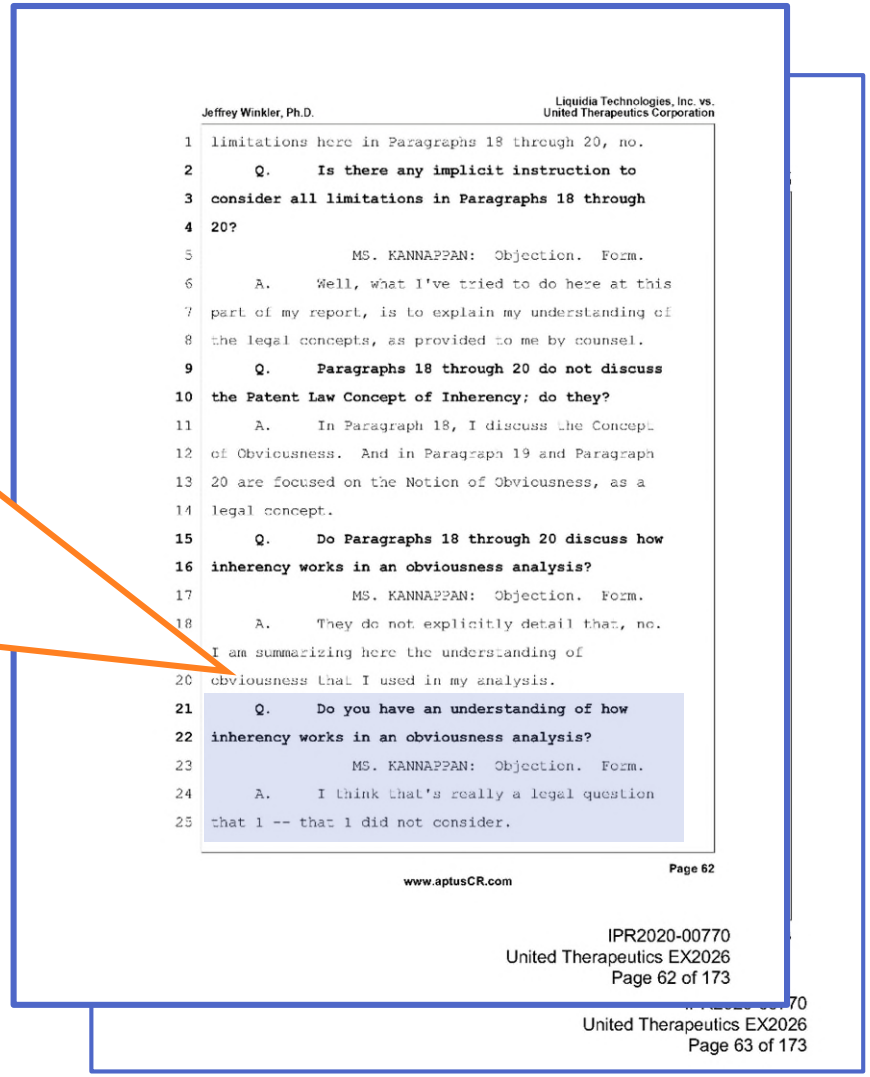
- Liquidia asserts that Phares inherently discloses, *e.g.*,:
  - The same synthesis of treprostinil as set forth in independent claim 1 of the '901 patent
  - The synthesis of both enantiomeric forms of treprostinil and of the benzindene triol and nitrile intermediates thereof
  - Treprostinil carboxylic acid starting material in solution/forming a solution comprising treprostinil
  - That polymorphic Form B of treprostinil diethanolamine is stable at ambient temperature and therefore could be stored at ambient temperature

Paper 1 (Petition), 29, 36-37, 43, 59-61, 68, 72; EX2002, ¶¶59, 62, 79, 85, 89, 91, 114, 124, 128, 130, 167, 171, 175, 177, 203, 217, 223, 225; *id.*, ¶68; Paper 25 (Sur-Reply), 18; Paper 12 (POR), 1, 21-22, 27-30, 35-39, 48, 51, 62-66.

DR. WINKLER BUILT CASE ON INHERENCY BUT DID NOT CONSIDER HOW INHERENCY WORKS FOR OBVIOUSNESS

Q: "Do you have an understanding of how inherency works in an obviousness analysis?"

Dr. Winkler: "I think that's really a legal question that I – that **I did not consider**."



Jeffrey Winkler, Ph.D. — Liquidia Technologies, Inc. vs. United Therapeutics Corporation

limitations here in Paragraphs 18 through 20, no.
Q. **Is there any implicit instruction to consider all limitations in Paragraphs 18 through 20?**
MS. KANNAPPAN: Objection. Form.
A. Well, what I've tried to do here at this part of my report, is to explain my understanding of the legal concepts, as provided to me by counsel.
Q. **Paragraphs 18 through 20 do not discuss the Patent Law Concept of Inherency; do they?**
A. In Paragraph 18, I discuss the Concept of Obviousness. And in Paragraph 19 and Paragraph 20 are focused on the Notion of Obviousness, as a legal concept.
Q. **Do Paragraphs 18 through 20 discuss how inherency works in an obviousness analysis?**
MS. KANNAPPAN: Objection. Form.
A. They do not explicitly detail that, no. I am summarizing here the understanding of obviousness that I used in my analysis.
Q. **Do you have an understanding of how inherency works in an obviousness analysis?**
MS. KANNAPPAN: Objection. Form.
A. I think that's really a legal question that I -- that I did not consider.

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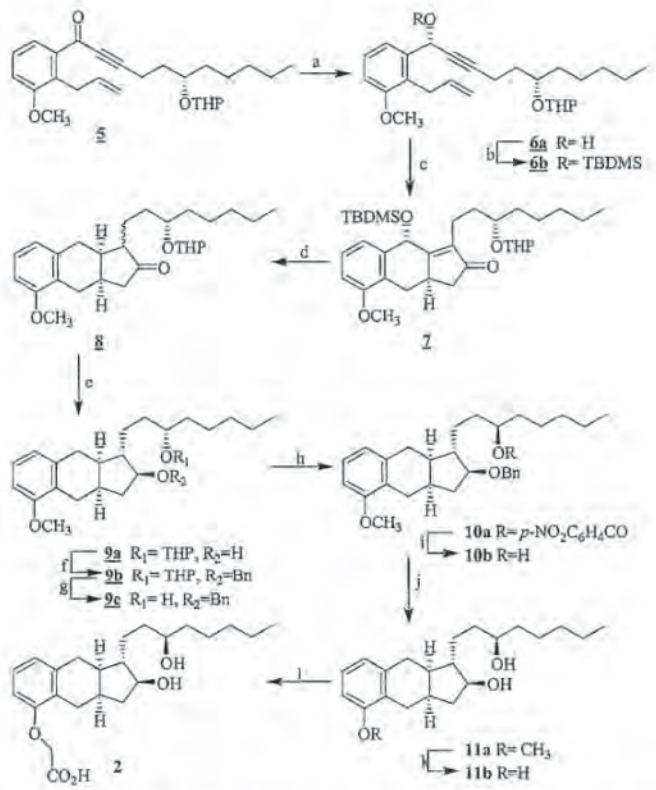
EX2026 (Winkler Depo #1), 62:21-63:5; Paper 12 (Sur-Reply), 1, 21-22; Paper 31 (MtE), 6-8; EX2025 (Pinal Response), ¶¶126-36, 205-07, 247; EX2007 (901 Complete File History; 393 IPR Winkler Depo), 193:3-14.

LIQUIDIA DOES NOT MEET ITS BURDEN TO SHOW THAT PHARES TEACHES TREPROSTINIL SYNTHESIS

PHARES DOES NOT TEACH A USEFUL SYNTHESIS OF TREPROSTINIL

- No scale, equivalents, or concentrations
- No work-up steps
- No purification details
- No characterization information



(a) (S)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}SMe_2$, THF, -30°C, 85%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2hr. r.t., then CH_3CN, 2hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$. 95%. (f) BnBr, NaH, THF, 98%. (g).CH_3OH, TsOH. 96%. (h) i. p-nitrobenzoic acid, DEAD, TPP,benzene. (i) CH_3OH, KOH. 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k). Ph_2PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps).

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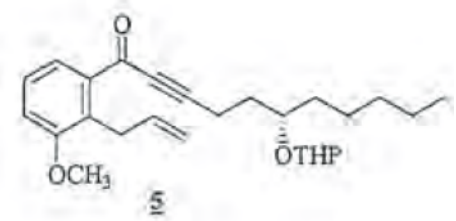
Paper 12 (POR), 41-42; Paper 6 (POPR), 59-60; EX2002 (Pinal), ¶¶220, 279-83; EX2025 (Pinal Response), ¶¶115-17.

PHARES'S SYNTHETIC SCHEME DOES NOT START AT A COMMERCIALLY AVAILABLE STARTING POINT

A. Which exhibit number is Phares, please?
Q. I believe that is 1008.
(Exhibit 1008, Phares WO 2005/007081 A9, was marked for identification.)
A. I think Phares discloses a synthesis of treprostinil on page 40 of Phares.
Q. Okay. When you say "discloses the synthesis on page 40," what part of page 40 are you referring to?
A. I'm referring specifically to the flow chart that teaches how to go from Compound 5 to Compound 2.
I'm sorry. 40 of the document, not 40 of the Liquidia Exhibit 1008. That's page 42 at the bottom right.
Q. Okay. Just so we're on the same, so to speak, we're talking about Exhibit its exhibit number page 42?
A. Correct.
Q. Okay. All right. Very good. Is Compound 5 a commercially available starting material?
MS. KANNAPPAN: Objection. Form. Calls for speculation.
A. I don't know.



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Q: "Is compound 5 a commercially available starting material?"

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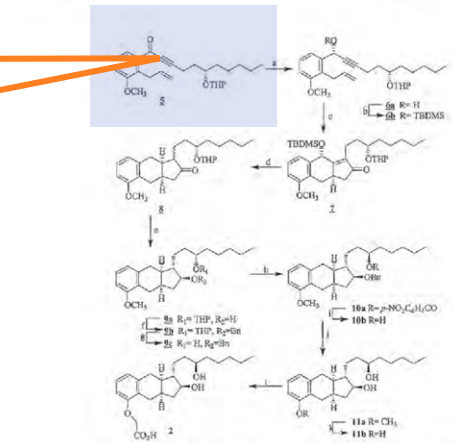
Dr. Winkler: "I don't know."



(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3·SMe_2, THF, -30°C, 85%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2hr. r.t., then CH_3CN, 2hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$. 95%. (f) BnBr, NaH, THF, 98%. (g).CH_3OH, TsOH. 96%. (h) i. p-nitrobenzoic acid, DEAD, TPP,benzene. (i) CH_3OH, KOH. 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k). Ph_3PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps).

Briefly, the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group. The absolute configuration of (-)-Treprostinil was confirmed by an X-ray structure of the L-valine amide derivative.

Paper 12 (POR), 41-42; EX2025 (Pinal Response), ¶115; EX2026 (Winkler Dep #1), 114:15-115:25.

LIQUIDIA DID NOT MEET ITS BURDEN TO SHOW PHARES TEACHES CLAIMED IMPURITIES

LIQUIDIA'S ARGUMENT ON IMPURITIES IS NONSENSICAL

- **Phares does not teach anything about impurities.**
- Liquidia invokes Phares' teachings of two different polymorphs of a treprostinil salt to address the claimed impurities.
- Liquidia argues because Phares' Form A is used to make Form B, and Form A has a lower melting point than Form B, Form A must be less pure.
  - This is scientifically inaccurate.
  - This does not read on the claims or address the source of the impurities, which claim 1 states must result from the recited process steps.

Paper 6 (POPR), 39, 58-59; EX2002, ¶¶177-79, 188-89; EX2010, 79 (melting points change "in a rather unpredictable way"; POSAs use **magnitude** of melting point **range** as a criteria of purity, and even that is "only a rough indication because the range depends on a number of factors which are not easily taken into account"); *see* Paper 1 (Petition), 32; EX1002, ¶68.

LIQUIDIA RESTED ITS SYNTHESIS, IMPURITY, AND STORAGE STABILITY ARGUMENTS ON POLYMORPHS + DSC TRACES…

Phares discloses two crystalline forms of treprostinil diethanolamine salt, Form A and Form B. (Ex. 1008, 85-89; Winkler Decl., ¶68.) Form A has an endotherm, 103 °C and Form B has an endotherm, 107 °C. (Ex. 1008, 87, 88.) The higher melting point of Form B is consistent and compatible with a higher degree of purity in Form B in comparison with Form A based on these endotherm temperatures. (Winkler Decl., ¶68.) Further, Form A is utilized as the starting material for the formation of Form B. (Ex. 1008, 87; Winkler Decl., ¶69.) A POSA would understand that through this transformation, similar to that described in the '901 patent, one is typically removing impurities. (*Id.*) As such, Form A should be more pure than the starting batch and Form B more pure than Form A. (*Id.*)

This shows that Phares necessarily discloses and/or renders obvious the same process steps to make treprostinil and a salt thereof disclosed in claim 1 of the '901 patent (treprostinil diethanolamine salt). (Winkler Decl., ¶71.) This treprostinil or

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Paper 1 (Petition), 32; Paper 25 (Sur-Reply), 18-19.

…AND THEN ARGUES UT'S RESPONSE ADDRESSING POLYMORPHS + DSC ARGUMENTS IS "IRRELEVANT"

[3] In his Reply Declaration, Dr. Winkler specifically addressed Dr. Pinal's criticisms that Patent Owner now points to. *See, e.g.*, Ex. 1017, ¶¶ 90-91 (explaining the '075 patent describes synthesis of treprostinil), 96 (explaining Dr. Pinal's attempt to complicate the record with extensive discussion of differential scanning calorimetry is "ultimately irrelevant" because the patent does not claim a specific polymorph), 103 (explaining that Dr. Pinal's argument that a POSA would have to first neutralize KOH before adding diethanolamine is incorrect), 156 (explaining Dr. Pinal's arguments that relate to the stability of one polymorph over another are irrelevant because the claims are not specific to one polymorph).

Paper 32 (Reply to UT's MtE), 6; Paper 31 (MtE), 6-8, Paper 37 (Reply to Opposition to MtE), 3-4; *see also* Paper 15 (Reply), 22 ("UTC's focus on the purity of the treprostinil diethanolamine polymorphic forms disclosed in Phares is misplaced.").

LIQUIDIA FAILED TO MEET ITS BURDEN ON 2.9 G SCALE

PHARES DOES NOT TEACH 2.9 G OF ANYTHING

- Liquidia asserts “Phares teaches a reaction of ~1 g scale-quantities.”

- Only one reaction is ~1 gram scale—a reaction to form treprostinil methyl ester, which is irrelevant to treprostinil diethanolamine.
  - Uses 1.087 g treprostinil as a starting material to yield crude treprostinil methyl ester.
  - The methyl ester was not merely a final product, rather it was used as an intermediate to make other prodrugs.

Paper 6 (POPR), 60; EX2002 (Pinal), ¶¶220, 279-83; Paper 12 (POR), 43-44; EX2025 (Pinal Response), ¶¶102, 165-71, 270-74; Paper 1 (Petition), 39; EX1002 (Winkler), ¶102; EX1008 (Phares), 18-19, 22.

THE SCALE IN QUESTION IS PRODUCT, NOT STARTING MATERIAL

- Dr. Winkler cites his own experience in asserting reactions can be scaled up "by a factor of 3" with a reasonable expectation of success.
  - Scaling up an irrelevant synthesis of treprostinil methyl ester by a factor of 3 does not inform scale-up of a treprostinil salt.

- Dr. Winkler repeatedly confuses the amount of starting materials and the amount of product a synthesis yields.
  - Cites, *e.g.*, EX1031 to support contention that benchtop scale-type work in a lab includes working on over 2.9 grams, but EX1021 results in just 5 mg of end product.

Paper 6 (POPR), 60; Paper 25 (Sur-Reply), 15-16; EX2002 (Pinal), ¶¶220, 279-83; EX2025 (Pinal Response), ¶¶ 102, 165-71, 270-74, 293-94, 297; *see* EX2032 (Winkler Depo #2), 306:6-307:11.

OBJECTIVE INDICIA CONFIRM PATENTABILITY

LIQUIDIA IMPROPERLY SHIFTS BURDEN OF PROOF

- Liquidia asserted in its petition: "Patent Owner has not identified any evidence of secondary indicia."
  - This is an improper burden shift that ignores objective indicia set forth in the '901 patent's specification.

"The principle applies most often to the less predictable fields, such as **chemistry**, where **minor changes in a product or process may yield substantially different results**."

- *In re Soni,* 54 F.3d 746, 750 (Fed. Cir. 1995)

Paper 6 (POPR), 7, 69-71; Paper 12 (POR), 2, 7-8, 66-69; Paper 1 (Petition), 71.

OBJECTIVE INDICIA CONFIRM PATENTABILITY

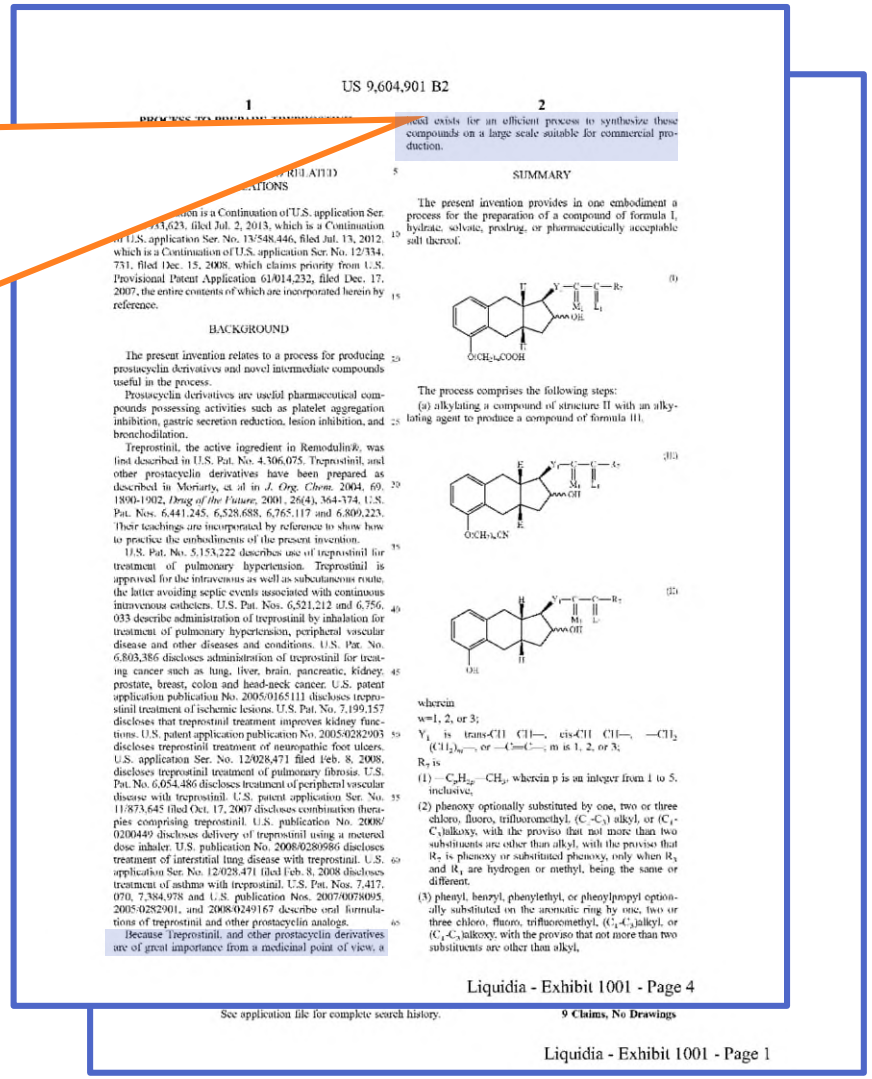
- The claimed inventions provide batch production of treprostinil for use as an active ingredient in a pharmaceutical composition or pharmaceutical product.

- Treprostinil is the active ingredient in three FDA-approved drugs:
  - Remodulin® (treprostinil) Injection
  - Tyvaso® (treprostinil) Inhalation Solution
  - Orenitram® (treprostinil) Extended-Release Tablets

Paper 6 (POPR), 2, 36, 69-71; Paper 12 (POR), 2, 7-8, 66-69; EX2002 (Pinal), ¶136, EX1001 (901 Patent), [12], [57], 6:4-18, 16:66-17:12.

THE ’901 PATENT FILLED A LONG-FELT, UNMET NEED

“Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, **a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production**.” - The ’901 Patent



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need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.

BACKGROUND

The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

Treprostinil, the active ingredient in Remodulin®, was first described in U.S. Pat. No. 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drugs of the Future*, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

U.S. Pat. No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. Pat. Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. Pat. No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. Pat. No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008, discloses treprostinil treatment of pulmonary fibrosis. U.S. Pat. No. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application Ser. No. 11/873,645 filed Oct. 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application Ser. No. 12/028,471 filed Feb. 8, 2008 discloses treatment of asthma with treprostinil. U.S. Pat. Nos. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a

The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III.

wherein

w=1, 2, or 3;

Y_1 is trans-CH CH—, cis-CH CH—, —CH_2 $(CH_2)_m$—, or —C≡C—; m is 1, 2, or 3;

R_3 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from 1 to 5, inclusive;

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_3 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different.

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

See application file for complete search history.

9 Claims, No Drawings

Liquidia - Exhibit 1001 - Page 4

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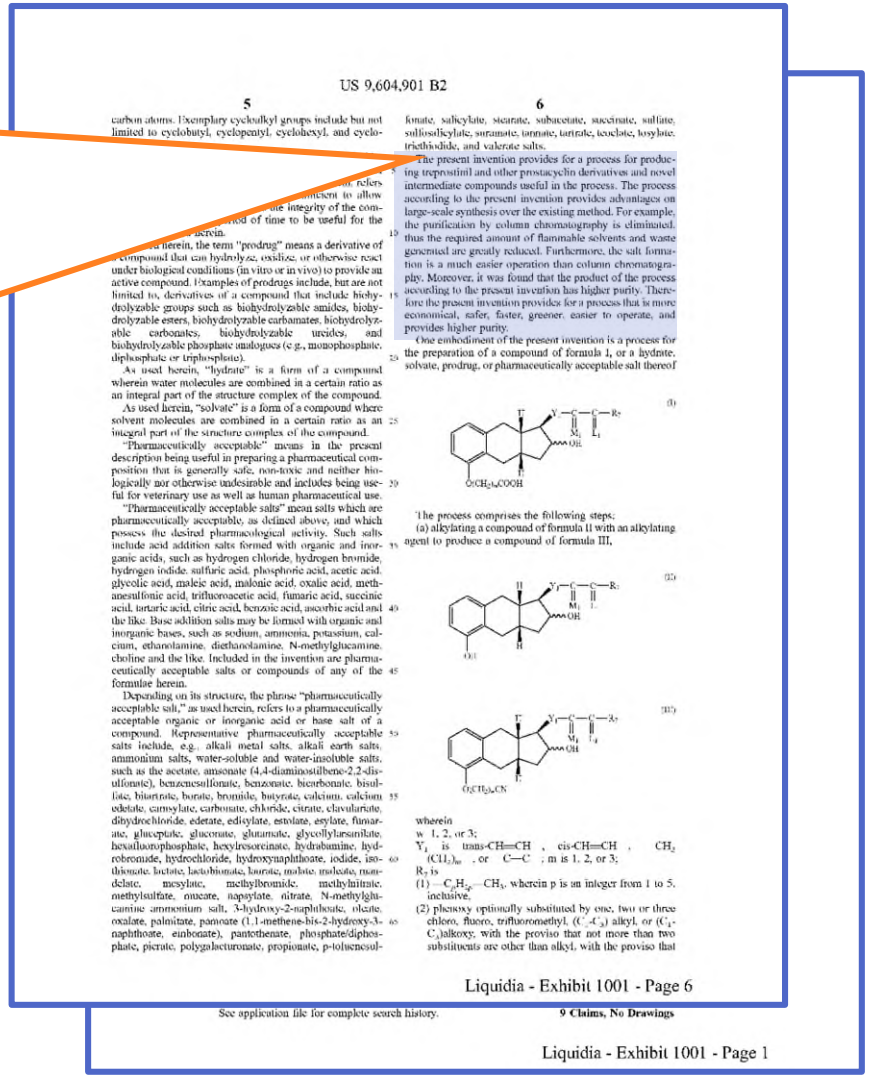
EX1001 (901 Patent), 1:66-2:3; Paper 6 (POPR), 70-71; Paper 12 (POR), 2, 7-8, 66-69.

THE ’901 PATENT IMPROVES ON EXISTING MANUFACTURING

“Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore, **the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity**.”

- The ’901 Patent



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carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cyclo-

herein, the term "prodrug" means a derivative of compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound. Examples of prodrugs include, but are not limited to, derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (e.g., monophosphate, diphosphate or triphosphate).

As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

"Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bisarbonate, bisulfite, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof

The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,

wherein

w 1, 2, or 3;

Y_1 is trans-CH=CH, cis-CH=CH, CH_2, $(CH_2)_m$, or C≡C; m is 1, 2, or 3;

R_5 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that

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See application file for complete search history.

9 Claims, No Drawings

Liquidia - Exhibit 1001 - Page 1

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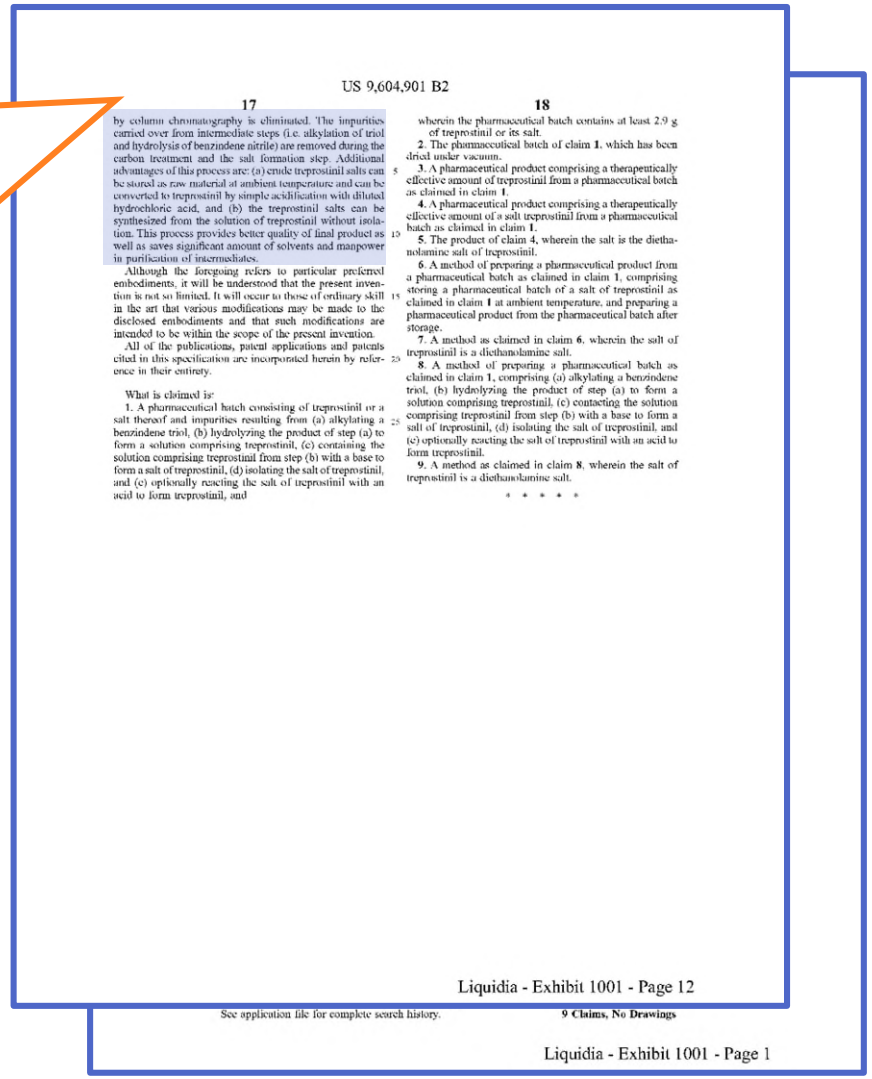
EX1001 (901 Patent), 6:4-18; Paper 6 (POPR), 34-35, 69-71; EX2002 (Pinal), ¶¶130-32; Paper 12 (POR), 2, 7-8, 66-69.

THE ’901 PATENT IMPROVES ON TREPROSTINIL MANUFACTURING

“Additional advantages of this process are (a) **crude treprostinil salts can be stored as raw material at ambient temperature** and can be converted to treprostinil by simple acidification with diluted hydrochloric acid...” - The ’901 Patent



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by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and

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wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim 1, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim 1.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim 1.

5. The product of claim 4, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim 6, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim 1, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim 8, wherein the salt of treprostinil is a diethanolamine salt.

* * * * *

Liquidia - Exhibit 1001 - Page 12

See application file for complete search history.

9 Claims, No Drawings

Liquidia - Exhibit 1001 - Page 1

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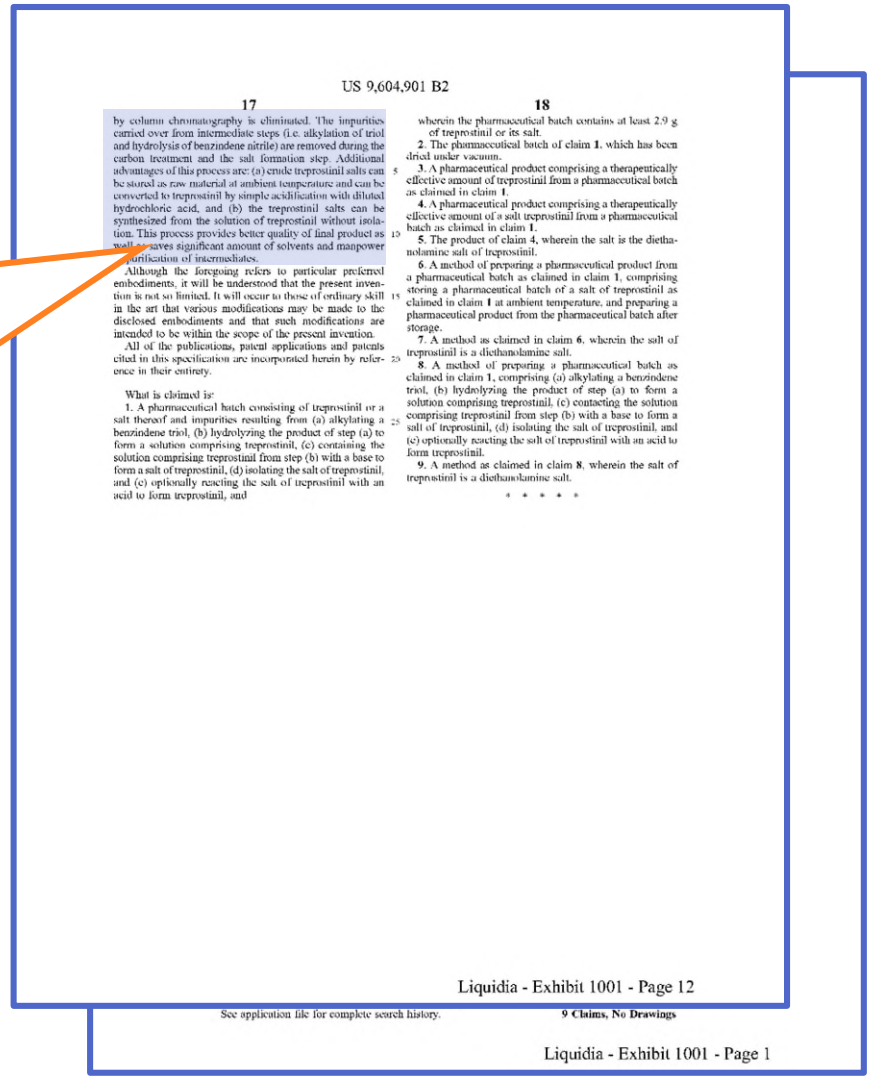
EX1001 (901 Patent), 17:1-12; Paper 6 (POPR), 35-36, 69-71; EX2002 (Pinal), ¶135; Paper 12 (POR), 2, 7-8, 66-69.

THE ’901 PATENT IMPROVES ON TREPROSTINIL MANUFACTURING

“This **process provides better quality of final product as well as saves significant amount of solvents and manpower** in purification of intermediates.”

- The ’901 Patent



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by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower purification of intermediates.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and

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wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim 1, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim 1.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim 1.

5. The product of claim 4, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim 6, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim 1, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim 8, wherein the salt of treprostinil is a diethanolamine salt.

* * * * *

Liquidia - Exhibit 1001 - Page 12

See application file for complete search history.

9 Claims, No Drawings

Liquidia - Exhibit 1001 - Page 1

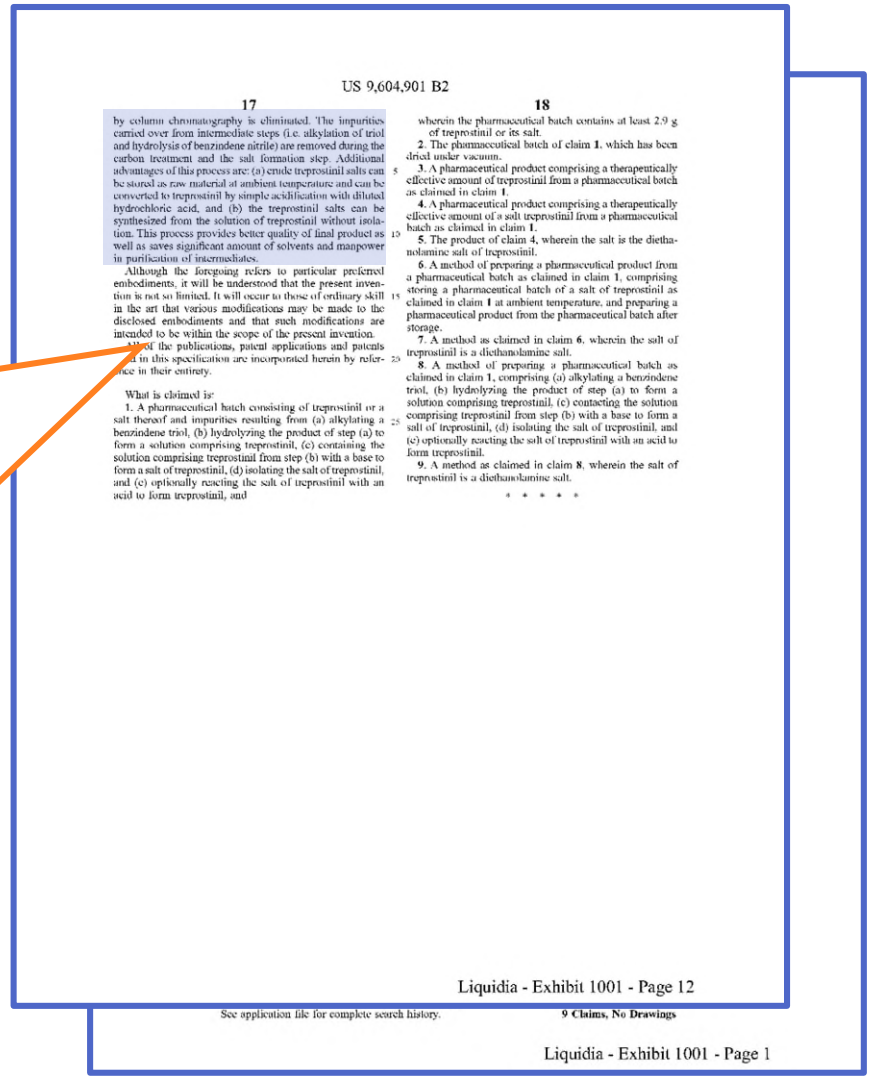
UT EX2037

EX1001 (901 Patent), 17:1-12; Paper 6 (POPR), 35-36, 69-71; EX2002 (Pinal), ¶¶135-36; Paper 12 (POR), 2, 7-8, 66-69.

AMBIENT TEMPERATURE STORAGE STABILITY WAS UNEXPECTED

"Additional advantages of this process are: (a) **crude treprostinil salts can be stored as raw material at ambient temperature** and can be converted to treprostinil by simple acidification with diluted hydrochloric acid."

- The '901 Patent



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by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

What is claimed is:

1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and

18

wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

2. The pharmaceutical batch of claim 1, which has been dried under vacuum.

3. A pharmaceutical product comprising a therapeutically effective amount of treprostinil from a pharmaceutical batch as claimed in claim 1.

4. A pharmaceutical product comprising a therapeutically effective amount of a salt treprostinil from a pharmaceutical batch as claimed in claim 1.

5. The product of claim 4, wherein the salt is the diethanolamine salt of treprostinil.

6. A method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage.

7. A method as claimed in claim 6, wherein the salt of treprostinil is a diethanolamine salt.

8. A method of preparing a pharmaceutical batch as claimed in claim 1, comprising (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil.

9. A method as claimed in claim 8, wherein the salt of treprostinil is a diethanolamine salt.

* * * * *

Liquidia - Exhibit 1001 - Page 12

See application file for complete search history.

9 Claims, No Drawings

Liquidia - Exhibit 1001 - Page 1

UT EX2037

EX1001 (901 Patent), 17:4-10; Paper 25 (Sur-Reply), 24-25; EX2025 (Pinal Response), ¶¶91, 218; Paper 12 (POR), 2, 7-8, 66-69.

UT’S MOTION TO EXCLUDE

UT EX2037

EX1002 SHOULD BE EXCLUDED

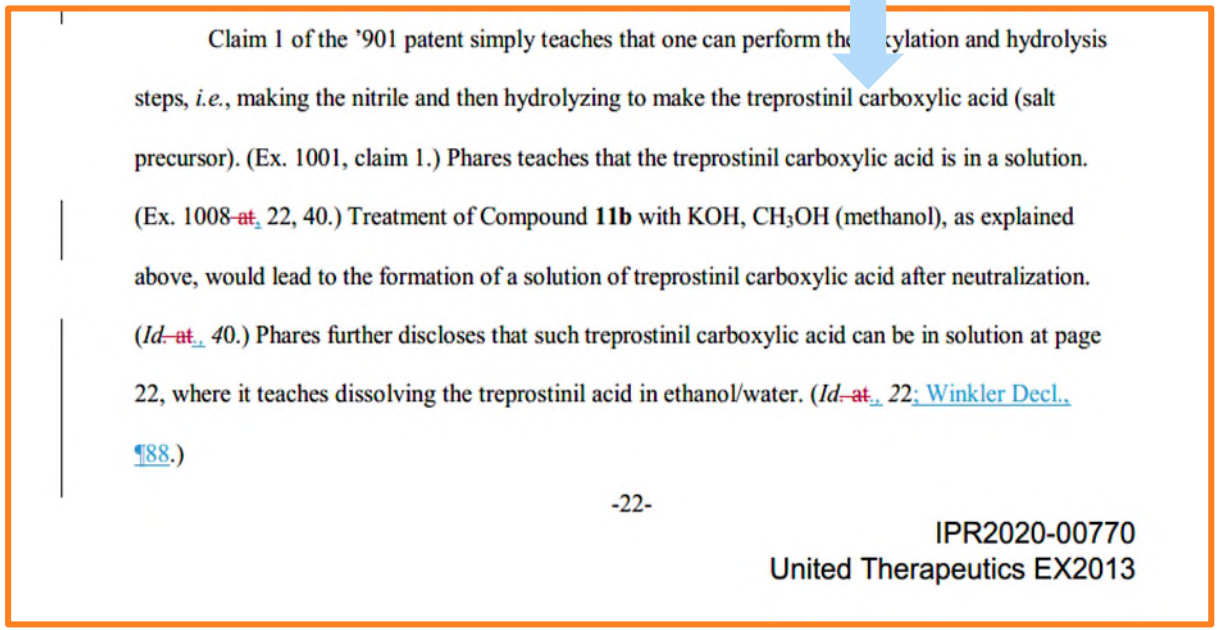
Fatal flaws of Exhibit 1002 include:

- Lacks statutorily-required oath or caveat for a declaration
  - 35 U.S.C. § 25; 37 C.F.R. § 42.2
- Hearsay without exception
- Dr. Winkler is unqualified to testify on the relevant subject matter
  - FRE 701, 701
  - Incorrect scientific analysis
  - Incorrect characterizations of the prior art

Paper 31 (MtE), 2-10; Paper 12 (POR), 17-22; Paper 36 (UT Reply to Opposition to MtE), 1-4.

REDLINE SHOWS NEAR IDENTICAL PETITION + "DECLARATION"

- Identical analyses throughout, including:
  - Claims in view of Moriarty + Phares
  - Claims in view of Phares



Claim 1 of the '901 patent simply teaches that one can perform the ~~c~~ylation and hydrolysis steps, *i.e.*, making the nitrile and then hydrolyzing to make the treprostinil carboxylic acid (salt precursor). (Ex. 1001, claim 1.) Phares teaches that the treprostinil carboxylic acid is in a solution. (Ex. 1008~~at~~, 22, 40.) Treatment of Compound **11b** with KOH, CH_3OH (methanol), as explained above, would lead to the formation of a solution of treprostinil carboxylic acid after neutralization. (*Id.*~~at~~, 40.) Phares further discloses that such treprostinil carboxylic acid can be in solution at page 22, where it teaches dissolving the treprostinil acid in ethanol/water. (*Id.*~~at~~, 22; Winkler Decl., ¶88.)

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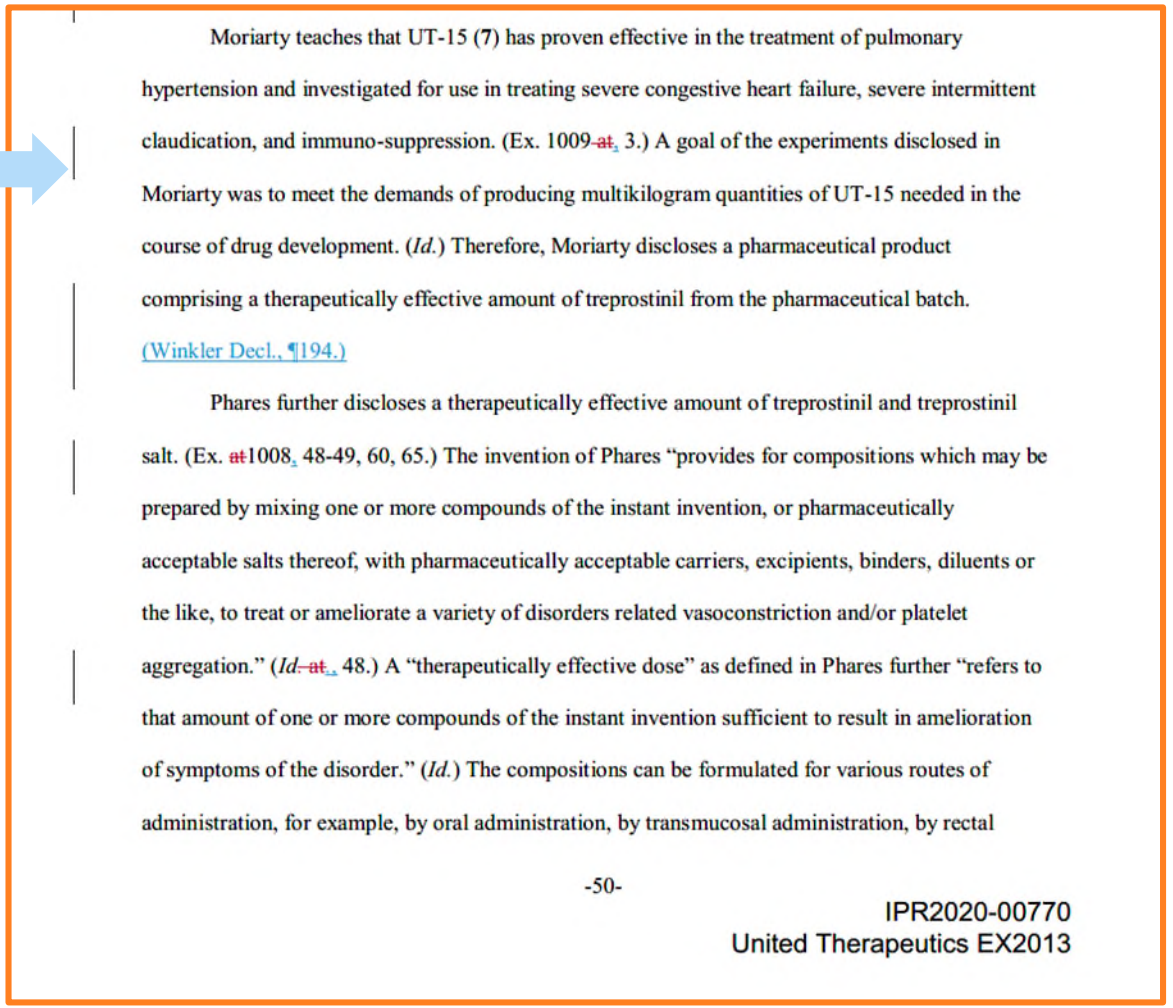
IPR2020-00770
United Therapeutics EX2013



Moriarty teaches that UT-15 (7) has proven effective in the treatment of pulmonary hypertension and investigated for use in treating severe congestive heart failure, severe intermittent claudication, and immuno-suppression. (Ex. 1009~~at~~, 3.) A goal of the experiments disclosed in Moriarty was to meet the demands of producing multikilogram quantities of UT-15 needed in the course of drug development. (*Id.*) Therefore, Moriarty discloses a pharmaceutical product comprising a therapeutically effective amount of treprostinil from the pharmaceutical batch. (Winkler Decl., ¶194.)

Phares further discloses a therapeutically effective amount of treprostinil and treprostinil salt. (Ex. ~~at~~1008, 48-49, 60, 65.) The invention of Phares "provides for compositions which may be prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, to treat or ameliorate a variety of disorders related vasoconstriction and/or platelet aggregation." (*Id.*~~at~~, 48.) A "therapeutically effective dose" as defined in Phares further "refers to that amount of one or more compounds of the instant invention sufficient to result in amelioration of symptoms of the disorder." (*Id.*) The compositions can be formulated for various routes of administration, for example, by oral administration, by transmucosal administration, by rectal

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IPR2020-00770
United Therapeutics EX2013

EX2013 (901 Petition + Winkler "Declaration" Redline); Paper 6 (POPR), 29-30; Paper 12 (POR), 18-21.

UT EX2037

DR. WINKLER'S TESTIMONY IS RIDDLED WITH SCIENTIFIC ERRORS

- Incorrect differential scanning calorimetry analysis
- Conflation of stability concepts
- Errors in applying introductory level acid/base chemistry to salt formation

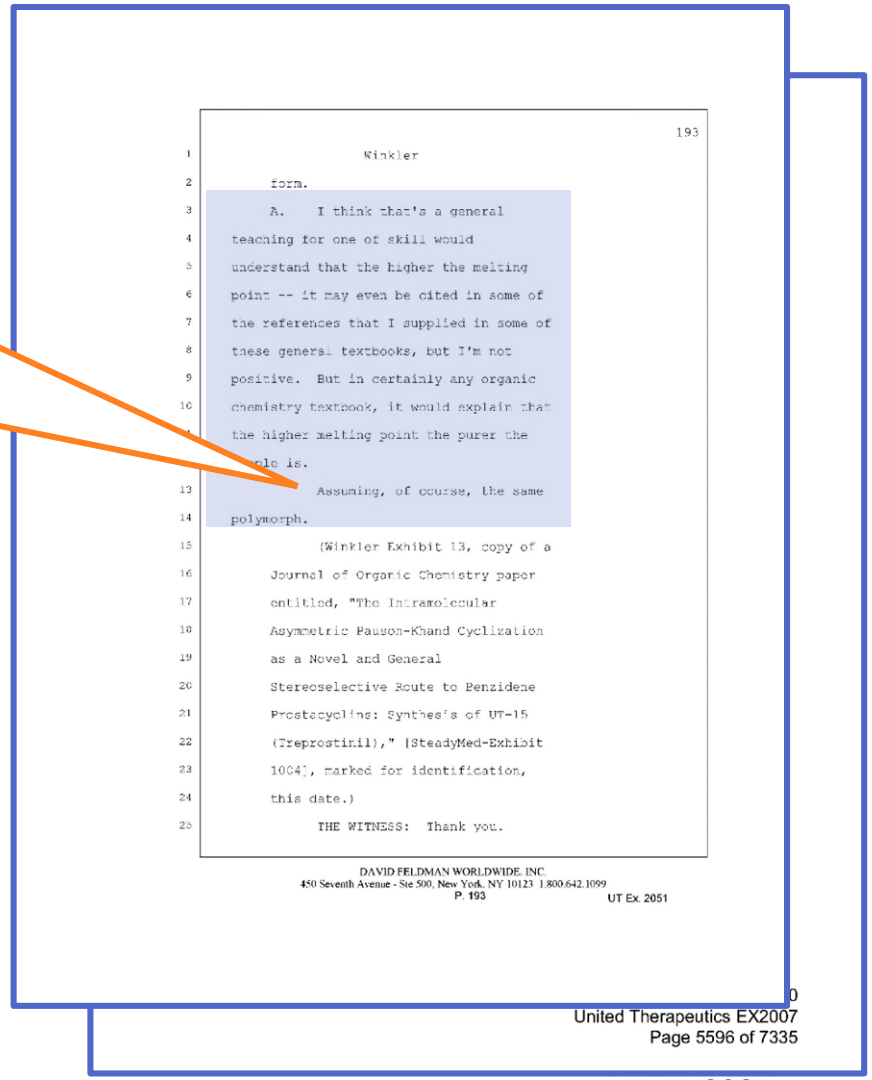
Paper 31 (MtE), 6-8; Paper 36 (UT Reply to Opposition to MtE), 1-4.

DR. WINKLER'S DSC TESTIMONY CHANGES OVER TIME

Then: The '393 IPR

"[I]n certainly any organic chemistry textbook, it would explain that the higher melting point the purer the sample is. **Assuming, of course, the same polymorph**."

- Dr. Winkler



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Winkler

form.

A. I think that's a general teaching for one of skill would understand that the higher the melting point -- it may even be cited in some of the references that I supplied in some of these general textbooks, but I'm not positive. But in certainly any organic chemistry textbook, it would explain that the higher melting point the purer the sample is.

Assuming, of course, the same polymorph.

(Winkler Exhibit 13, copy of a Journal of Organic Chemistry paper entitled, "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzidene Prostacyclins: Synthesis of UT-15 (Treprostinil)," (SteadyMed-Exhibit 1004), marked for identification, this date.)

THE WITNESS: Thank you.

DAVID FELDMAN WORLDWIDE, INC.
450 Seventh Avenue - Ste 500, New York, NY 10123 1.800.642.1099
P. 193 UT Ex. 2051

United Therapeutics EX2007
Page 5596 of 7335

UT EX2037

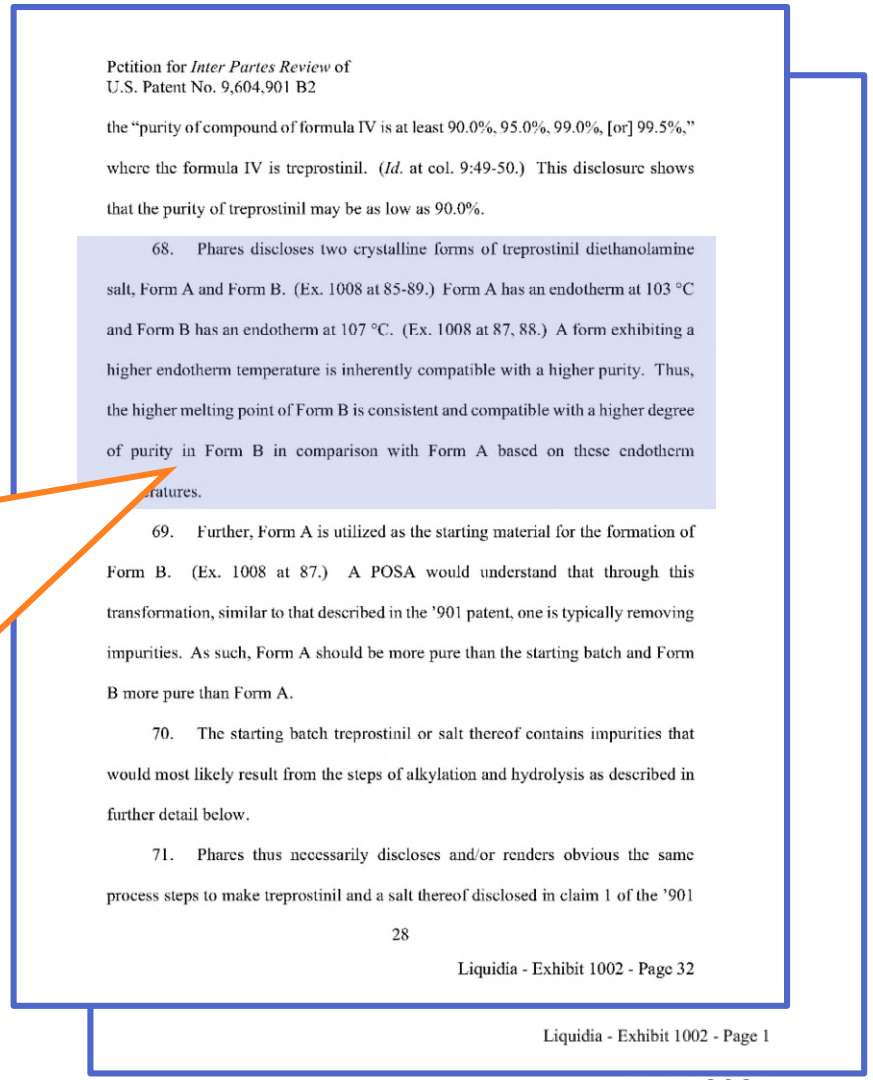
EX2007 (901 File History, 393 IPR Winkler Depo), 5788, 193:3-14; Paper 12 (POR), 35; EX2025 (Pinal Response), ¶130.

DR. WINKLER'S DSC TESTIMONY CHANGES OVER TIME

Now: The '901 IPR

"Phares discloses two crystalline forms of treprostinil diethanolamine salt, Form A and Form B… **A form exhibiting a higher endotherm temperature is inherently compatible with a higher purity.** Thus, the higher melting point of Form B is consistent and compatible with a higher degree of purity in Form B in comparison with Form A based on these endotherm temperatures."

- Dr. Winkler



Petition for *Inter Partes Review* of
U.S. Patent No. 9,604,901 B2

the "purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, [or] 99.5%," where the formula IV is treprostinil. (*Id.* at col. 9:49-50.) This disclosure shows that the purity of treprostinil may be as low as 90.0%.

68. Phares discloses two crystalline forms of treprostinil diethanolamine salt, Form A and Form B. (Ex. 1008 at 85-89.) Form A has an endotherm at 103 °C and Form B has an endotherm at 107 °C. (Ex. 1008 at 87, 88.) A form exhibiting a higher endotherm temperature is inherently compatible with a higher purity. Thus, the higher melting point of Form B is consistent and compatible with a higher degree of purity in Form B in comparison with Form A based on these endotherm temperatures.

69. Further, Form A is utilized as the starting material for the formation of Form B. (Ex. 1008 at 87.) A POSA would understand that through this transformation, similar to that described in the '901 patent, one is typically removing impurities. As such, Form A should be more pure than the starting batch and Form B more pure than Form A.

70. The starting batch treprostinil or salt thereof contains impurities that would most likely result from the steps of alkylation and hydrolysis as described in further detail below.

71. Phares thus necessarily discloses and/or renders obvious the same process steps to make treprostinil and a salt thereof disclosed in claim 1 of the '901

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Liquidia - Exhibit 1002 - Page 32

Liquidia - Exhibit 1002 - Page 1

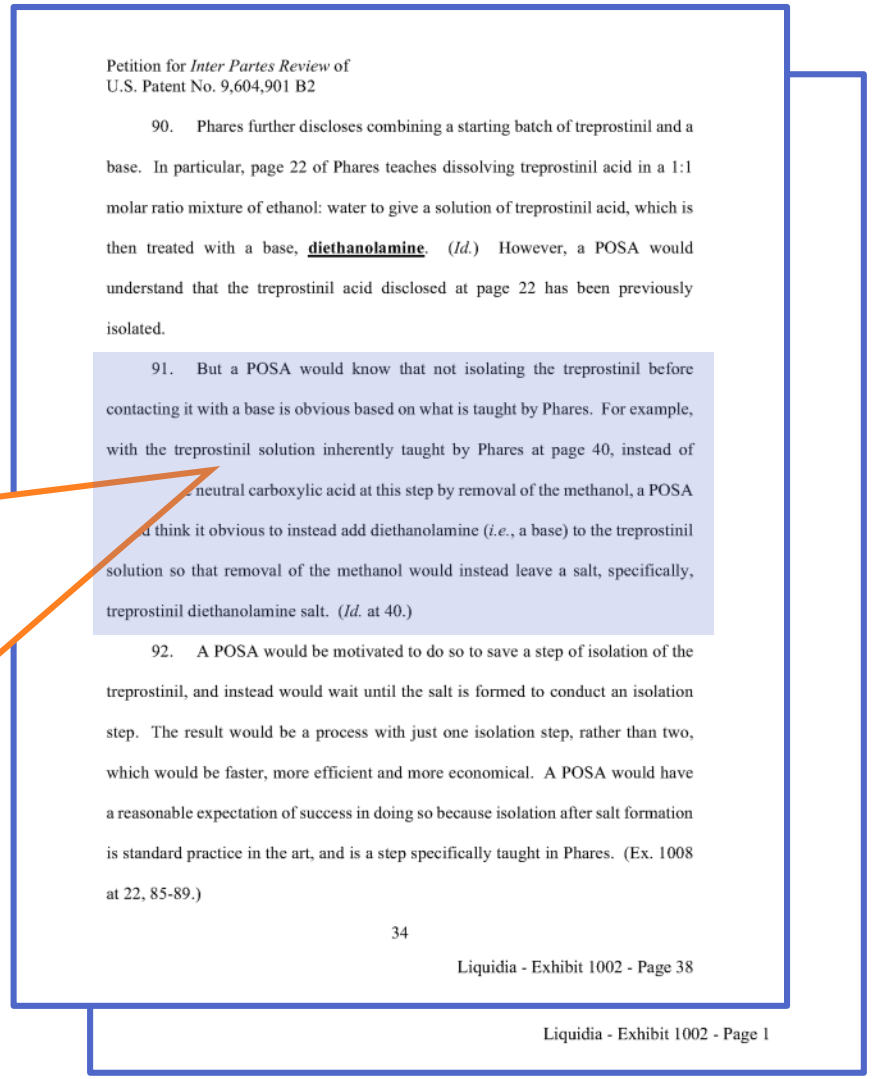
UT EX2037

EX2002, ¶68; Paper 25 (Sur-Reply), 35; EX2025 (Pinal Response), ¶130.

DR. WINKLER ERRS IN APPLYING INTRODUCTORY LEVEL ACID/BASE CHEMISTRY REGARDING SALT FORMATION

"[I]nstead of isolating the neutral carboxylic acid at this step by removal of the methanol, a POSA would think it **obvious to instead add diethanolamine (i.e., a base) to the treprostinil solution so that removal of the methanol would instead leave a salt**, specifically, treprostinil diethanolamine salt."

- Dr. Winkler



Petition for *Inter Partes Review* of
U.S. Patent No. 9,604,901 B2

90. Phares further discloses combining a starting batch of treprostinil and a base. In particular, page 22 of Phares teaches dissolving treprostinil acid in a 1:1 molar ratio mixture of ethanol: water to give a solution of treprostinil acid, which is then treated with a base, **diethanolamine**. (*Id.*) However, a POSA would understand that the treprostinil acid disclosed at page 22 has been previously isolated.

91. But a POSA would know that not isolating the treprostinil before contacting it with a base is obvious based on what is taught by Phares. For example, with the treprostinil solution inherently taught by Phares at page 40, instead of [illegible] neutral carboxylic acid at this step by removal of the methanol, a POSA [illegible]d think it obvious to instead add diethanolamine (*i.e.*, a base) to the treprostinil solution so that removal of the methanol would instead leave a salt, specifically, treprostinil diethanolamine salt. (*Id.* at 40.)

92. A POSA would be motivated to do so to save a step of isolation of the treprostinil, and instead would wait until the salt is formed to conduct an isolation step. The result would be a process with just one isolation step, rather than two, which would be faster, more efficient and more economical. A POSA would have a reasonable expectation of success in doing so because isolation after salt formation is standard practice in the art, and is a step specifically taught in Phares. (Ex. 1008 at 22, 85-89.)

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Liquidia - Exhibit 1002 - Page 38

Liquidia - Exhibit 1002 - Page 1

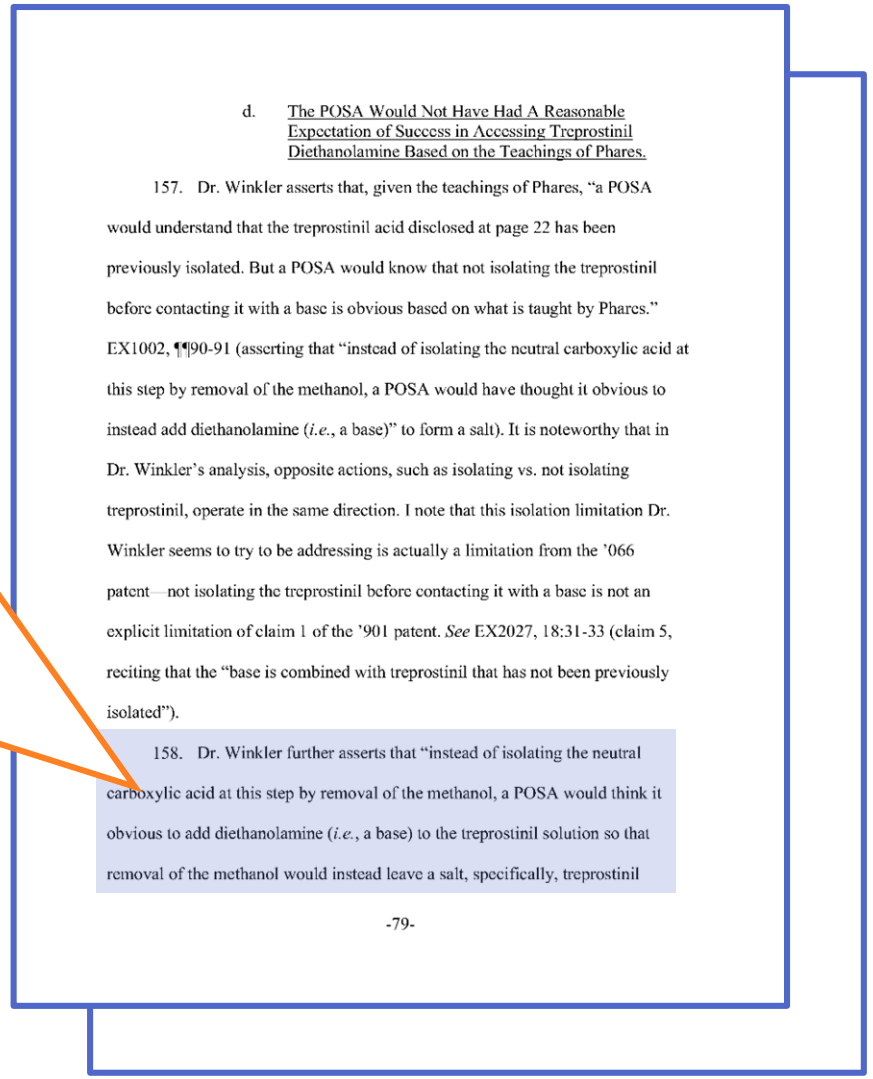
UT EX2037

EX1002 (Winkler), ¶91; EX2025 (Pinal Response), ¶¶158, 185, 232; Paper 31 (MtE), 6-8.

DR. WINKLER ERRS IN APPLYING INTRODUCTORY LEVEL ACID/BASE CHEMISTRY REGARDING SALT FORMATION

"Dr. Winkler leaves out the fact that the final step of Phares is carried out in methanol with potassium hydroxide (KOH, a strong base). Potassium hydroxide is a much stronger base than diethanolamine, and **any chemist would know that simply adding diethanolamine in the presence of KOH would not result in the diethanolamine salt**."

- Dr. Pinal



d. The POSA Would Not Have Had A Reasonable Expectation of Success in Accessing Treprostinil Diethanolamine Based on the Teachings of Phares.

157. Dr. Winkler asserts that, given the teachings of Phares, "a POSA would understand that the treprostinil acid disclosed at page 22 has been previously isolated. But a POSA would know that not isolating the treprostinil before contacting it with a base is obvious based on what is taught by Phares." EX1002, ¶¶90-91 (asserting that "instead of isolating the neutral carboxylic acid at this step by removal of the methanol, a POSA would have thought it obvious to instead add diethanolamine (*i.e.*, a base)" to form a salt). It is noteworthy that in Dr. Winkler's analysis, opposite actions, such as isolating vs. not isolating treprostinil, operate in the same direction. I note that this isolation limitation Dr. Winkler seems to try to be addressing is actually a limitation from the '066 patent—not isolating the treprostinil before contacting it with a base is not an explicit limitation of claim 1 of the '901 patent. *See* EX2027, 18:31-33 (claim 5, reciting that the "base is combined with treprostinil that has not been previously isolated").

158. Dr. Winkler further asserts that "instead of isolating the neutral carboxylic acid at this step by removal of the methanol, a POSA would think it obvious to add diethanolamine (*i.e.*, a base) to the treprostinil solution so that removal of the methanol would instead leave a salt, specifically, treprostinil

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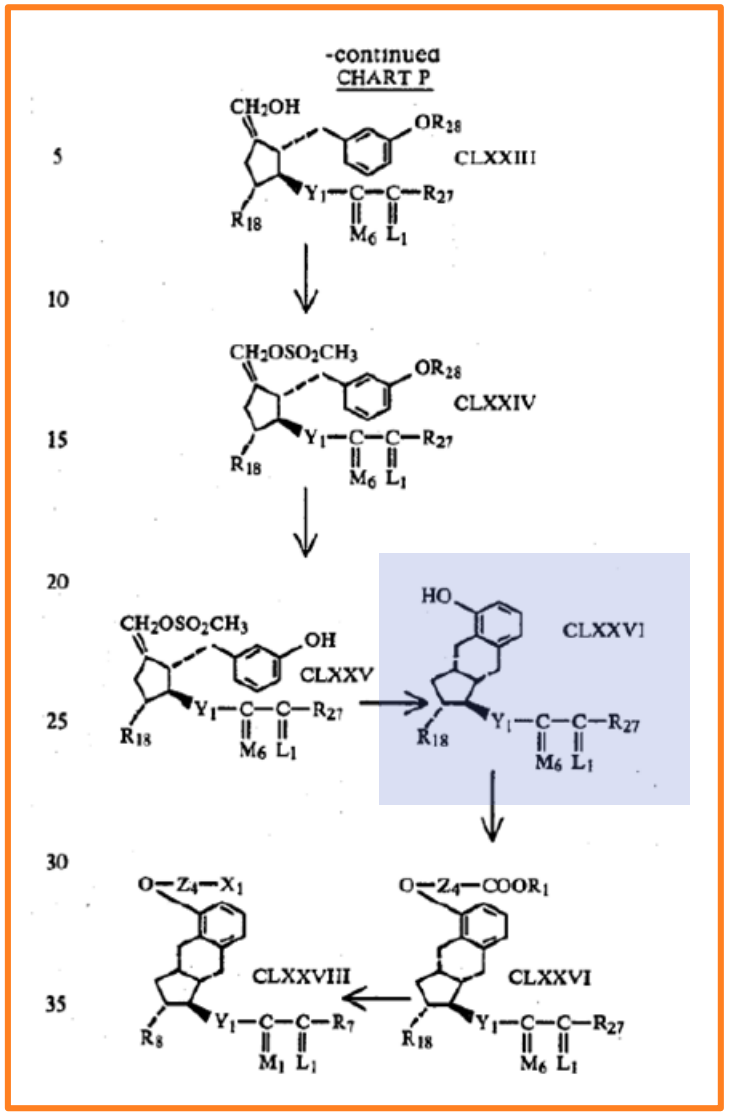
UT EX2037

EX2025 (Pinal Response), ¶¶158, 185, 232; Paper 31 (MtE), 6-8.

DR. WINKLER WRONGLY CHARACTERIZES PRIOR ART

- Dr. Winkler asserted Chart P of Exhibit 1014 teaches selective alkylation of a treprostinil triol intermediate.
  - It doesn't. Alkylation occurs on CLXXVI which has a single OH group—not three.

- Aristoff (Exhibit 1014) explicitly describes this compound by noting the "presence of protected R_{18} [and] M_6 hydroxyl groups."



EX1002 (Winkler), ¶¶82-83; EX2002 (Pinal), ¶¶216-19; EX2025 (Pinal Response) ¶¶185-88; EX1014 (Aristoff), 26:21-36, 89:14-90:37; Paper 6 (POPR), 41; Paper 12 (POR), 45-46; Paper 31 (MtE), 6-8.

DR. WINKLER INCORRECTLY CITES ARISTOFF PRODRUG TEACHING FOR ALKYLATION PROPOSITION

187. Dr. Winkler also refers to this exhibit in asserting that Phares cites to the '075 patent for teaching this alleged alkylation of the triol. It does not. Rather, Phares at 9 is discussing prodrugs, including "chemically derivatizing treprostinil to make stable esters, and in some instances, the compounds were derivatized from the hydroxyl groups." With regard to the '075 patent, Phares is limited to say: "Compounds of the present invention can also be provided by modifying the compounds found in U.S. Patent Nos. 4,306,075 and 5,153,222 in the like manner." EX1008 (Phares), 9.

EX1002 (Winkler), ¶¶82-83; EX2025 (Pinal Response), ¶¶185-88; Paper 6 (POPR), 61; Paper 12 (POR), 45-46; Paper 31 (MtE), 6-8.

DR. WINKLER: UNSWORN DECLARANT, EVASIVE, UNWILLING TO ENGAGE WITH MATERIAL ELEMENTS OF THE CASE

- Refusal to answer questions or extreme evasiveness regarding complexity of science and basic chemistry topics:
  - Acid Neutralization
  - Counterion Selection
  - Crystal Morphology

Q. I understand that may or may not have been your intention. You say it was your intention. That's fine.

My question was very different. My question is, you agree with me that if you add HCl to a KOH solution to bring it to pH 10 to 12 you have not neutralized the KOH, correct?

MS. KANNAPPAN: Objection, form, misstates.

THE WITNESS: Well, again, what I had intended to do here was to quote the experimental procedure to -- to -- not even to neutralization, but to the acidification that's described at the top of the right column of page 13. And so what I intended to do here today was to correct that to indicate that my intention had been to include this entire portion of the experimental.

UT EX2037

EX2032 (Winkler Depo #2), 171:23-175; Paper 25 (Sur-Reply), 1.

EX1012 SHOULD BE EXCLUDED

Fatal flaws of Exhibit 1012 include:

- Lack of purported Japanese document being translated
- Lack of a verified translator's declaration
- **Liquidia has repeatedly failed to cure these defects.**

Paper 6 (POPR), 42 (first noting at the preliminary response stage that the document lacks an original Japanese copy and certificate of translation in violation of 37 C.F.R. §42.63(b); Paper 31 (MtE), 2, 10-11.

FATAL FLAWS OF EXHIBIT 1012 INCLUDE:

- Liquidia's failure to establish it is a true and accurate representation of the original purported Japanese-language patent
  - FRE 802; 37 C.F.R. §42.63(b)

- Liquidia's failure to establish sufficient indicia to support a finding that EX1012 is what it purports to be; EX1012 is not self-authenticating
  - FRE 901, 902

- Liquidia's failure to provide certification by the appropriate foreign certifying authority
  - FRE 902(3)

Paper 6 (POPR), 42 (first noting at the preliminary response stage that the document lacks an original Japanese copy and certificate of translation in violation of 37 C.F.R. §42.63(b); Paper 31 (MtE), 2, 10-11; Paper 36 (UT Reply to Opposition to MtE), 4-5.

LIQUIDIA’S NEW TESTIMONY

EX1049: "AFFIDAVIT OF BORIS LEVINE"

- **EX1049 is hearsay under FRE 802 without exception.**
  - Liquidia offers this "declaration" testimony for its truth, but Mr. Levine has not been subject to cross examination.
- **EX1049 is unfairly prejudicial under FRE 403.**
  - UT identified Kawakami, EX1012, as improper in its POPR, filed on July 14, 2020.
  - UT timely objected to EX1012 on October 27, 2020.
  - **37 C.F.R. 42.64(b)(2)** gives Petitioner ten business days to respond with supplemental evidence.
  - Liquidia filed EX1049 on June 1, 2021, 144 business days (217 days) after UT's objections.

Paper 36 (UT Objections), 1-3; Paper 10 (UT Objections), 9 (objecting to EX1012 under, *e.g.*, FRE 802).

EX1052: "SUPPLEMENTAL DECLARATION OF SYLVIA HALL-ELLIS"

- **EX1052 is hearsay under FRE 802 without exception.**
  - Liquidia offers this "declaration" testimony for its truth, but Dr. Hall-Ellis has not been subject to cross examination.
- **EX1052 is unfairly prejudicial under FRE 403.**
  - UT identified problems with the original Hall-Ellis declaration, EX1015, in its POPR, filed on July 14, 2020.
  - UT timely objected to EX1015 on October 27, 2020.
  - **37 C.F.R. 42.64(b)(2)** gives Petitioner ten business days to respond with supplemental evidence.
  - Liquidia filed EX1052 on June 1, 2021, 144 business days (217 days) after UT's objections.

Paper 36 (UT Objections), 3-4; Paper 10 (UT Objections), 11-13 (objecting to EX1015 under, *e.g.*, FRE 702(b) as unreliable); Paper 36 (UT Reply to Opposition to MtE), 4-5; Paper 6 (POPR), 42.

LIQUIDIA'S REQUEST TO STRIKE

PATENT OWNER'S "CONTACTING" CONSTRUCTIONS HAVE BEEN CONSISTENT—PLAIN + ORDINARY MEANING

Passages of POR (Paper 12) to Be Stricken

- 11:10-14
- 15:12-13
- 25:7-8
- 29:5-6, 16-17
- 34:11-17
- 53:9-12
- 56:15-16, 18
- 58:14
- 59:7
- 62:12-13

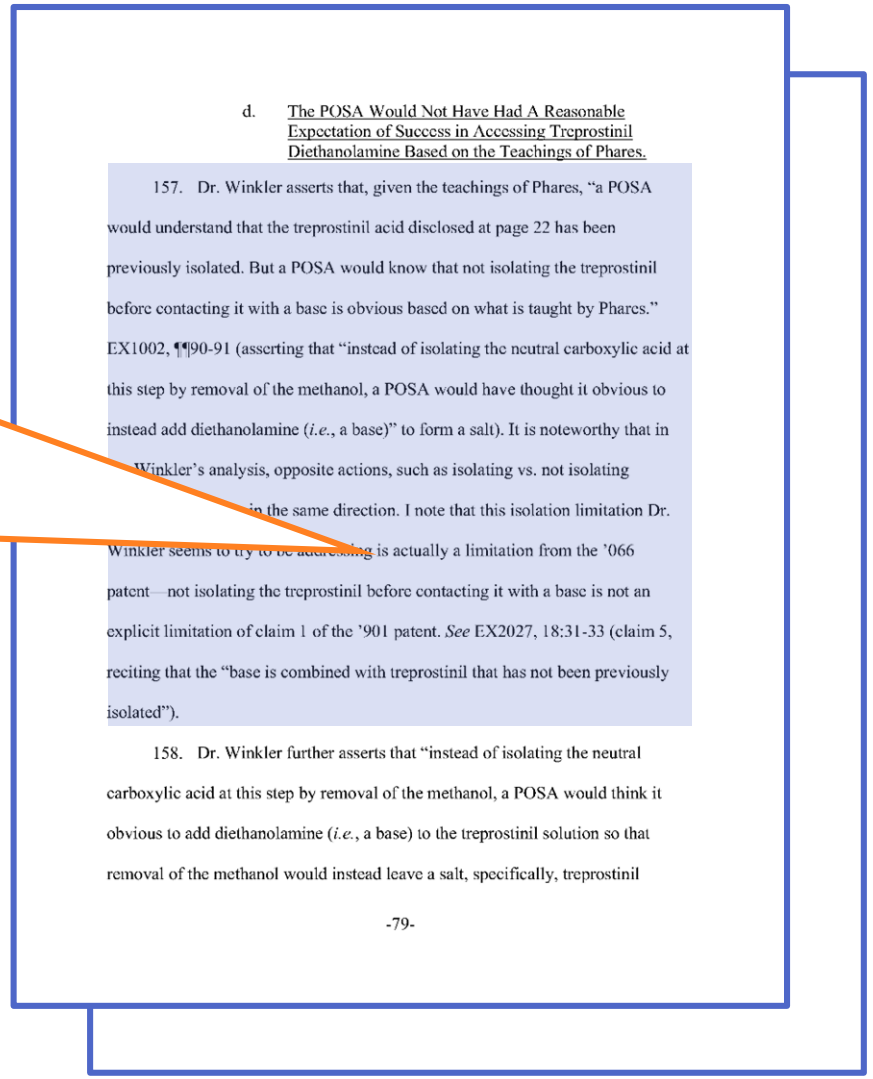
- Liquidia identified a number of instances where Patent Owner appeared to suggest no purification was allowed.
- Those statements were facially inconsistent with Dr. Pinal's testimony and were made in error.
- Patent Owner expeditiously withdrew those statements.

Paper 29 (Joint Paper), 1-2; Paper 25 (Sur-Reply), 7-8.

UT HAS NEVER CHANGED ITS CLAIM CONSTRUCTION POSITION

"I note that this isolation limitation Dr. Winkler seems to try to be addressing is actually a limitation from the '066 patent—**not isolating the treprostinil before contacting it with a base is not an explicit limitation of claim 1 of the '901 patent**."

- Dr. Pinal



d. The POSA Would Not Have Had A Reasonable Expectation of Success in Accessing Treprostinil Diethanolamine Based on the Teachings of Phares.

157. Dr. Winkler asserts that, given the teachings of Phares, "a POSA would understand that the treprostinil acid disclosed at page 22 has been previously isolated. But a POSA would know that not isolating the treprostinil before contacting it with a base is obvious based on what is taught by Phares." EX1002, ¶¶90-91 (asserting that "instead of isolating the neutral carboxylic acid at this step by removal of the methanol, a POSA would have thought it obvious to instead add diethanolamine (*i.e.*, a base)" to form a salt). It is noteworthy that in Winkler's analysis, opposite actions, such as isolating vs. not isolating in the same direction. I note that this isolation limitation Dr. Winkler seems to try to be addressing is actually a limitation from the '066 patent—not isolating the treprostinil before contacting it with a base is not an explicit limitation of claim 1 of the '901 patent. *See* EX2027, 18:31-33 (claim 5, reciting that the "base is combined with treprostinil that has not been previously isolated").

158. Dr. Winkler further asserts that "instead of isolating the neutral carboxylic acid at this step by removal of the methanol, a POSA would think it obvious to add diethanolamine (*i.e.*, a base) to the treprostinil solution so that removal of the methanol would instead leave a salt, specifically, treprostinil

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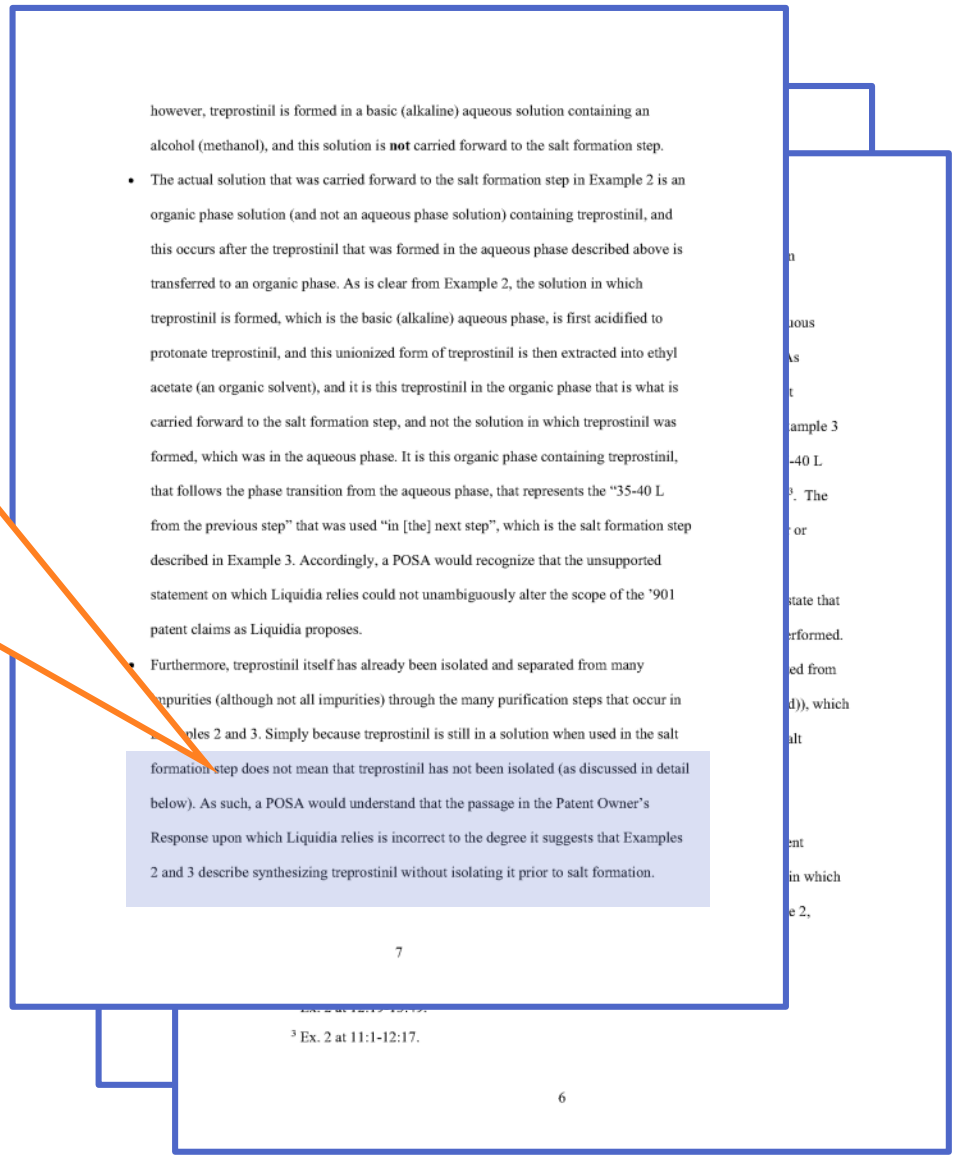
UT EX2037

Paper 25 (Sur-Reply), 8-9; EX2025 (Pinal Response), ¶157.

DR. RUFFOLO CONFIRMS DR. PINAL'S UNDERSTANDING

"[A] POSA would understand that the passage in the Patent Owner's Response upon which Liquidia relies is incorrect to the degree it suggests that Examples 2 and 3 describe synthesizing treprostinil without isolating it prior to salt formation." - Dr. Ruffolo



however, treprostinil is formed in a basic (alkaline) aqueous solution containing an alcohol (methanol), and this solution is **not** carried forward to the salt formation step.

- The actual solution that was carried forward to the salt formation step in Example 2 is an organic phase solution (and not an aqueous phase solution) containing treprostinil, and this occurs after the treprostinil that was formed in the aqueous phase described above is transferred to an organic phase. As is clear from Example 2, the solution in which treprostinil is formed, which is the basic (alkaline) aqueous phase, is first acidified to protonate treprostinil, and this unionized form of treprostinil is then extracted into ethyl acetate (an organic solvent), and it is this treprostinil in the organic phase that is what is carried forward to the salt formation step, and not the solution in which treprostinil was formed, which was in the aqueous phase. It is this organic phase containing treprostinil, that follows the phase transition from the aqueous phase, that represents the "35-40 L from the previous step" that was used "in [the] next step", which is the salt formation step described in Example 3. Accordingly, a POSA would recognize that the unsupported statement on which Liquidia relies could not unambiguously alter the scope of the '901 patent claims as Liquidia proposes.
- Furthermore, treprostinil itself has already been isolated and separated from many impurities (although not all impurities) through the many purification steps that occur in Examples 2 and 3. Simply because treprostinil is still in a solution when used in the salt formation step does not mean that treprostinil has not been isolated (as discussed in detail below). As such, a POSA would understand that the passage in the Patent Owner's Response upon which Liquidia relies is incorrect to the degree it suggests that Examples 2 and 3 describe synthesizing treprostinil without isolating it prior to salt formation.

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[3] Ex. 2 at 11:1-12:17.

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UT EX2037

Paper 25 (Sur-Reply), 8-9; EX2033 (Ruffolo), ¶15.

MOTIONS TO STRIKE ARE RARE + UNCOMMONLY GRANTED

- Motions to strike need to be justified for a significant reason.
- Liquidia's litany of proposed argument and testimony to strike is inconsistent with the withdrawn statements.
  - Benefits in specification still fall within the scope of the '901 patent claims.

"[S]triking the entirety or a portion of a party's brief is an **exceptional remedy** that the Board expects will be **granted rarely**."

- *Consolidated Trial Practice Guide, November 2019, 80-81*

Paper 29 (Joint Paper), 5-8.

LIQUIDIA'S LITANY OF ARGUMENT + TESTIMONY TO BE STRICKEN

POR (Paper 12)	EX2002	EX2025	Sur-Reply (Paper 25)
– 4:17-5:1 – 5:13-15, 17-6:8 – 11:5-14 – 12:6-9 – 15:6-8, 12-16:5 – Footnote 1 – 19:8-20:18 – 24:14-15 – 25:1-3 – 29:3-6, 16-34:18 – 37:15-38:10 – 50:7-51:8 – 51:10-14, 18-52:2 – 53:9-12 – 56:14-60:16 – 61:16-64:17 – 65:2-18 – 66:19-67:13 – 68:7-69:4	– ¶¶124-26 – ¶¶135-40 – ¶170 – ¶¶222-24 – ¶¶229-30 – ¶¶235-36 – ¶240 – ¶¶243-44 – ¶¶274-77 – ¶¶294-95 – ¶¶304-05	– ¶81 – ¶¶90-91 – ¶95 – ¶¶156-60 – ¶201 – ¶¶204-06 – ¶210-12 – ¶¶217-18 – ¶222 – ¶256 – ¶258 – ¶276 – ¶¶283-85 – ¶291	– 4:8-9 – 10:11-11:5 – 17:18-18:5 – 18:9-19:2 – 19:12-13 – 20:18-19 – 22:10-16 – 23:1-24:2 – 24:13-25:10 – Footnote 3

Paper 29 (Joint Paper), 1-2, 8.

THERE IS NO BASIS TO STRIKE ANY ARGUMENT OR TESTIMONY PERTAINING TO STORAGE

"Because an expert witness is charged with the duty of giving his or her expert opinion regarding the matter before the court, **we fail to comprehend how an expert witness**, who is not an agent of the party who called him, **can be authorized to make an admission for that party**."

- *Kirk v. Raymark Indus., Inc.*, 61 F.3d 147, 164 (3rd Cir. 1995)

- In the district court action, Dr. Ruffolo was retained to testify about the meaning of the word "storage," not the legal requirements of practicing the claim.
  - Liquidia went beyond claim construction and asked Dr. Ruffolo about the legal question of infringement.
- UT has consistently taken the view that the claims actually require storage.
  - The parties agree that the material must be stored in order to meet the requirements of the claim.
- Dr. Pinal opined what a POSA would understand the term means, not the legal question of what the claims require.

Paper 29 (Joint Paper), 5-8; *see also* EX2034 (Ruffolo Deposition), 130:12-136:11.