

NOVARTIS PHARMACEUTICALS CORP.  
v.  
REGENTS OF THE UNIVERSITY OF MICHIGAN  
AND UNIVERSITY OF SOUTH FLORIDA

IPR2023-01346

Oral Hearing January 8, 2025

Patent Owners' Presentation

# Overview

---

- The '344 Patent is entitled to a priority date of no later than the filing date of U.S. Application No. 19/378,956, March 3, 2003.
- The '956 Application provides written description support for the claims.
- Based on the disclosure of the '956 Application, a POSITA would have been able to predict whether a co-crystal would form and could have utilized high-throughput crystallization and screening to assess the conditions under which formation would occur.

# The Invention of the '344 Patent

# Overview of the '344 Patent

The '344 Patent claims priority to at least as early as March 2003

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <br>US910633344B2                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| <b>(12) United States Patent</b><br><b>Zaworotko et al.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| <b>(10) Patent No.: US 10,344,482</b><br><b>(45) Date of Patent:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |
| <b>(54) MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |
| <b>(71) Applicant:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| <b>(72) Inventors:</b> Michael J. Zaworotko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)                                                                                                                                                                                                                                                                                                                                                                                           |  |
| <b>(73) Assignees:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| <b>(*) Notice:</b> Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 69 days.                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| <b>(21) Appl. No.:</b> 14/179,862                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| <b>(22) Filed:</b> Feb. 13, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| <b>(65) Prior Publication Data</b><br>US 2014/0162989 A1 Jan. 12, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| <b>Related U.S. Application Data</b><br><b>(63)</b> Continuation of application No. 10/378,956, filed on Mar. 3, 2003.<br>(Continued)                                                                                                                                                                                                                                                                                                                                                                                                       |  |
| <b>(51) Int. Cl.</b><br>C07D 223/26 (2006.01)<br>A61K 9/36 (2006.01)<br>A61K 31/067 (2006.01)<br>A61K 31/392 (2006.01)<br>A61K 31/4166 (2006.01)<br>A61K 31/55 (2006.01)<br>A61K 31/616 (2006.01)<br>A61K 47/10 (2017.01)<br>A61K 47/32 (2006.01)<br>C07C 51/41 (2006.01)<br>C07C 51/43 (2006.01)<br>C07C 233/25 (2006.01)<br>C07C 233/74 (2006.01)<br>C07C 47/54 (2006.01)<br>C07C 53/00 (2006.01)<br>C07C 53/24 (2006.01)<br>C07C 57/30 (2006.01)<br>C07C 57/58 (2006.01)<br>C07C 61/35 (2006.01)<br>C07D 233/74 (2006.01)<br>(Continued) |  |
| <b>(52) U.S. Cl.</b><br>CPC ..... C07D 223/26 (2013.01); A61K 9/36 (2013.01); A61K 31/067 (2013.01); A61K 31/392 (2013.01); A61K 31/4166 (2013.01); A61K 31/55 (2013.01); A61K 31/616 (2013.01); A61K 47/10 (2013.01); A61K 47/32 (2013.01)                                                                                                                                                                                                                                                                                                 |  |
| <b>(58) Field of Classification Search</b><br>CPC ..... C07D 223/26; C07D 233/74; C07D 233/25; C07D 233/79; C07D 233/22; C07D 233/00; C06C 63/00; C06C 61/00; C06C 57/30; C06C 53/00; C06C 47/54; C06C 51/43; A61K 31/067; A61K 31/4166; A61K 31/55                                                                                                                                                                                                                                                                                         |  |
| <b>(56) References Cited</b><br>U.S. PATENT DOCUMENTS<br>2,554,318 A 5/1991 Clapp et al.<br>2,665,277 A 1/1994 Hines et al.<br>(Continued)<br>FOREIGN PATENT DOCUMENTS<br>CA 1 101 840 5/1981<br>CA 1 148 029 A1 6/1983<br>(Continued)<br>OTHER PUBLICATIONS<br>Notice of Reasons for Rejection dated Oct. 5, 2003.<br>Application No. 2003-072966, 11 pages.<br>(Continued)<br>Primary Examiner — Sahar Inamdar<br>(74) Attorney, Agent, or Firm — Wolf, Greenfield & Sacks, P.C.                                                          |  |
| <b>(57) ABSTRACT</b><br>The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular system. The subject invention also pertains to binary phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions.                                                                                                                                                                                                                |  |
| 21 Claims, 25 Drawing Sheets<br>(23 of 25 Drawing Sheet(s) Filed in Color)                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |

The present application is a continuation of U.S. application Ser. No. 10/378,956, filed Mar. 3, 2003, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings. U.S. application Ser. No. 10/378,956 claims the benefit of priority of U.S. Provisional Application Ser. No. 60/360,768, filed Mar. 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

# Overview of the '344 Patent

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <br>US01063344B2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                       |
| (12) <b>United States Patent</b><br><b>Zaworotko et al.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | (10) <b>Patent No.:</b> US 10,633,344 B2<br>(45) <b>Date of Patent:</b> Apr. 28, 2020 |
| (54) <b>MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                       |
| (71) <b>Applicants:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                       |
| (72) <b>Inventors:</b> Michael J. Zaworotko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                       |
| (73) <b>Assignees:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                       |
| (*) <b>Notice:</b> Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 69 days.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                       |
| (21) <b>Appl. No.:</b> 14/179,862                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                       |
| (22) <b>Filed:</b> Feb. 13, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                       |
| (65) <b>Prior Publication Data</b><br>US 2014/0162989 A1 Jan. 12, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                       |
| <b>Related U.S. Application Data</b><br>(63) Continuation of application No. 10/578,956, filed on Mar. 3, 2003.<br>(Continued)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                       |
| (51) <b>Int. Cl.</b><br>C07D 223/26 (2006.01)<br>A61K 9/36 (2006.01)<br>A61K 31/067 (2006.01)<br>A61K 31/392 (2006.01)<br>A61K 31/4166 (2006.01)<br>A61K 31/55 (2006.01)<br>A61K 31/616 (2006.01)<br>A61K 47/30 (2017.01)<br>A61K 47/32 (2006.01)<br>C07C 41/01 (2006.01)<br>C07C 51/43 (2006.01)<br>C07C 233/25 (2006.01)<br>C07C 233/74 (2006.01)<br>C07C 47/544 (2006.01)<br>C07C 53/00 (2006.01)<br>C07C 53/24 (2006.01)<br>C07C 57/30 (2006.01)<br>C07C 57/58 (2006.01)<br>C07C 61/35 (2006.01)<br>C07D 233/74 (2006.01)                                                                                                                                                                                                                                                                                               |                                                                                       |
| (52) <b>U.S. Cl.</b><br>CPC ..... C07D 223/26 (2013.01); A61K 9/3652 (2013.01); A61K 31/392 (2013.01); A61K 31/4166 (2013.01); A61K 31/55 (2013.01); A61K 31/616 (2013.01); A61K 47/30 (2013.01); A61K 47/32 (2013.01)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                       |
| (58) <b>Field of Classification Search</b><br>CPC ..... C07D 223/26; C07D 275/06; C07D 213/82; C07D 213/79; C07D 213/69; C07D 213/22; C07D 213/06; C07D 233/74; C06C 31/704; C06C 233/75; C06C 233/03; C06C 205/57; C06C 60/57; C06C 63/07; C06C 61/35; C06C 57/58; C06C 57/30; C06C 53/124; C06C 53/08; C06C 53/02; C06C 47/544; C06C 233/25; C06C 51/43; C06C 51/412; A61K 47/32; A61K 47/30; A61K 31/616; A61K 31/55; A61K 31/4166; A61K 31/392; A61K 31/167; A61K 9/1652                                                                                                                                                                                                                                                                                                                                                |                                                                                       |
| (56) <b>References Cited</b><br>U.S. PATENT DOCUMENTS<br>2,554,818 A 5/1991 Clapp et al.<br>2,665,277 A 1/1994 Hiney et al.<br>(Continued)<br>FOREIGN PATENT DOCUMENTS<br>CA 1 101 840 5/1981<br>CA 1 148 020 A1 6/1983<br>(Continued)<br>OTHER PUBLICATIONS<br>Notice of Reasons for Rejection dated Oct. 8, 2009 for Japanese Application No. 2003-572066, 11 pages.<br>(Continued)<br>Primary Examiner—Suhair Inattamad<br>(74) Attorney, Agent, or Firm—Wolf, Greenfield & Sacks, P.C.<br>(57) <b>ABSTRACT</b><br>The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon. The subject invention also pertains to binary phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions. |                                                                                       |
| 21 Claims, 25 Drawing Sheets<br>(23 of 25 Drawing Sheets) Filed in Color                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                       |

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

# Overview of the '344 Patent

The Parties agree on the definition of  
“co-crystal”

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <br>US910633344B2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| <b>(12) United States Patent</b><br><b>Zawortko et al.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| <b>(54) MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |
| <b>(71) Applicants:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| <b>(72) Inventors:</b> Michael J. Zawortko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| <b>(73) Assignees:</b> University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |
| <b>(*) Notice:</b> Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 09 days.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| <b>(21) Appl. No.:</b> 14/179,862                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |
| <b>(22) Filed:</b> Feb. 13, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| <b>(65) Prior Publication Data</b><br>US 2014/0162989 A1 Jan. 12, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
| <b>Related U.S. Application Data</b><br><b>(63)</b> Continuation of application No. 10/578,956, filed Mar. 3, 2003.<br>(Continued)                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| <b>(51) Int. Cl.</b><br>C07D 223/26 (2006.01)<br>A61K 9/36 (2006.01)<br>A61K 31/067 (2006.01)<br>A61K 31/392 (2006.01)<br>A61K 31/4166 (2006.01)<br>A61K 31/55 (2006.01)<br>A61K 31/616 (2006.01)<br>A61K 47/20 (2017.01)<br>A61K 47/32 (2006.01)<br>C07C 51/01 (2006.01)<br>C07C 51/43 (2006.01)<br>C07C 233/25 (2006.01)<br>C07C 233/74 (2006.01)<br>C07C 47/54 (2006.01)<br>C07C 53/00 (2006.01)<br>C07C 53/24 (2006.01)<br>C07C 57/20 (2006.01)<br>C07C 57/58 (2006.01)<br>C07C 61/35 (2006.01)<br>C07D 233/74 (2006.01)<br>(Continued)                                                           |  |
| <b>(52) U.S. Cl.</b><br>CPC ..... C07D 223/26 (2013.01); A61K 9/36 (2013.01); A61K 31/067 (2013.01); A61K 31/392 (2013.01); A61K 31/4166 (2013.01); A61K 31/55 (2013.01); A61K 31/616 (2013.01); A61K 47/20 (2013.01); A61K 47/32 (2013.01);<br>21 Claims, 25 Drawing Sheets<br>(23 of 25 Drawing Sheet(s) Filed in Color)                                                                                                                                                                                                                                                                            |  |
| <b>OTHER PUBLICATIONS</b><br>Notice of Reasons for Rejection dated Oct. 8, 2009 for Japanese Application No. 2003-572986, 11 pages.<br>(Continued)<br><b>Provisional Examiner — Sahar Issamoud</b><br>(74) Attorney, Agent, or Firm — Wolf, Greenfield & Sacks, P.C.<br>(57) <b>ABSTRACT</b><br>The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon. The subject invention also pertains to binary phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions. |  |

proposed construction that “co-crystal” means “[a] multiple-component, single crystalline phase, having a fixed stoichiometry of its component compounds.”

The '344 Patent describes the different components of the claimed co-crystals.

The terms “pharmaceutical entity,” pharmaceutical moiety”, “pharmaceutical component”, “pharmaceutical molecule”, and “active pharmaceutical ingredient (API)”, and grammatical variations thereof, are used interchangeably herein to refer to any biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration.

# Overview of the '344 Patent

The '344 Patent describes the different components of the claimed co-crystals.

US910633344B2

(12) United States Patent  
Zaworotko et al.

(10) Patent No.: US 10,633,442  
(45) Date of Patent: 2019-12-24

(54) MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

(71) Applicant: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)

(72) Inventors: Michael J. Zaworotko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)

(73) Assignees: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 09 days.

(21) Appl. No.: 14/179,862

(22) Filed: Feb. 13, 2014

(65) Prior Publication Data  
US 2014/0162989 A1 Jan. 12, 2014

Related U.S. Application Data  
(63) Continuation of application No. 10/578,956, filed on Mar. 3, 2003.  
(Continued)

(51) Int. Cl.  
C07D 223/26 (2006.01)  
A61K 9/36 (2006.01)  
A61K 31/067 (2006.01)  
A61K 31/392 (2006.01)  
A61K 31/4166 (2006.01)  
A61K 31/55 (2006.01)  
A61K 31/616 (2006.01)  
A61K 47/30 (2017.01)  
A61K 47/32 (2006.01)  
C07C 51/01 (2006.01)  
C07C 51/43 (2006.01)  
C07C 233/25 (2006.01)  
C07C 233/74 (2006.01)  
C07C 47/54 (2006.01)  
C07C 53/00 (2006.01)  
C07C 53/24 (2006.01)  
C07C 57/30 (2006.01)  
C07C 57/58 (2006.01)  
C07C 61/35 (2006.01)  
C07D 233/74 (2006.01)  
(Continued)

(52) U.S. Cl.  
CPC ..... C07D 223/26 (2013.01); A61K 9/3652 (2013.01); A61K 31/392 (2013.01); A61K 31/4166 (2013.01); A61K 31/55 (2013.01); A61K 31/616 (2013.01); A61K 47/30 (2013.01); A61K 47/32 (2013.01)

(58) Field of Classification Search  
CPC ..... C07D 223/26; C07D 233/74; C07D 233/79; C07D 233/22; C07D 233/21; C06C 31/704; C06C 63/007; C06C 63/00; C06C 57/30; C06C 57/58; C06C 53/02; C06C 53/43; A61K 47/30; A61K 31/4166; A61K 31/

USPC .....  
See application file for complete search history.

(56) References Cited  
U.S. PATENT DOCUMENTS  
2,554,818 A 5/1951 Clapp et al.  
2,665,277 A 1/1954 Himmelfarb et al.  
(Continued)

FOREIGN PATENT DOCUMENTS  
CA 1 101 840 5/1981  
CA 1 148 029 A1 6/1983  
(Continued)

OTHER PUBLICATIONS  
Notice of Reasons for Rejection dated Oct. 8, 2009 for Japanese Application No. 2003-572966, 11 pages.  
(Continued)

Primary Examiner—Sahar Issamoud  
(74) Attorney, Agent, or Firm—Wolf, Greenfield & Sacks, P.C.

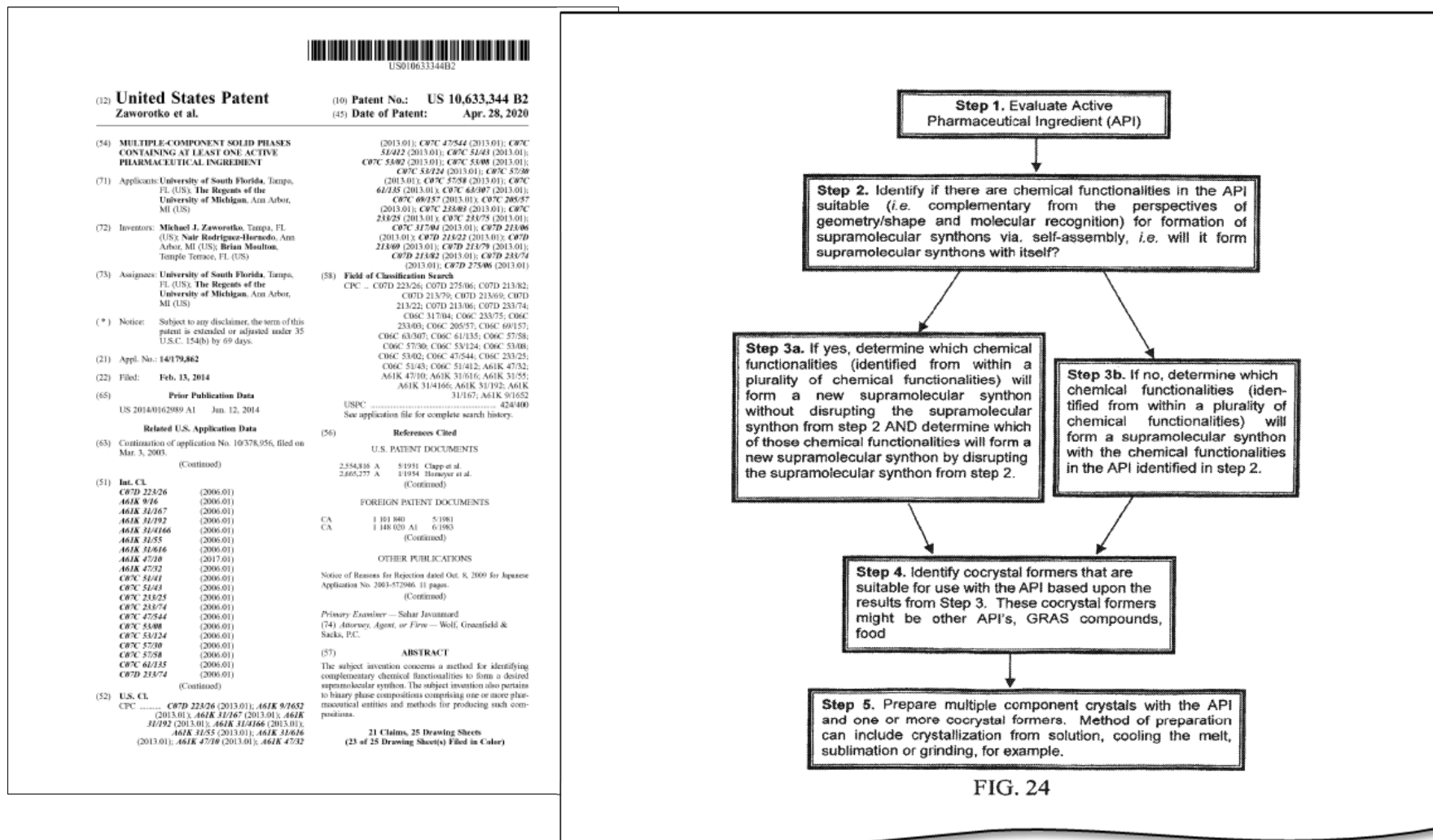
(57) ABSTRACT  
The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular system. The subject invention also pertains to binary phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions.

21 Claims, 25 Drawing Sheets  
(23 of 25 Drawing Sheet(s) Filed in Color)

The cocrystal formers can be, but are not limited to, solvent molecules, other drug molecules, GRAS compounds, or approved food additives.

# Overview of the '344 Patent

The '344 Patent describes how the claimed co-crystals are formed.



# Overview of the '344 Patent

The '344 Patent provides 19 examples of co-crystals  
– illustrating the claim limitations of claims 10, 11,  
and 18.

| Condition                                                                                                                                                                   | Example |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|
|                                                                                                                                                                             | 1       | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Supramolecular synthons formed from stoichiometric amounts of at least one API and at least one co-former                                                                   | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding                                           | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form                                                                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | N  | Y  | Y  | N  | N  | N  | N  | Y  |
| Supramolecular synthons formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former | N       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is a carboxamide                                                                                                                               | Y       | Y | N | N | N | N | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is an amine                                                                                                                                    | N       | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |
| Supramolecular synthon is a heterosynthon dimer formed by non-covalent hydrogen bonding of the API and co-former                                                            | N       | N | Y | Y | Y | Y | N | N | N | N  | Y  | Y  | Y  | N  | Y  | N  | N  | Y  | Y  |

# Background of the '344 Patent

# Principles of Hydrogen Bonding were Well-Known

# The Parties Agree on Definition of POSITA

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

REGENTS OF THE UNIVERSITY OF MICHIGAN AND  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

U.S. Patent No. 10,633,344

DECLARATION OF ROBIN D. ROGERS, Ph.D.  
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW

NOVARTIS EXHIBIT 1002  
Novartis v. Regents, IPR2023-01346  
Page 1 of 222

19. In my opinion, a POSA as of 2002/2003 or 2014 would have had a Ph.D. in chemistry or a related field with at least two years of experience in solid state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures, and the POSA would consult with others having ordinary experience in other disciplines, such as formulation of pharmaceutical compositions comprising such multiple-component crystalline solids. Alternatively, a POSA as of 2002/2003 or 2014 would have had a Ph.D. in chemistry, pharmacy, or a related field with at least two years of experience in formulation of pharmaceutical compositions, and the POSA would consult with others having ordinary experience in other disciplines, such as solid-state chemistry, including experience preparing multiple-component crystalline solids and evaluating their single crystal structures. Alternatively, a POSA could have had a Master's degree in one of the above disciplines plus relatively more experience.

# The Parties Agree That Level of Skill is High

UNITED STATES PATENT AND TRADEMARK OFFICE  
\_\_\_\_\_  
BEFORE THE PATENT TRIAL AND APPEAL BOARD  
\_\_\_\_\_

NOVARTIS PHARMACEUTICALS CORPORATION  
Petitioner,

v.

REGENTS OF THE UNIVERSITY OF MICHIGAN AND  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

\_\_\_\_\_  
U.S. Patent No. 10,633,344  
\_\_\_\_\_

DECLARATION OF ROBIN D. ROGERS, Ph.D.  
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW

NOVARTIS EXHIBIT 1002  
Novartis v. Regents, IPR2023-01346  
Page 1 of 222

## d. The Relative Skill of Those in the Art

126. I defined the person of ordinary skill in the art of the '344 patent as of 2002/2003 (or 2014) in paragraph 19 above. The relative skill of a POSA is high.

# Hydrogen Bonding Principles Were Well-Known

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN,  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

38. Fundamental hydrogen bonding principles were well-known in the art as of 2002/2003. See Ex. 2009 (Yusov) at 756-58 (describing the history of the discovery and study of hydrogen bonding, beginning as early as 1912); see also Ex. 2010 (Etter 1990) 257 (“Since hydrogen bonds were first proposed, efforts to characterize them, measure them, and understand them have proliferated. . . . As it became obvious that these interactions occurred in many kinds of materials, and were important for determining the properties and activities of most biochemicals, hydrogen-bond classifications were developed[.]”); *id.* (discussing methods “allow[ing] one to characterize subsets of crystal structure or arrays, namely, the hydrogen-bonded subset”).

1

EXHIBIT 2014  
Novartis v. The Regents of Univ. of MI  
IPR2023-01346

# Dr. Margaret "Peggy" Etter Published Rules for Hydrogen Bonding in the 1990s

suitable for such exploitation, e.g., for selective oxidation of hydrocarbons.

## Concluding Remarks

It should be encouraging, for organic chemists and chemical engineers alike, to know that enzymes can work not only in water but also in organic solvents. The still-existing prejudices against enzymes as practical catalysts will be lessened further by the forthcoming greater availability of a wider variety of enzymes at a lower cost, brought about by modern biotechnology. Moreover, protein engineering, particularly redesigning enzymes by site-directed mutagenesis,<sup>90</sup> has an exciting potential of altering the enzymatic properties at will, e.g., broadening substrate specificity,<sup>91</sup> as well as enhancing enzyme action in organic media.<sup>92</sup>

(90) Perletti, A. R.; et al. *Angew. Chem., Int. Ed. Engl.* 1984, 23, 467-472. Kacelnik, J. R. *Science* 1987, 236, 1252-1255.  
(91) Bane, R.; Sillescu, J. L.; Agard, D. A. *Nature* 1988, 332, 151-155.

The ever intensifying search for novel biologically active compounds inevitably results in increasingly complex molecules, often containing stereocenters and existing as distinct structural isomers. Usually, one of the enantiomers or isomers has a higher biological activity than others. Consequently, there is mounting pressure on the manufacturers of pharmaceuticals and agricultural chemicals to produce only the desired stereoisomer, which would enhance the compound's benefit-to-harm ratio. As a result, the need for simple and scalable asymmetric conversions will grow. Hopefully, this Account demonstrates that enzymatic catalysis in organic solvents provides a useful methodology toward that aim.

I am grateful to David Voth and Paul Burke for their help in the preparation of this manuscript and to the National Institutes of Health for financial support (Grant GM38794).

(92) Arnold, F. H. *Protein Eng.* 1988, 2, 21-25.

## Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds

MARGARET C. ETTER

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received

Are hydrogen-bond patterns in acids form cyclic dimers. Salicylic acid molecular hydrogen bond. These terms seem obvious because they criteria of pairing a somewhat acidic electronegative atom, and because crystallographic studies have confirmed intuition about how and when they form in these and in similar features.<sup>1</sup> But what about other, less compounds like diacetamide? If proton acceptors, one proton donor conforms each of which could centered hydrogen-bonded chain the hydrogen-bond possibilities 1 and 3 are found in the two polymers. Besides these patterns, diacetamide with many other hydrogen-bond inherent complexities in making apparent in the intricate hydrogen

Margaret C. Etter, a native of Wilmington, Delaware, received her B.S. in chemistry from the University of Pennsylvania, a M.S. in 1974 under the direction of J. Z. Gasiot solid-state chemist and crystallographer at the time, returned to the University of Minnesota to G. Bryant in solid-state NMR spectroscopy. Professor of Chemistry at the University of Minnesota, solid-state organic chemistry involves intermolecular and properties of small-molecule organic solid-state interactions and crystal growth. Alfred P. Sloan Fellowship.

0001-4842/94

## Table I Hydrogen-Bond Rules for Organic Compounds

### A. General Rules

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
3. The best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another.

# In 2002/2003, a POSITA Would Have Been Aware of Dr. Etter's work

suitable for such exploitation, e.g., for selective oxidation of hydrocarbons.

## Concluding Remarks

It should be encouraging, for organic chemists and chemical engineers alike, to know that enzymes can work not only in water but also in organic solvents. The still-existing prejudices against enzymes as practical catalysts will be lessened further by the forthcoming greater availability of a wider variety of enzymes at a lower cost, brought about by modern biotechnology. Moreover, protein engineering, particularly redesigning enzymes by site-directed mutagenesis,<sup>92</sup> has an exciting potential of altering the enzymatic properties at will, e.g., broadening substrate specificity,<sup>93</sup> as well as enhancing enzyme action in organic media.<sup>92</sup>

(92) Parsh, A. R.; et al. *Angew. Chem., Int. Ed. Engl.* 1994, 33, 467-472. Kacelnik, J. R. *Science* 1987, 236, 1252-1253.  
(93) Bess, R.; Sillescu, J. L.; Agard, D. A. *Nature* 1989, 339, 121-125.

## Encoding and Decoding Hydrogen Bonding in Organic Compounds

MARGARET C. ETTER

Department of Chemistry, University of Minnesota  
Received June 20, 1989 (Revised Manuscript Received August 1, 1989)

Are hydrogen-bond patterns predictable? Benzoic acids form cyclic dimers. Salicylic acid has an intramolecular hydrogen bond. These hydrogen-bond patterns seem obvious because they satisfy the chemical criteria of pairing a somewhat acidic hydrogen with an electronegative atom, and because spectroscopic and crystallographic studies have confirmed our chemical intuition about how and when hydrogen bonds should form in these and in similar frequently studied structures.<sup>1</sup> But what about other, less studied, yet simple compounds like diacetamide? Diacetamide has two proton acceptors, one proton donor, and three possible conformers each of which could form two- or three-centered hydrogen-bonded chains or dimers. Four of the hydrogen-bond possibilities are shown. Patterns 1 and 3 are found in the two polymorphs of diacetamide.<sup>2</sup> Besides these patterns, diacetamide also cocrystallizes with many other hydrogen-bonding molecules.<sup>3</sup> The inherent complexities in making such predictions are apparent in the intricate hydrogen-bond pattern observed in the crystal structure of diacetamide.

Margaret C. Etter, a native of Wilmington, DE, obtained her B.A. in chemistry from the University of Pennsylvania, an M.Sc. from the University of Delaware, and her Ph.D. in organic chemistry from the University of Minnesota in 1974 under the direction of J. Z. Groves. After seven years as a solid-state chemist and crystallographer at the 3M Company in St. Paul, MN, she returned to the University of Minnesota to do postdoctoral work with R. G. Bryant in solid-state NMR spectroscopy. She is currently an Associate Professor of Chemistry at the University of Minnesota, where her work on solid-state organic chemistry involves interdisciplinary studies of structure and properties of small-molecule organic solids, with special interests in hydrogen-bonded interactions and crystal growth. She was recently awarded an Alfred P. Sloan Fellowship.

0001-4842/90/0123-0120\$02.50/0 © 1990

The ever intensifying search for novel biologically active compounds inevitably results in increasingly complex molecules, often containing stereocenters and existing as distinct structural isomers. Usually, one of the difficulties in the design of such molecules is the lack of a reliable method for predicting the stereochemistry of the product.

It is not in the state of the art to predict the stereochemistry of the product of a reaction.

Q. Do you agree that a person of ordinary skill as of 2002-2003 would have been aware of Margaret Etter's work in hydrogen bonding?

A. I believe that they would, yes.

Novartis v. The Regents of Univ. of Minn.  
IPR2023-01346

# Etter's Rules Were and Remain Important in Field

A. It depends what you mean by

"importance" and "in the field." I think that they were important in the early generation of the field called crystal engineering.

Q. And when you say "early," what time frame are you talking about?

A. The papers were around the '90s, and the field of crystal engineering came up probably in the early '90s, and it came up in the late '90s, early 2000s, and continues today.

suitable for such exploitation, of  
tion of hydrocarbons.

#### Concluding Remarks

It should be encouraging, for  
chemical engineers alike, to know  
work not only in water but also in  
still-existing prejudices against  
catalysts will be lessened, further  
greater availability of a wider variety  
lower cost, brought about by it.  
Moreover, protein engineering, of  
enzymes by site-directed mutagenesis  
potential of altering the enzyme  
e.g., broadening substrate specificity  
enhancing enzyme action in organic

(80) Parikh, A. R.; et al. *Angew. Chem.*  
487-472. Knochel, J. R. *Science* 1987, 235,  
921. Bane, R.; Sillescu, J. L.; Agard, D. A.

#### Encoding and

Department  
Received

Are hydrogen-bond patterns  
acids form cyclic dimers. Salicylic  
molecular hydrogen bond. These  
terms seem obvious because the  
criteria of pairing a somewhat  
electronegative atom, and because  
crystallographic studies have  
intuition about how and when  
form in these and in similar  
features.<sup>1</sup> But what about other  
compounds like diacetamide?  
proton acceptors, one proton donor  
conformers each of which could  
centered hydrogen-bonded chain  
the hydrogen-bond possibilities  
and 3 are found in the two polymers.  
Besides these patterns, diacetamide  
with many other hydrogen-bond  
inherent complexities in making  
apparent in the intricate hydrogen

Margaret C. Etter, a native of Wilmington,  
Mary from the University of Pennsylvania, in  
Delaware, and her Ph.D. in organic chemistry  
in 1974 under the direction of J. Z. Groshel  
solid-state chemist and crystallographer at the  
she returned to the University of Minnesota.  
G. Bryant in solid-state NMR spectroscopy.  
Professor of Chemistry at the University of  
solid-state organic chemistry involves intramolecular  
and properties of simultaneous organic and  
hydrogen-bond interactions and crystal growth.  
Alfred P. Sloan Fellowship.

0001-4842/97

A POSITA Had Resources to  
Select Appropriate Solvents  
And Excipients

# Background of the '344 Patent

A POSITA would have been aware of guidance available from HHS that identified solvents not to use or to avoid.

## Guidance for Industry

### Q3C — Tables and List

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
November 2003  
ICH  
Revision 1

1

Novartis v. The Regent

Table 1. – Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)

| Solvent              | Concentration Limit (ppm) | Concern                        |
|----------------------|---------------------------|--------------------------------|
| Benzene              | 2                         | Carcinogen                     |
| Carbon tetrachloride | 4                         | Toxic and environmental hazard |

Table 2. – Class 2 Solvents in Pharmaceutical Products

| Solvent       | PDE (mg/day) | Concentration Limit (ppm) |
|---------------|--------------|---------------------------|
| Acetonitrile  | 4.1          | 410                       |
| Chlorobenzene | 3.6          | 360                       |
| Chloroform    | 0.6          | 60                        |
| Cyclohexane   | 38.8         | 3,880                     |

# Background of the '344 Patent

A POSITA would have had several references in hand to choose excipients.

US 10,633,344 B2

(12) United States Patent  
Zaworotko et al.

(10) Patent No.: US 10,633,344 B2  
(45) Date of Patent: Apr. 28, 2020

(54) MULTIPLE-COMPONENT SOLID PHASES  
CONTAINING AT LEAST ONE ACTIVE  
PHARMACEUTICAL INGREDIENT

(71) Applicant: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)

(72) Inventors: Michael J. Zaworotko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)

(73) Assignees: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 09 days.

(21) Appl. No.: 14/179,862

(22) Filed: Feb. 13, 2014

(65) Prior Publication Data  
US 2014/0162989 A1 Jan. 12, 2014

Related U.S. Application Data

(63) Continuation of application No. 10/578,956, filed on Mar. 3, 2003.  
(Continued)

(51) Int. Cl.  
C07D 223/26 (2006.01)  
A61K 9/36 (2006.01)  
A61K 31/067 (2006.01)  
A61K 31/092 (2006.01)  
A61K 31/4166 (2006.01)  
A61K 31/55 (2006.01)  
A61K 31/616 (2006.01)  
A61K 47/30 (2017.01)  
A61K 47/32 (2006.01)  
C07C 51/01 (2006.01)  
C07C 51/43 (2006.01)  
C07C 233/25 (2006.01)  
C07C 233/74 (2006.01)  
C07C 47/54 (2006.01)  
C07C 53/00 (2006.01)  
C07C 53/24 (2006.01)  
C07C 57/30 (2006.01)  
C07C 57/58 (2006.01)  
C07C 61/35 (2006.01)  
C07C 233/74 (2006.01)  
(Continued)

(52) U.S. Cl.  
CPC ..... C07D 223/26 (2013.01); A61K 9/3652 (2013.01); A61K 31/067 (2013.01); A61K 31/092 (2013.01); A61K 31/4166 (2013.01); A61K 31/55 (2013.01); A61K 31/616 (2013.01); A61K 47/30 (2013.01); A61K 47/32 (2013.01)

35 Claims, 25 Drawing Sheets  
(23 of 25 Drawing Sheet(s) Filed in Color)

Optionally, the pharmaceutical compositions can include a pharmaceutically acceptable carrier or diluent. Formulations are described in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin E W [1995] Eastone Pa., Mack Publishing Company, 19th ed.) a) describes formulations that can be used in connection with the subject invention.

## Background of the '344 Patent

A POSITA would have had several references in hand to choose excipients.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <br>US010633344B2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                       |
| (12) <b>United States Patent</b><br><b>Zaworotko et al.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (10) <b>Patent No.:</b> US 10,633,344 B2<br>(45) <b>Date of Patent:</b> Apr. 28, 2020 |
| (54) <b>MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | (210) <b>Classification</b><br>(210) <b>Field of Classification</b>                   |
| (71) Applicants: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (72) Inventors: Michael J. Zaworotko, Tampa, FL (US); Nair Rodriguez-Hernandez, Ann Arbor, MI (US); Brian Moulton, Temple Terrace, FL (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (73) Assignees: University of South Florida, Tampa, FL (US); The Regents of the University of Michigan, Ann Arbor, MI (US)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 69 days.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (21) Appl. No.: 14/179,862                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (22) Filed: Feb. 13, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (65) <b>Prior Publication Data</b><br>US 2014/0162989 A1 Jun. 12, 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (65) <b>Related U.S. Application Data</b><br>Continuation of application No. 10/378,956, filed on Mar. 3, 2003.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (51) <b>Int. Cl.</b><br>C07D 223/26 (2006.01)<br>A61K 9/06 (2006.01)<br>A61K 47/10 (2006.01)<br>A61K 47/12 (2006.01)<br>A61K 47/14 (2006.01)<br>A61K 47/16 (2006.01)<br>A61K 47/18 (2006.01)<br>A61K 47/20 (2006.01)<br>A61K 47/22 (2006.01)<br>A61K 47/24 (2006.01)<br>A61K 47/26 (2006.01)<br>A61K 47/28 (2006.01)<br>A61K 47/30 (2006.01)<br>A61K 47/32 (2006.01)<br>A61K 47/34 (2006.01)<br>A61K 47/36 (2006.01)<br>A61K 47/38 (2006.01)<br>A61K 47/40 (2006.01)<br>A61K 47/42 (2006.01)<br>A61K 47/44 (2006.01)<br>A61K 47/46 (2006.01)<br>A61K 47/48 (2006.01)<br>A61K 47/50 (2006.01)<br>A61K 47/52 (2006.01)<br>A61K 47/54 (2006.01)<br>A61K 47/56 (2006.01)<br>A61K 47/58 (2006.01)<br>A61K 47/60 (2006.01)<br>A61K 47/62 (2006.01)<br>A61K 47/64 (2006.01)<br>A61K 47/66 (2006.01)<br>A61K 47/68 (2006.01)<br>A61K 47/70 (2006.01)<br>A61K 47/72 (2006.01)<br>A61K 47/74 (2006.01)<br>A61K 47/76 (2006.01)<br>A61K 47/78 (2006.01)<br>A61K 47/80 (2006.01)<br>A61K 47/82 (2006.01)<br>A61K 47/84 (2006.01)<br>A61K 47/86 (2006.01)<br>A61K 47/88 (2006.01)<br>A61K 47/90 (2006.01)<br>A61K 47/92 (2006.01)<br>A61K 47/94 (2006.01)<br>A61K 47/96 (2006.01)<br>A61K 47/98 (2006.01)<br>A61K 48/00 (2006.01) | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |
| (52) <b>U.S. Cl.</b><br>CPC ..... C07D 223/26 (2013.01); A61K 9/06 (2013.01); A61K 31/167 (2013.01); A61K 31/192 (2013.01); A61K 31/196 (2013.01); A61K 31/215 (2013.01); A61K 31/216 (2013.01); A61K 47/10 (2013.01); A61K 47/32                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | (210) <b>Field of Classification</b><br>(210) <b>Field of Classification</b>          |

# The '956 Application Provides Written Description Support for the Claimed Co-crystals

# Written Description Support of the '344 Patent

Written description support exists for the claimed pharmaceutical compositions.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

53. Under the legal standards discussed in Section III above, there is sufficient written description support for claims 10, 11, and 18 at least because the specification provides examples that have common structural features as the members of the genus, including the claimed co-crystals. *See Appendix C*. Specifically, the examples inform a POSA how to implement each of the claim limitations of claims 10, 11, and 18 by providing at least one example of each limitation.

# Written Description Support of the '344 Patent

The '344 Patent provides 19 examples of co-crystals  
– illustrating the claim limitations of claims 10, 11,  
and 18.

| Condition                                                                                                                                                                   | Example |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|
|                                                                                                                                                                             | 1       | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Supramolecular synthons formed from stoichiometric amounts of at least one API and at least one co-former                                                                   | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding                                           | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form                                                                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | N  | Y  | Y  | N  | N  | N  | N  | Y  |
| Supramolecular synthons formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former | N       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is a carboxamide                                                                                                                               | Y       | Y | N | N | N | N | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is an amine                                                                                                                                    | N       | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |
| Supramolecular synthon is a heterosynthon dimer formed by non-covalent hydrogen bonding of the API and co-former                                                            | N       | N | Y | Y | Y | Y | N | N | N | N  | Y  | Y  | Y  | N  | Y  | N  | N  | Y  | Y  |

# Written Description Support of the '344 Patent

Written description support exists for the claimed pharmaceutical compositions.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

1

EXHIBIT 23  
Novartis v. The Regents of Univ. of  
IPR2023-013

54. Additionally, the well-known principles of hydrogen bonding, including those set forth by Dr. Etter, would allow a POSA to postulate whether a co-crystal of an API satisfying claims 10, 11, and/or 18 would likely form, regardless of whether a particular polymorph of a co-crystal forms or not. Specifically, in 2002/2003 a POSA would have understood the likelihood of certain functional groups (e.g., carboxylic acids, amines, nitro, amides, pyridines, alcohols) to form supramolecular synthons and crystal packing motifs defined by those synthons, based on numerous examples in single-component crystals and literature descriptions of hydrogen-bonding patterns. This was codified by Dr. Etter's seminal paper describing the "rules" for predicting hydrogen bonding motifs (a.k.a. graph sets) based on the "strength" of hydrogen-bond donors and acceptors. *See supra* Section VI.b. Thus, a POSA in 2002/2003 would also have a good understanding of the likelihood of certain functional groups forming supramolecular synthons, and indeed would understand the ranking of the likelihood of their formation in the event multiple hydrogen-bonding groups were present.

# Written Description Support of the '344 Patent

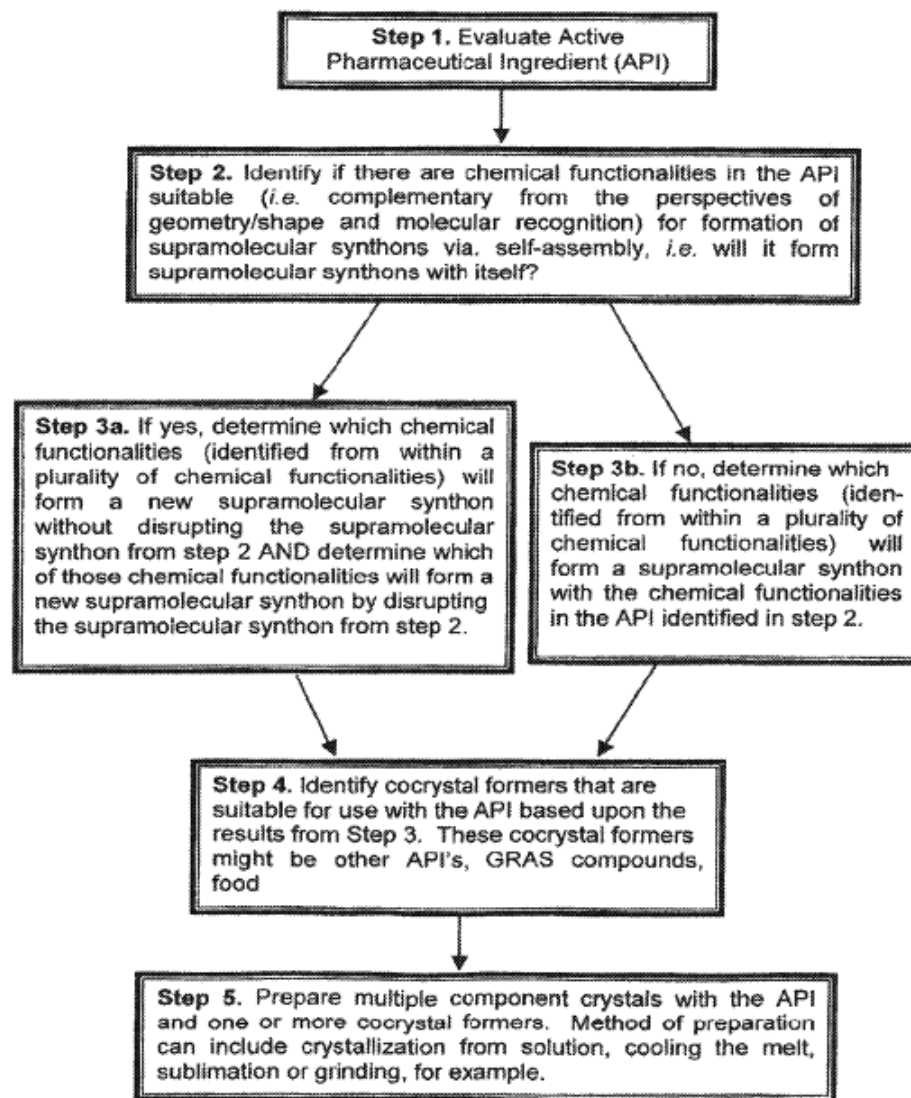


FIG. 24

## The Specification Did Not Need To Cite Etter's Rules

---

The law does not require reciting what a POSITA would already know in the specification – to the contrary, it is *discouraged* to make a specification a treatise of what a POSITA would bring to the table already. As the MPEP states, “What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.” MPEP 2163; *see also Streck*, 665 F.3d at 1288 (“It is well-established, however, that a specification need not disclose what is well-known in the art.”); *Koito Mfg. Co. v. Turn-Key Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (“This Court has repeatedly explained that a patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art.”); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (“Furthermore, a patent need not teach, and preferably omits, what is well known in the art.”).

## Preformulation Work Would Give POSITA Significant Knowledge Before Starting The Process

---

A POSITA would also have understood the basic principles of formulating a pharmaceutical composition, including testing the various properties of a formulation such as solubility. *Id.* First, a POSITA would need to understand the goals of formulating the pharmaceutical composition, such as the desired stability. EX2015 (Appel Deposition) at 33:17-35:17. Then a POSITA would enter the pre-formulation stage, where they would run tests to understand the physicochemical properties of the drug, such as the pH and solubility. *Id.* at 35:19-36:14. Based on the physicochemical properties of the API, a POSITA would ascertain how that API may be appropriately formulated so that there is good bioavailability. *Id.* at 36:22-38:4. This process would be the same for formulating an API not in a co-crystal as well as formulating a multiple-component co-crystal comprising an API. *Id.* at 72:7-74:16.

## Preformulation Work Would Give POSITA Significant Knowledge Before Starting The Process

---

A POSA, in 2002/2003, would have viewed co-crystallization of an API as a purification step in the formulation of a pharmaceutical composition. *See* Ex. 2011 (Morissette) at 276 (“Most APIs . . . are purified and isolated by crystallization from an appropriate solvent during the final step in the synthetic process.”). Put differently, by the time a POSA arrived at the co-crystallization stage of the formulation process for a given API, he or she would have already tested and understood the solubility parameters of that API and any suitable co-formers, the types of available solvents and co-formers appropriate for pharmaceutical use, and the solvent(s) and co-former(s) in which the API and co-former prospects would or would not be soluble.

## POSITA Would Have Understood Which APIs and Co-Crystals Would Form a Synthon

---

the POSITA would have: (1) an understanding of the likelihood of certain functional groups forming supramolecular synthons; (2) an understanding of a ranking of certain functional groups to form supramolecular synthons in the event multiple hydrogen bonding groups were present; and (3) sufficient working knowledge of whether hydrogen bonds between the API and some collection of co-formers were likely and, in the event of multiple potential synthons, the POSITA would have had a working knowledge of which ones would be preferred, even though other factors could impact synthon formation. *See* EX2014 at ¶¶54-55.

## Dr. Ward Identified Common Structural Features

---

Patent Owners provided expert testimony that in 2003, “a POSA would have understood the likelihood of certain functional groups (e.g., carboxylic acids, amines, nitro, amides, pyridines, alcohols) to form supramolecular synthons and crystal packing motifs defined by those synthons, based on numerous examples in single-component crystals and literature descriptions of hydrogen-bonding patterns.” EX2014 at ¶54

# The '956 Application Enables the Claimed Co-Crystals

# Enablement of the '344 Patent

The level of skill in the art is high.

5/23/2024 Novartis Pharmaceuticals Corporation v. Regents of the University of Michigan et al. Robin D. Rogers, Ph.D.

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE  
-----  
BEFORE THE PATENT TRIAL AND APPEAL BOARD  
-----  
NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,  
v.  
REGENTS OF THE UNIVERSITY OF MICHIGAN  
and UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.  
-----  
Case IPR2023-01346  
U.S. Patent No. 10,633,344  
-----  
DEPOSITION OF  
ROBIN D. ROGERS, Ph.D.  
May 23, 2024  
9:00 a.m. EDT  
4 Times Square  
151 West 42nd Street  
New York, New York  
REPORTED BY: MARIE FOLEY, RMR CRR  
-----  
DIGITAL EVIDENCE GROUP  
1730 M Street, NW, Suite 812  
Washington, D.C. 20036  
(202) 232-0646  
-----  
www.DigitalEvidenceGroup.com Digital Evidence Group C't 2024 202-232-0646  
EXHIBIT 2016  
Novartis v. The Regents of Univ. of MI  
IPR2023-01346  
1

Q. Do you think your definition of a person of ordinary skill in the art requires a relatively high level of education and training?

A. I believe I -- I do, and I note that when I'm analyzing inability.

# A POSITA Would Have Been Aware of High-Throughput Screening

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

49. In 2002/2003 a POSA would have been aware of the emerging use of high-throughput screening principles to evaluate which crystallization methods and/or other chemical and physical variables positively or negatively impact the crystallization of an API, either as a polymorph or co-crystal of the API, via high-throughput crystallization screening.

# Enablement of the '344 Patent

The quantity of experimentation necessary is low – in favor of enablement.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

64. As discussed above in Section VI.d, a POSA would have known that high-throughput crystallization screening was available for testing of co-crystals in 2002/2003. The availability of this technique would have significantly reduced the length of time and effort required for a POSA to test for co-crystals under various conditions. Specifically, a POSA would have understood that various crystallization conditions would be tested for crystallizing co-crystals, not unlike screening for polymorphs.

# Enablement of the '344 Patent

The state and predictability of the art weigh in favor of enablement.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

74. In addition, I would have viewed a 20% success rate in co-crystallizing an API as an acceptable benchmark for success, and I believe other POSAs at that time also would have. Further, Dr. Rogers fails to note the successes in the remainder of the references he cites allegedly showing the exemplary “failed attempts to predict” co-crystallization. *See, e.g.*, Ex. 1027 (Reddy 2004) at 90, 92 (reporting formation of carboxylic acid and amide co-crystal); Ex. 1025 (Aakeroy 2003) at 164 (reporting that three compounds out of four formed co-crystals with at least one co-former); Ex. 1007 (Ueto 2012) at 487 (reporting, in Table 2, FS-NCT cocrystals formed in 15 of the 16 crystallization solvents).

# Enablement of the '344 Patent

The amount of direction or guidance presented and presence of working examples weigh in favor of enablement

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

| Condition                                                                                                                                                                   | Example |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|
|                                                                                                                                                                             | 1       | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Supramolecular synthons formed from stoichiometric amounts of at least one API and at least one co-former                                                                   | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former has a second chemical functionality complementary to the first chemical functionality via non-covalent hydrogen bonding                                           | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| Co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form                                                                    | Y       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | N  | Y  | Y  | N  | N  | N  | N  | Y  |
| Supramolecular synthons formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former | N       | Y | Y | Y | Y | Y | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is a carboxamide                                                                                                                               | Y       | Y | N | N | N | N | Y | Y | Y | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| First chemical functionality is an amine                                                                                                                                    | N       | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |
| Supramolecular synthon is a heterosynthon dimer formed by non-covalent hydrogen bonding of the API and co-former                                                            | N       | N | Y | Y | Y | Y | N | N | N | N  | Y  | Y  | Y  | N  | Y  | N  | N  | Y  | Y  |

# Enablement of the '344 Patent

The nature of the invention weighs in favor of enablement.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVARTIS PHARMACEUTICALS CORPORATION,  
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN and  
UNIVERSITY OF SOUTH FLORIDA,  
Patent Owners.

Case IPR2023-01346  
U.S. Patent No. 10,633,344

DECLARATION OF MICHAEL WARD, PH.D.

80. I agree with Dr. Rogers that the nature of the purported invention of claims 10, 11, and 18 of the '344 patent is a pharmaceutical composition comprising co-crystals containing an API and a co-former having certain properties and non-covalent hydrogen bond interactions.

81. Given the highly sophisticated nature of the field and the high level of skill in the art for a POSA, I believe this factor weighs in favor on enablement.