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# UTILITY PATENT APPLICATION TRANSMITTAL

*(Only for new nonprovisional applications under 37 CFR 1.53(b))*

| | |
|---|---|
| *Attorney Docket No.* | U0157.70023US03 |
| *First Named Inventor* | Michael J. Zaworotko |
| *Title* | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| *Express Mail Label No.* | |

## APPLICATION ELEMENTS

*See MPEP chapter 600 concerning utility patent application contents.*

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [X] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] **Specification** [*Total Pages* 42 ]
   Both the claims and abstract must start on a new page.
   *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [X] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 22 ]
6. **Inventor's Oath or Declaration** [*Total Pages* 3 ]
   *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [X] A copy from a prior application (37 CFR 1.63(d))
7. [X] **Application Data Sheet** * *See note below.*
   See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

*ADDRESS TO:* **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

## ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [ ] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [X] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] **Other:**

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

## 19. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 23628 **OR** [ ] Correspondence address below

| | | | | | |
|---|---|---|---|---|---|
| Name | | | | | |
| Address | | | | | |
| City | | State | | Zip Code | |
| Country | | Telephone | | Email | |

| | | | |
|---|---|---|---|
| Signature | /Edward R. Gates/ | Date | June 30, 2017 |
| Name (Print/Type) | Edward R. Gates | Registration No. (Attorney/Agent) | 31,616 |

5572568.1

**Application Data Sheet**

**Inventor Information**

| | |
|---|---|
| Inventor Number:: | 1 |
| Name Prefix:: | Mr. |
| Given Name:: | Michael |
| Middle Name:: | J. |
| Family Name:: | Zaworotko |
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| | |
|---|---|
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| Postal or Zip Code of mailing address:: | 33637 |

**Correspondence Information**

| | |
|---|---|
| Correspondence Customer Number:: | 23628 |

**Application Information**

| | |
|---|---|
| Application Type:: | Regular |
| Subject Matter:: | Utility |
| CD-ROM or CD-R?:: | None |

| | |
|---|---|
| Sequence submission?:: | None |
| Computer Readable Form (CRF)?:: | No |
| Title:: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Attorney Docket Number:: | U0157.70023US03 |
| Request for Early Publication?:: | No |
| Request for Non-Publication?:: | No |
| Total Drawing Sheets:: | 22 |
| Small Entity?:: | Yes |
| Petition included?:: | No |
| Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2:: | No |
| This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013:: | No |

**Representative Information**

| | |
|---|---|
| Representative Customer Number:: | 23628 |

**Domestic Priority Information**

| Application:: | Continuity Type:: | Parent Application:: | Parent Filing Date:: | Prior Appl Status:: |
|---|---|---|---|---|
| This Application | Continuation of | 10/378956 | 03/03/03 | Pending |
| 10/378956 | An application claiming the benefit under 35 USC 119(e) | 60/360768 | 03/01/02 | Expired |

**Foreign Priority Information**

**Applicant Information**

| | |
|---|---|
| Applicant Number:: | 1 |
| Applicant Type:: | Assignee |
| Organization Name:: | University of South Florida |
| Street of mailing address:: | 3802 Spectrum Boulevard |
| | Suite 100 |
| City of mailing address:: | Tampa |
| State or Province of mailing address:: | FL |
| Country of mailing address:: | US |
| Postal or Zip Code of mailing address:: | 33612 |

| | |
|---|---|
| Applicant Number:: | 2 |
| Applicant Type:: | Assignee |
| Organization Name:: | The Regents of the University of Michigan |

| | |
|---|---|
| Street of mailing address:: | Wolverine Tower |
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| State or Province of mailing address:: | MI |
| Country of mailing address:: | US |
| Postal or Zip Code of mailing address:: | 48109-1280 |

**Assignee Information Including Non-Applicant Assignee Information**

## Authorization or Opt-Out of Authorization to Permit Access

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE**: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

**1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)**

**A. Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

**B. Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

**2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)**

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

**NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

## Signature:

**NOTE:** This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

| | | | |
|---|---|---|---|
| **Signature** | /Edward R. Gates/ | Date (YYYY-MM-DD) | 2017-06-30 |
| Name | Edward R. Gates | Registration Number | 31,616 |

## DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

| | |
|---|---|
| Title of Invention | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable):

The above-identified application was made or authorized to be made by me.

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

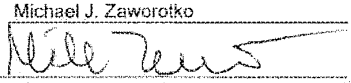
I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: Feb 4th 2014

Signature:  Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: _____

Signature: _____ Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: _____

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 9 of 415

## DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

| | |
|---|---|
| **Title of Invention** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable);

The above-identified application was made or authorized to be made by me.

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: _____

Signature: _____ Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: Jan. 27, 2014

Signature: Nair Rodriguez-Hornedo Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: _____

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 10 of 415

## DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

| | |
|---|---|
| **Title of Invention** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable);

The above-identified application was made or authorized to be made by me.

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

I believe I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. § 1001 by fine or imprisonment of not more than five (5) years, or both.

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: _____

Signature: _____ Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: _____

Signature: _____ Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: 01.28.14

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | Not Yet Assigned |
| Confirmation No.: | N/A |
| Filed: | Concurrently Herewith |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | Not Yet Assigned |
| Art Unit: | N/A |

**Certificate of Electronic Filing under 37 CFR §1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 30, 2017 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

## FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

**Amendments to the Specification** begin on page 2 of this paper.

**Remarks/Arguments** begin on page 3 of this paper.

## AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph under "CROSS-REFERENCE TO RELATED APPLICATION" on page 1 with the following paragraph:

The present application is a continuation of U.S. Application Serial No. 10/378,956, filed March 2, 2003, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings. U.S. Application Serial No. 10/378,956 claims the benefit of priority of U.S. Provisional Application Serial No. 60/360,768, filed March 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 13 of 415

## REMARKS

Applicant has amended the specification to update the section under "CROSS-REFERENCE TO RELATED APPLICATION".

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: June 30, 2017

Respectfully submitted,

By: /Edward R. Gates/

Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 14 of 415

# DESCRIPTION

# MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

## CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of priority of U.S. Provisional Application Serial No. 60/360,768, filed March 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

## BACKGROUND OF THE INVENTION

**[0001]** The last decade has witnessed tremendous advances in the understanding of, and the ability to manipulate, molecular and supramolecular assemblies (Moulton, B. *et al.*, *Chem. Rev.*, 2001, 101:1629-1658). There are new paradigms concerning the design and synthesis of a new generation of functional materials and molecules. Such advances are a consequence of the fundamental importance of intermolecular interactions, structure and cooperativity in many aspects of molecular science, from environmental science to molecular biology, to pharmacology, to materials science. Thus, the prospects for control and manipulation of materials at the molecular level, particularly in areas related to non-covalent bonding and nanotechnology, are now truly exceptional. However, whereas crystal structure determination has been a tool used by scientists since the 1920's, crystal structure prediction remains a largely unmet goal (Ball, P. *Nature*, 1996, 381:648-650; Gavezzotti, A. *Acc. Chem. Res.*, 1994, 27:309-314). Furthermore, the existence of more than one crystalline form of a given molecular compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity (Desiraju, G.R. *Science*, 1997, 278:404-405; Bernstein, J. *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1999, 38:3441-3461). This is particularly true for the pharmaceutical industry.

**[0002]** Crystal engineering (Schmidt, G.M.J. *Pure Appl. Chem.*, 1971, 27:647-678; Desiraju, G.R. *Crystal Engineering: the Design of Organic Solids*, 1989, Elsevier: Amsterdam) is predicated on the assumption that crystals are *de facto* examples of self-assembly, *i.e.* crystals are comprised from a series of molecular recognition events or *supramolecular synthons*

(Desiraju, G.R. *Angew. Chem., Int. Ed. Engl.*, 1995, 34:2311-2327). It also offers a more realizable goal than crystal structure prediction since it relies on design and allows for careful selection of substrates, *i.e.* substrates that are predisposed to form predictable self-assembled superstructures can be targeted for study. Furthermore, the prototypal molecules used in crystal engineering contain exofunctional molecular recognition sites and they can be complementary with themselves (self-assembly) (Boucher, E. *et al.*, *J. Org. Chem.*, 1995, 60:1408-1412) or with other molecules (modular self-assembly) (Zaworotko, M.J. *Chem. Soc. Rev.*, 1994, 23:283-288; Sharma, C.V.K. and M.J. Zaworotko *Chem. Commun.*, 1996, 2655-2656). Coincidentally, most pharmaceutical molecules also contain exterior molecular recognition sites and, although this makes them susceptible to polymorphism and solvate formation, it also makes them attractive candidates for crystal engineering studies.

**[0003]** The ability of crystalline self-assemblies to be built from a bottom-up approach (Feynman, R. *Engineering and Science*, 1960, 22-36) could provide an exceptional control of the design of new phases at a molecular level. This contrasts with the current state-of-the-art: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound" (McCrone, W.C. *Polymorphism in Physics and Chemistry of the Organic Solid-State*, pp. 726, Fox *et al.* Eds., Interscience: New York, 1965). This statement summarizes the predicaments and opportunities that one faces when dealing with a need to assert control over the composition and structure of pharmaceutical compounds in the solid state. Specifically, physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order. However, crystal structure prediction and even prediction of composition remains a largely unmet goal. Nonetheless, crystal engineering offers the intriguing possibility of using molecular components for their ability to impart functional characteristics (such as solubility, dissolution rate and stability) for the development of new delivery systems.

**[0004]** Undesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs. This has motivated research in drug delivery systems for poorly soluble, poorly absorbed and labile substances. Crystalline self-assemblies represent a promising delivery modality for improving drug solubility, dissolution rate, stability and bioavailability. In addition, enhancement of drug activity can be achieved by means of

inclusion complexation or molecular encapsulation. These systems offer various advantages over amorphous polymeric delivery systems both from design and stability perspectives. In this context, the existence of more than one crystalline form of a given compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity. Several factors further complicate the situation. For example, the Food and Drug Administration's (FDA's) strict purity requirements effectively mean that a particular crystalline phase of a drug must be selected and that its composition must be established. This has typically meant that a consistent X-ray powder diffraction (XPD) pattern is required (Federal Drug Administration *Fed. Regist.*, 1997, 62:62893-62894). The need to ensure that processing produces both purity and ease of processing is problematic because many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase. The commercial and public image costs of not ensuring that processing is reliable and reproducible is at best very high, as demonstrated by the recent pull back and reformulation of NORVIR by ABBOTT LABORATORIES).

**[0005]** That XPD patterns have been relied on for quality control is convenient but is in many ways unfortunate since XPD is not as foolproof as single crystal X-ray crystallography (*e.g.* similar patterns can be obtained for different phases, composition is not unambiguously determined), and XPD does not determine crystal packing. Knowledge of crystal packing is important because it helps explain the solubility and composition of a particular phase and provides other valuable information. However, the materials properties of pharmaceuticals and the existence of polymorphs are generally investigated at the tail end of the drug development process.

**[0006]** Accordingly, it would be advantageous to provide a wide range of novel solid phases having properties, such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability, which are different from existing solid forms of the pharmaceutical molecule upon which they are based.

## BRIEF SUMMARY OF THE INVENTION

**[0007]** The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical phases that contain more than one molecular component.

**[0008]** The subject invention concerns multiple-component solids having at least one active pharmaceutical ingredient. Examples of pharmaceutical molecules that may be utilized as active pharmaceutical ingredients in the multiple-component solids of the subject invention include, but are not limited to, aspirin, one or more members of the profen series (*e.g.*, ibuprofen and flurbiprofen), carbamazepine, phenytoin, and acetaminophen. Multiple-component solids, such as multiple-component crystals, containing these pharmaceutical ingredients and complementary molecules (hereafter referred to as "cocrystal formers") have been characterized by various techniques and can exhibit physical and/or chemical properties that are the same or different from the parent pharmaceutical ingredient as a direct result of alternative molecular recognition patterns. These novel crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability.

**[0009]** The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical solid phases, such as multiple-component phases, using cocrystal formers that are complementary in the sense of supramolecular chemistry, *i.e.* they form supramolecular synthons with pharmaceutical molecules or ions. The cocrystal formers can be, but are not limited to, solvent molecules, other drug molecules, GRAS compounds, or approved food additives. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.* acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.* acid/amide; pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

**[0010]** In one aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

**[0011]** In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of

chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

**[0012]** As indicated above, certain aspects of the subject invention can involve selecting a chemical functionality that is capable of disrupting the non-covalent bonding between identical functionalities (homosynthon) and form a non-covalent bond between different, yet complementary, functionalities (heterosynthon); selecting a plurality of molecular entities that comprise the complementary functionality (preferably GRAS compounds or approved food additives); identifying additional chemical features on the molecular entities that will not interfere with the formation of the desired supramolecular synthon and that will impart the desired physical properties to the target phase; and, optionally, preparing a new solid phase that is composed of the pharmaceutical moiety and the complementary molecular entity (such as a multiple-component phase or two component phase) by crystallization techniques comprising reactions in solvent, and/or solventless reactions, that afford crystalline materials. Optionally, the methods can further include at least one of the subsequent steps of determining the structure of the new solid phase formed; and analyzing the physical properties of the new solid phase.

**[0013]** The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition can be, for example, a discrete supramolecular entity or a polymeric structure.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0014] Figure 1** shows the chemical structure of ibuprofen. The external functionalities are an isopropyl group (encircled on the left, in cyan) and a carboxylic acid (encircled on the right, in magenta).

**[0015] Figure 2** shows a scheme with the synthon of pure ibuprofen on the left and the supramolecular entity containing the synthon on the right, demonstrating that pure phases of ibuprofen are sustained by carboxylic acid-carboxylic acid interactions. The standard chemical color correlation appears in all the figures where color is utilized (*e.g.*, red = oxygen; white = oxygen; dark blue = nitrogen; light blue = fluorene; yellow = sulfur).

**[0016] Figure 3** shows a scheme wherein the carboxylic acid-carboxylic acid interactions of ibuprofen are disrupted by co-crystallization with an aromatic amine. Specifically, by using diamines, 2:1 multiple-component phases are produced.

**[0017] Figures 4A–4B** show an acetaminophen 1-D polymeric chain and an acetaminophen/4,4'-bipyridine/water crystal, respectively. Reported forms are monoclinic ($P2_1/n$) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1974, 30:2510) and orthorhombic (*Pbca*) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1976, 32:1283) polymorphs. The monoclinic polymorph forms pleated sheets with all hydrogen bonding donors and acceptors interacting. The orthorhombic polymorph forms form 1-D polymeric chains with all donors and acceptors interacting.

**[0018] Figures 5A-5B** show pure phenytoin and a phenytoin/pyridone co-crystal, respectively. Phenytoin has one known pure form (Carmerman, A. *et al.*, *Acta Crystallogr., Sect B*, 1971, 27:2207). The crystal structure reveals a two dimensional polymeric network formed by hydrogen bonds between both the carbonyl and 2° amine.

**[0019] Figures 6A-6D** show supramolecular entities containing synthons and corresponding crystal structures of pure aspirin and aspirin/4,4'-bipyridine. Figures 3A and 3B show the supramolecular entity containing the synthon of pure aspirin and corresponding crystal structure, respectively. Figures 6C and 6D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin/4,4'-bipyridine, respectively. The pure phase (Chiari, G. *et al.*, *Acta Crystallogr., Sect B*, 1981, 37:1623) of acetylsalicylic acid, has centrosymmetric carboxylic acid homodimers and crystallizes in the space group $P2_1/c$, packing in 2D polymeric sheets with hydrophobic planes.

**[0020] Figures 7A-7D** show supramolecular entities containing synthons and corresponding crystal structures of pure ibuprofen [2-(4-isobutylphenyl) propionic acid] and ibuprofen/4,4'-bipyridine. Figures 7A and 7B show the supramolecular entity containing the synthon of pure ibuprofen and corresponding crystal structure, respectively. Figures 7C and 7D

show the supramolecular entity containing the synthon of ibuprofen/4,4'-bipyridine and corresponding co-crystal, respectively. The reported crystal structures of ibuprofen are racemic (McConnell, J.F. *Cryst. Strucut. Commun.*, 1974, 3:73) and S (+) forms (Freer, A.A. *et al.*, *Acta Crystallogr., Sect C (Cr. Str. Comm)*, 1993, 49:1378). Both contain hydrogen bonded carboxylic acid homodimers. Racemic dimers have centers of inversion across the dimer, which crystallize in the space group $P2_1/c$. The S (+) form contains asymmetric dimers, which crystallize in the space group $P2_1$. Both crystals pack in 2-D polymeric sheets sustained by π-π stacking and hydrophobic in-layer interactions.

**[0021] Figures 8A-8D** show supramolecular entities containing synthons and corresponding crystal structures of pure flurbiprofen [2-(2-fluror-4-biphenyl) propionic acid] and flurbiprofen/4,4'-bipyridine. Figures 8A and 8B show the supramolecular entity containing the synthon of pure flurbiprofen and corresponding crystal structure, respectively. Figures 5C and 5D show the supramolecular synthon of flurbiprofen/4,4'-bipyridine and corresponding co-crystal, respectively. Flurbiprofen has one reported pure form (Flippen, J.L. *et al.*, *Acta Crystallogr., Sect. B*, 1975, 31:926) and contain hydrogen bonded carboxylic acid homodimers with a center of inversion and crystallizes in the *P-1* space group. 2-D polymeric sheets are formed through π-π and hydrophobic interactions from the phenyl rings.

**[0022] Figures 9A and 9B** show the supramolecular entity containing the synthon of flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene and the corresponding crystal structure, respectively.

**[0023] Figures 10A and 10B** show the crystal structures of pure carbamazepine and carbamazepine/*p*-phthalaldehyde, respectively. Carbamazepine [5H-Dibenz(b, f) azepine-5-carboxamide] (CBZ) has been shown to exist in at least three anhydrous forms and two solvated forms (a dihydrate and an acetonate) (Himes, V.L. *et al.*, *Acta Crystallogr.*, 1981, 37:2242-2245; Lowes, M.M.J. *et al.*, *J. Pharm. Sci.*, 1987, 76:744-752; Reck, G. *et al.*, *Cryst. Res. Technol.*, 1986, 21:1463-1468). The primary intermolecular interaction in these crystal forms is the dimer formed between the carboxamide moieties of each CBZ molecule forming centrosymmetric dimers. The anhydrous polymorphs are monoclinic, trigonal, and triclinic. The polymorphs are enantiotropically related with the monoclinic form being the most thermodynamically stable at room temperature.

**[0024] Figure 11** shows the crystal structure of carbamazepine/nicotinamide (vitamin B3).

**[0025] Figure 12** shows the crystal structure of carbamazepine/saccharin, engineered using the carbamazepine/nicotinamide co-crystal as a model.

**[0026] Figures 13A-13C** show the chemical structures of ibuprofen, flurbiprofen, and aspirin, respectively.

**[0027] Figures 14A** and **14B** show the crystal structures of carbamazepine and carbamazepine/2,6-pyridinedicarboxylic acid, respectively.

**[0028] Figures 15A and 15B** show the crystal structures of carbamazepine and carbamazepine/5-nitroisophthalic acid, respectively.

**[0029] Figures 16A** and **16B** show the crystal structures of carbamazepine and carbamazepine/acetic acid.

**[0030] Figures 17A** and **17B** show the crystal structure of carbamazepine and carbamazepine/adamantanetetracarboxylic acid.

**[0031] Figures 18A** and **18B** show the crystal structure of carbamazepine and carbamazepine/benzoquinone.

**[0032] Figures 19A** and **19B** show the crystal structure of carbamazepine and carbamazepine/butyric acid.

**[0033] Figures 20A** and **20B** show the crystal structure of carbamazepine and carbamazepine/DMSO.

**[0034] Figures 21A** and **21B** show the crystal structure of carbamazepine and carbamazepine/formamide.

**[0035] Figures 22A** and **22B** show the crystal structure of carbamazepine and carbamazepine/formic acid.

**[0036] Figures 23A** and **23B** show the crystal structure of carbamazepine and carbamazepine/trimesic acid.

**[0037] Figure 24** shows an exemplified scheme for preparing multiple-component phase compositions of the subject invention.

## DETAILED DISCLOSURE OF THE INVENTION

**[0038]** The subject invention relates to the application of the concepts of crystal engineering towards the design of new multiple-component solid phases, such as multiple-component crystals, having at least one active pharmaceutical component. Examples of multiple-component crystals of the subject invention include, but are not limited to, acetominophen/4,4'-bipyridine/water, phenytoin/pyridone, aspirin/4,4'-bipyridine, ibuprofen/4,4'-bipyridine, flurbiprofen/4,4'-bipyridine, flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene, carbamazepine/*p*-phthalaldehyde, carbamazepine/nicotinamide (GRAs), carbamazepine/saccharin (GRAs), carbamazepine/2,6-pyridinedicarboxylic acid, carbamazepine/5-nitroisophthalic acid, carbamazepine/acetic acid, carbamazepine/1,3,5,7-adamantanetetracarboxylic acid, carbamazepine/benzoquinone, carbamazepine/butyric acid, carbamazepine/dimethyl sulfoxide (DMSO), carbamazepine/formamide, carbamazepine/formic acid, and carbamazepine/trimesic acid, which have been characterized by various techniques and exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction. These crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability, for example.

**[0039]** In one aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

**[0040]** In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the

method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

**[0041]** In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

**[0042]** In each of the three aspects of the methods described above, the methods can further comprise preparing a multiple-component solid phase composition composed of the API and at least one of the identified co-crystal formers. The identified co-crystal former can be, for example, a different API, a GRAS compound, a food additive, a low toxicity organic, or a metal-organic complex. Various methods can be utilized for preparing the multiple-component solid phase composition, such as crystallization from solution, cooling the melt, sublimation and grinding. In addition, the methods of the subject invention can further comprise either or both of the following steps: determining the structure of the new multiple-component solid phase composition, and analyzing the physical and/or chemical properties of the new multiple-component solid phase composition.

**[0043]** The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition of the subject invention can be, for example, a discrete supramolecular entity or a polymeric structure. The multiple-component phase compositions of the subject invention can have properties, such as melting point, solubility, dissolution rate, stability, and/or bioavailability, which are different from the pharmaceutical compound, or compounds, upon which they are based.

**[0044]** By way of example, the external functionalities of ibuprofen are an isopropyl group and a carboxylic acid, as shown in Figure 1.

**[0045]** Using the methods of the subject invention, it has been determined that this interaction can be disrupted by co-crystallization with an aromatic amine, as shown in Figure 2. Specifically, by using diamines, 2:1 multiple-component phases of ibuprofen have been prepared, as shown in Figure 3, as well as other phases exemplified herein. Therefore, the methods of the subject invention can be used to identify complementary chemical functionalities and produce multiple-component phase compositions for a variety of pharmaceuticals, including those pharmaceutical compounds with structures very different those of ibuprofen, flurbiprofen, and aspirin, which are shown in Figures 13A-13C, respectively.

**[0046]** As used herein, the term "multiple-component phase" refers to any solid material (phase) that is sustained by intermolecular interactions between at least two independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. Examples of intermolecular interactions include, but are not limited to one or more of the following: hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions. Each independent molecular entity can be a discrete supramolecular entity or polymeric structure, for example. Preferably, one or more of the independent molecular entities comprises a molecule of a "GRAS" compound, that is, a compound "Generally Regarded as Safe by the Food and Drug Administration (FDA)". More preferably, the GRAS compound is a non-pharmaceutical entity.

**[0047]** 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. Therefore, pharmaceutical entities useful as the active pharmaceutical ingredients in the multiple phase solids of the subject invention can be administered to a human or animal, which may or may not be suffering from a pathological condition, and the pharmaceutical entity can have a prophylactic effect, a palliative effect, and/or be a curative intervention. As used herein, these pharmaceutical entities are intended to include pharmaceutically acceptable salts of a given pharmaceutical entity that retain all or a portion of their pharmaceutical activity. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.*, acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.*, acid/amide; pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

**[0048]** As used herein, the term "supramolecular synthon" refers to the sum of the components of a multi-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality. A supramolecular synthon can be a dimer, trimer, or *n*-mer, for example.

**[0049]** The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. Such pharmaceutical compositions can be adapted for various forms of administration, such as oral, parenteral, nasal, topical, transdermal, *etc.* The multiple-component phase solids of the subject invention can be made into solutions or amorphous compounds, as injections, pills, or inhalants, for example. 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 EW [1995] Easton Pennsylvania, Mack Publishing Company, 19$^{th}$ ed.) describes formulations that can be used in connection with the subject invention. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, or tablets of the multiple-component phase compositions of the subject invention, for example. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

**[0050]** In terms of superstructure, three general types of compounds generated by interaction of a pharmaceutical molecule with another molecule include: (1) multiple-component compounds, in which superstructure is generated by two or more molecules, both of which are integral components of the network and complementary; (2) clathrate inclusion compounds, in which the compounds' superstructure is generated by self-assembly of one or more molecules and a guest molecules is enclosed within the superstructure; and (3) porous inclusion compounds, in which the superstructure is open framework in nature.

**[0051]** The subject invention concerns multiple-component compositions, and it is demonstrated herein that the concepts of crystal engineering and supramolecular synthons can be applied to prepare a wide range of novel pharmaceutical materials that are based on rational

design. Therefore, the multiple-component compounds of the subject invention can be generated in such a fashion that they have desirable composition, structure and properties. More specifically, an issue that is particularly relevant to pharmaceutical compositions of matter and processing is addressed by the subject invention: the diversity of compositions, superstructures and solubilities that can be generated when drug molecules form multiple-component phases with complementary molecules. Multiple-component phases involving the following drugs are exemplified herein: aspirin, acetaminophen, ibuprofen (and related compounds), phenytoin and carbamazepine and appropriate molecular additives. These novel phases include both "model multiple-component phases" that illustrate the concept of crystal engineering and multiple-component phases that incorporate pharmaceuticals with "GRAS" compounds, that is, compounds "Generally Regarded as Safe by the FDA", and/or food additives.

**[0052]** In the context of organic and pharmaceutical solids, the subject invention addresses these issues by demonstrating that crystal engineering offers a paradigm for the supramolecular synthesis (Chang, Y.L. *et al.*, *J. Am. Chem. Soc.*, 1993, 115:5991-6000) of a wide range of new multiple-component phases that have predetermined compositions and, in some instances, predetermined topology. Such an ability to build hierarchical structures from molecular or supramolecular modules facilitates precise control of structure and function of solid phases. These multiple-component phases have the following advantages over single component phases and traditional multiple-component phases (solid dispersions): high thermodynamic stability (thereby reducing problems associated with solid phase transformations), modified bioavailability (finely tunable solubility and delivery), and enhanced processability (crystal morphology, mechanical properties, hygroscopicity).

**[0053]** The subject invention has the following implications from a scientific perspective: (a) protocols are now available for the rational design of a new generation of pharmaceutical phases that contain at least two components that are sustained by supramolecular synthons; (b) correlation of structure and function of the new pharmaceutical phases via characterization of structure, crystal energy, solubility, dissolution rate, and stability is now possible; and (c) a new range of novel phases for the treatment of pathological conditions in humans and animals are available.

**[0054]** The subject invention extends the state-of-the-art in at least three ways: (1) by generating a rational, supramolecular strategy for the design of novel, multiple-component

crystalline phases; (2) by extending this strategy to pharmaceutical phases; and (3) by using this strategy to control the delivery properties and stability of pharmaceutical compounds.

**[0055]** The following pages describe examples of multiple-component crystalline phases that have been characterized using single crystal X-ray crystallography and structure-sensitive analytical techniques: FT-IR, XRPD, DSC, TGA. They represent prototypal examples of the invention as they are all based upon pharmaceutical molecules that are inherently predisposed to form supramolecular synthons with other complementary functional groups. They were chosen for study because of well-known limitations in their solubility/bioavailibility. In each example, the nature of the pure phase is discussed and it is sustained by a supramolecular homosynthon (self-complementary functionalities). The multiple-component phases prepared confirm the ability to persistently and rationally disrupt the homosynthon by judicious choice of a second molecular component that is predisposed to form a supramolecular heterosynthon. That these new solid phases will have different solubility profiles than their pure phases is to be expected. Examples designated as GRAS are those in which second a component that is "Generally Regarded as Safe by the FDA" was used.

Example 1—Multi-Component Crystal of Acetaminophen: Acetominophen/4,4'-bipyridine/water (1:1:1 stoichiometry)

**[0056]** 50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen/4,4'-bipyridine/water co-crystal, as shown in Figure 4B.

**[0057]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{36}H_{44}N_2O_4$, M=339.84, triclinic, space group $P\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2), γ = 88.880(2)°, $U$ = 1308.1(3) Å$^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm$^{-1}$, $D_c$ = 1.294 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 537, $2\theta_{max}$ = 25.02°; 6289 reflections measured, 4481 unique ($R_{int}$ = 0.0261). Final residuals for 344 parameters were $R_1$ = 0.0751, $wR_2$ = 0.2082 for I>2σ(I), and $R_1$ = 0.1119, $wR_2$ = 0.2377 for all 4481data.

**[0058]** Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two

network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

**[0059]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77° C (endotherm); m.p. = 58-60° C (MEL-TEMP); (acetaminophen m.p. = 169° C, 4,4'-bipyridine m.p. = 111-114° C).

Example 2—Multi-Component Crystal of Phenytoin: Phenytoin/Pyridone (1:1 stoichiometry)

**[0060]** 28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin/pyridone co-crystal, as shown in Figure 5B.

**[0061]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic $P2_1/c$; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, β = 96.618(2)°, $U$ = 1750.2(3) Å$^3$, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm$^{-1}$, $D_c$ = 1.318 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 728, $2\theta_{max}$ = 56.60°; 10605 reflections measured, 4154 unique ($R_{int}$ = 0.0313). Final residuals for 247 parameters were $R_1$ = 0.0560, $wR_2$ = 0.1356 for I>2σ(I), and $R_1$ = 0.0816, $wR_2$ = 0.1559 for all 4154 data.

**[0062]** Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

**[0063]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2°amine found at 3311cm$^{-1}$, carbonyl (ketone) found at 1711cm$^{-1}$, olephin peak found at 1390cm$^{-1}$.

**[0064]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39° C (endotherm) and 271.33° C (endotherm); m.p. = 231-233° C (MEL-TEMP); (phenytoin m.p. = 295° C, pyridone m.p. = 148° C).

**[0065]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80° C, 48.72% weight loss starting at 238.27° C, and 18.38% loss starting at 260.17° C followed by complete decomposition.

**[0066]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. In all cases of recrystallization and solid state reaction, experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 3---Multi-Component Crystal of Aspirin (acetylsalicylic acid): Aspirin/4,4'-bipyridine (2:1 stoichiometry)

**[0067]** 50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin/4,4'-bipyridine co-crystal, as shown in Figure 6D. Alternatively, aspirin/4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

**[0068]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, $U$ = 2762.2(5) Å$^3$, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm$^{-1}$, $D_c$ = 1.242 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique ($R_{int}$ = 0.0419). Final residuals for 202 parameters were $R_1$ = 0.0419, $wR_2$ = 0.1358 for I>2σ(I), and $R_1$ = 0.0541, $wR_2$ = 0.1482 for all 2433 data.

**[0069]** Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

**[0070]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm$^{-1}$ was shifted up and less intense at 1694cm$^{-1}$, where as the lactone peak is shifted down slightly from 1750cm$^{-1}$ to 1744cm$^{-1}$.

**[0071]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14° C (endotherm); m.p. = 91-96° C (MEL-TEMP); (aspirin m.p. = 1345° C, 4,4'-bipyridine m.p. = 111-114° C).

**[0072]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62° C, 49.06% weight loss starting at 102.97° C followed by complete decomposition starting at 209.37° C.

Example 4—Multi-Component Crystal of Ibuprofen: Ibuprofen/4,4'-Bipyridine (2:1 stoichiometry)

**[0073]** 50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen/4,4'-bipyridine co-crystal, as shown in Figure 7D.

**[0074]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) Å$^3$, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm$^{-1}$, $D_c$ = 1.174 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique ($R_{int}$ = 0.0826). Final residuals for 399 parameters were $R_1$ = 0.0964, $wR_2$ = 0.2510 for I>2σ(I), and $R_1$ = 0.1775, $wR_2$ = 0.2987 for all 3362 data.

**[0075]** Crystal packing: The co-crystal contains ibuprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

**[0076]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm$^{-1}$; N--H bending and scissoring at 1886 cm.$_1$; C=O stretching at 1679 cm$^{-1}$; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm$^{-1}$ and 628 cm$^{-1}$.

**[0077]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85° C (endotherm) and 118.79° C (endotherm); m.p. = 113-120° C (MEL-TEMP); (ibuprofen m.p. = 75-77° C, 4,4'-bipyridine m.p. = 111-114° C).

**[0078]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02° C immediately followed by complete decomposition.

**[0079]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 5—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/4,4'-bipyridine (2:1 stoichiometry)

**[0080]** 50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/4,4'-bipyridine co-crystal, as shown in Figure 8D.

**[0081]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, $M = 644.69$, monoclinic $P2_1/n$; $a = 5.860(4)$, $b = 47.49(3)$, $c = 5.928(4)$ Å, $\beta = 107.382\ (8)°$, $U = 1574.3(19)$ Å$^3$, $T = 200(2)$ K, $Z = 2$, $\mu$(Mo-Kα) = 0.096 mm$^{-1}$, $D_c = 1.360$ Mg/m$^3$, $\lambda = 0.71073$ Å$^3$, $F(000) = 676$, $2\theta_{max} = 21.69°$; 4246 reflections measured, 1634 unique ($R_{int} = 0.0677$). Final residuals for 226 parameters were $R_1 = 0.0908$, $wR_2 = 0.2065$ for $I>2\sigma(I)$, and $R_1 = 0.1084$, $wR_2 = 0.2209$ for all 1634 data.

**[0082]** Crystal packing: The co-crystal contains flurbiprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

**[0083]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm$^{-1}$ and 2981 cm$^{-1}$; N--H bending and scissoring at 1886 cm$^{-1}$; C=O stretching at 1690 cm$^{-1}$; C=C and C=N ring stretching at 1418 cm$^{-1}$.

**[0084]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47° C (endotherm); m.p. = 155-160° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, 4,4'-bipyridine m.p. = 111-114° C).

**[0085]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13° C and a 46.26% weight loss starting at 168.74° C followed by complete decomposition.

**[0086]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 6—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

**[0087]** 25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figure 9B.

**[0088]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic $P2_1/n$; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, $U$ = 1666.2(4) Å$^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm$^{-1}$, $D_c$ = 1.337 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 704, $2\theta_{max}$ = 21.69°, 6977 reflections measured, 2383 unique ($R_{int}$ = 0.0383). Final residuals for 238 parameters were $R_1$ = 0.0686, $wR_2$ = 0.1395 for I>2σ(I), and $R_1$ = 0.1403, $wR_2$ = 0.1709 for all 2383 data.

**[0089]** Crystal packing: The co-crystal contains flurbiprofen/1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 5 and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

**[0090]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm$^{-1}$ and 2850 cm$^{-1}$; N--H bending and scissoring at 1875 cm$^{-1}$; C=O stretching at 1707 cm$^{-1}$; C=C and C=N ring stretching at 1483 cm$^{-1}$.

**[0091]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01° C, 125.59° C and 163.54°C (endotherms); m.p. = 153-158° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153° C).

**[0092]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18° C followed by complete decomposition.

**[0093]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 7—Multi-Component Crystal of Carbamazepine: Carbamazepine/*p*-Phthalaldehyde (1:1 stoichiometry)

**[0094]** 25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/*p*-phthalaldehyde co-crystal, as shown in Figure 10B.

**[0095]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, *U* = 2941(3) Å$^3$, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm$^{-1}$, $D_c$ = 1.370 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique ($R_{int}$ = 0.0510). Final residuals for 268 parameters were $R_1$ = 0.0332, $wR_2$ = 0.0801 for I>2σ(I), and $R_1$ = 0.0403, $wR_2$ = 0.0831 for all 1559 data.

**[0096]** Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the CBZ.

**[0097]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm$^{-1}$; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm$^{-1}$; N-H in-plane bending at 1669 cm$^{-1}$; C-H aldehyde stretching at 2861 cm$^{-1}$ and H-C=O bending at 1391 cm$^{-1}$.

**[0098]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46° C (endotherm), m.p. = 121-124° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, *p*-phthalaldehyde m.p. = 116° C).

**[0099]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33° C then a 17.57% weight loss starting at 100.14° C followed by complete decomposition.

**[00100]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 8—Multi-Component Crystal of Carbamazepine: Carbamazepine/nicotinamide (GRAs) (1:1 stoichiometry)

**[00101]** 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/nicotinamide co-crystal, as shown in Figure 11.

**[00102]** Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine/nicotinamide microcrystals (XPD).

**[00103]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, M = 358.39, monoclinic *P2₁/n*; a = 5.0961(8), b = 17.595(3), c = 19.647(3) Å, β = 90.917(3)°, *U* = 1761.5(5) Å$^3$, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm$^{-1}$, $D_c$ = 1.351 Mg/m$^3$, λ = 0.71073 Å$^3$, F(000) = 752, $2\theta_{max}$ = 56.60°, 10919 reflections measured, 4041 unique ($R_{int}$ = 0.0514). Final residuals for 248 parameters were $R_1$ = 0.0732, $wR_2$ = 0.1268 for I>2σ(I), and $R_1$ = 0.1161, $wR_2$ = 0.1430 for all 4041 data.

**[00104]** Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the

adjoining dimer. The dimers form chains with $\pi$-$\pi$ interactions from the phenyl groups of the CBZ.

**[00105]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 $cm^{-1}$ and 3388 $cm^{-1}$ accounting for 1° amines; 1° amide C=O stretching at 1690 $cm^{-1}$; N-H in-plane bending at 1614 $cm^{-1}$; C=C stretching shifted down to 1579 $cm^{-1}$; aromatic H's from 800 $cm^{-1}$ to 500 $cm^{-1}$ are present.

**[00106]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49° C (endotherm) and 59.05° C (endotherm), m.p. = 153-158° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, nicotinamide m.p. = 150-160° C).

**[00107]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43° C followed by complete decomposition.

**[00108]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda$ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (22.); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 9—Multi-Component Crystal of Carbamazepine: Carbamazepine/saccharin (GRAs) (1:1 stoichiometry)

**[00109]** 25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/saccharin cocrystal, as shown in Figure 12. Solubility measurements indicate that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamazepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

**[00110]** Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S_1$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, $\alpha$ = 83.642(2)°, $\beta$ = 85.697(2) °, $\gamma$ = 75.411(2) °, *U* = 957.0(2) $Å^3$, T = 200(2) K, Z = 2, $\mu$(Mo-Kα) = 0.206 $mm^{-1}$, $D_c$ = 1.456 $Mg/m^3$, $\lambda$ = 0.71073 $Å^3$, F(000) = 436, $2\theta_{max}$ = 56.20°; 8426 reflections measured,

4372 unique ($R_{int}$ = 0.0305). Final residuals for 283 parameters were $R_1$ = 0.0458, $wR_2$ = 0.1142 for I>2σ(I), and $R_1$ = 0.0562, $wR_2$ = 0.1204 for all 4372 data.

**[00111]** Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the CBZ on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

**[00112]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 $cm^{-1}$ accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 $cm^{-1}$; N-H in-plane bending at 1649 $cm^{-1}$; C=C stretching shifted down to 1561 $cm^{-1}$; (O=S=O) sulfonyl peak at 1330 $cm^{-1}$ C-N aliphatic stretching 1175 $cm^{-1}$.

**[00113]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31° C (endotherm) and 177.32° C (endotherm), m.p. = 148-155°C (MEL-TEMP); (carbamazepine m.p. = 190.2° C, saccharin m.p. = 228.8° C).

**[00114]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03° C and a 55.09% weight loss starting at 118.71° C followed by complete decomposition.

**[00115]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 10—Multi-Component Crystal of Carbamazepine: Carbamazepine/2,6-pyridinedicarboxylic acid (2:3 stoichiometry)

**[00116]** 36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine/2,6-pyridinedicarboxylic acid co-crystal, as shown in Figure 14B.

**[00117]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å,α=90°, β=90°,

$\gamma$=90°, V=1858.0(2) Å$^3$, T=100 K, Z=4, $\mu$(MO-K$\alpha$)=0.104 mm$^{-1}$, $D_c$=1.442 Mg/m$^3$, $\lambda$=0.71073Å$^3$ , F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique ($R_{int}$=0.093). Final residuals for 271 parameters were $R_1$=0.0425 and $wR_2$=0.0944 for I>2$\sigma$(I).

**[00118]** Crystal packing: Each hydrogen on the CBZ 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the CBZ carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moitey.

**[00119]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm$^{-1}$, (N-H stretch, 1° amine, CBZ); 1734 cm$^{-1}$, (C=O); 1649 cm$^{-1}$, (C=C).

**[00120]** Melting Point: 214-216°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 2,6-pyridinedicarboxylic acid m.p. = 248-250°C).

**[00121]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215° C and a 17% weight loss starting at 392° followed by complete decomposition.

Example 11—Multi-Component Crystal of Carbamazepine: Carbamazepine/5-nitroisophthalic acid (1:1 stoichiometry)

**[00122]** 40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/5-nitroisophthalic acid co-crystal, as shown in Figure 15B.

**[00123]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{47}H_{40}N_6O_{16}$, M=944.85, monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å,$\alpha$=90°, $\beta$=93.952(6)°, $\gamma$=90°, V=4361.2(18)Å$^3$, T=200(2) K, Z=4, $\mu$(MO-K$\alpha$)=0.110 mm$^{-1}$, $D_c$=1.439 Mg/m$^3$, $\lambda$=0.71073Å$^3$ , F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique ($R_{int}$=0.0611). Final residuals for 311 parameters were $R_1$=0.0725, $wR_2$=0.1801 for I>2$\sigma$(I), and $R_1$=0.1441, $wR_2$=0.1204 for all 4459 data.

**[00124]** Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded

carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

**[00125]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 3178 $cm^{-1}$, (C-H stretch, alkene); 1688 $cm^{-1}$, (C=O); 1602 $cm^{-1}$, (C=C).

**[00126]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51°C (endotherm). m.p. = NA (decomposes at 197-200°C) (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 5-nitroisophthalic acid m.p. = 260-261°C).

**[00127]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202°, a 12.12% weight loss starting at 224° and a 17.94% weight loss starting at 285° followed by complete decomposition.

**[00128]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 12—Multi-Component Crystal of Carbamazepine: Carbamazepine/acetic acid (1:1 stoichiometry)

**[00129]** 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 2 mL acetic acid. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/acetic acid co-crystal, as shown in Figure 16B.

**[00130]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{17}H_{16}N_2O_3$, M=296.32, monoclinic P2(1)/c; a=5.1206(4), b=15.7136(13), c=18.4986(15) Å,α=90°, β=96.5460(10)°, γ=90°, V=1478.8(2)$Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.093 $mm^{-1}$, $D_c$=1.331 $Mg/m^3$, λ=0.71073$Å^3$ , F(000)624, $2\theta_{max}$=28.4°. 12951 reflections measured, 3529 unique ($R_{int}$=0.076). Final residuals for 203 parameters were $R_1$=0.0492, $wR_2$=0.1335 for I>2σ(I).

**[00131]** Crystal packing: The co-crystal is sustained by hydrogen bonded carboxamide-carboxylic heterodimers. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

**[00132]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3462 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 1699 $cm^{-1}$, (C=O); 1629 $cm^{-1}$, (C=C, CBZ); 1419 $cm^{-1}$, (COOH, acetic acid).

**[00133]** Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, acetic acid m.p. = 16.6°C).

**[00134]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 104° and a 77.05% weight loss starting at 200° followed by complete decomposition.

Example 13—Multi-Component Crystal of Carbamazepine: Carbamazepine/1,3,5,7-adamantanetetracarboxylic acid (1:1 stoichiometry)

**[00135]** 15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1 mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine/1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figure 17B.

**[00136]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_2O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, V=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 $mm^{-1}$, $D_c$=1.384 $Mg/m^3$, λ=0.71073$Å^3$, F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique ($R_{int}$=0.052). Final residuals for 263 parameters were $R_1$=0.0433 and $wR_2$=0.0913 for I>2σ(I).

**[00137]** Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

**[00138]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 3123 $cm^{-1}$, (C-H stretch, alkene); 1723 $cm^{-1}$, (C=O); 1649 $cm^{-1}$, (C=C).

**[00139]** Melting Point: (MEL-TEMP). 258-260°C (carbamazepine m.p. = 191-192°C, adamantanetetracarboxylic acid m.p. = >390°C).

**[00140]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189°C, a 52% weight loss starting at 251°C and a 31% weight loss starting at 374°C followed by complete decomposition.

Example 14—Multi-Component Crystal of Carbamazepine: Carbamazepine/benzoquinone (1:1 stoichiometry)

**[00141]** 25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine/benzoquinone co-crystal, as shown in Figure 18B.

**[00142]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, V=1392.9(4) $Å^3$, T=100(2) K, Z=3, $D_c$=1.232 $Mg/m^3$, μ(MO-Kα)=0.084 $mm^{-1}$, λ=0.71073$Å^3$, F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured, 3223 unique ($R_{int}$=0.1136). Final residuals for 199 parameters were $R_1$=0.0545 and $wR_2$=0.1358 for I>2σ(I), and $R_1$=0.0659 and $wR_2$=0.1427 for all 3223 data.

**[00143]** Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the CBZ is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

**[00144]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 2750 $cm^{-1}$, (aldehyde stretch); 1672 $cm^{-1}$, (C=O); 1637 $cm^{-1}$, (C=C, CBZ).

**[00145]** Melting Point: 170°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, benzoquinone m.p. = 115.7°C).

**[00146]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168° and a 78% weight loss starting at 223° followed by complete decomposition.

Example 15—Multi-Component Crystal of Carbamazepine: Carbamazepine/butyric acid (1:1 stoichiometry)

**[00147]** 10 mg (0.0423 mmol) carbamazepine was dissolved in approximately 1 mL butyric acid. Slow evaporation of the solvent mixture produced an average yield of yellow/brown crystals of a 1:1 carbamazepine/butyric acid co-crystal, as shown in Figure 19B.

**[00148]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{19}H_{20}N_2O_3$, M=324.37, triclinic P-1; a=9.1567, b=10.1745, c=10.5116 Å,α=72.850°, β=70.288°, γ=67.269°, V=832.17 $Å^3$, T=100° K, Z=2, μ(MO-Kα)=0.088 $mm^{-1}$, $D_c$=1.290 $Mg/m^3$, λ=0.71073$Å^3$ , F(000)344, $2\theta_{max}$=28.28°. 5315 reflections measured, 3686 unique ($R_{int}$=0.0552). Final residuals for 217 parameters were $R_1$=0.0499, $wR_2$=0.1137 for I>2σ(I), and $R_1$=0.0678, $wR_2$=0.1213 for all 3686 data.

**[00149]** Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide-carboxylic heterodimers between the carbamazepine moieties and the butyric acid moieties. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

**[00150]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 3307 $cm^{-1}$, (C-H stretch, alkene); 1684 $cm^{-1}$, (C=O); 1540 $cm^{-1}$, (C=C).

**[00151]** Melting Point: 63-64°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, butyric acid m.p. = -94°C).

**[00152]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA).16 % weight loss starting at 54°, a 16% weight loss starting at 134° and a 49% weight loss starting at 174° followed by complete decomposition.

Example 16—Multi-Component Crystal of Carbamazepine: Carbamazepine/DMSO (1:1 stoichiometry)

**[00153]** 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 1.5 mL DMSO. Slow evaporation of the solvent yielded colorless plates of a 1:1 carbamazepine/ DMSO co-crystal, as shown in Figure 20B.

**[00154]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{34}H_{36}N_4O_4S_2$, M=628.79, triclinic P-1; a=7.3254(19), b=8.889(2), c=12.208(3) Å,α=94.840(5)°, β=94.926(5)°, γ=100.048(5)°, V=775.8(3)$Å^3$, T=200(2) K, Z=2, μ(MO-Kα)=0.216 $mm^{-1}$, $D_c$=1.320 $Mg/m^3$, λ=0.71073$Å^3$ , F(000)320, $2\theta_{max}$=28.3°. 4648 reflections measured, 3390 unique ($R_{int}$=0.0459). Final residuals for 209 parameters were $R_1$=0.0929, $wR_2$=0.3043 for I>2σ(I).

**[00155]** Crystal packing: The co-crystals are sustained by the hydrogen bonded carboxamide homosynthon. The 1° amines are hydrogen bonded to the sulfoxide of the DMSO

on each side of the homosynthon. The crystal is stabilized by π-π interactions from the tricyclic azepine ring system groups of the CBZ.

**[00156]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3369 $cm^{-1}$ (N-H stretch, 1° amine, CBZ); 1665 $cm^{-1}$ (C=O stretching); 1481$cm^{-1}$ (C=C).

**[00157]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 100°C, 193°C (endotherms). m.p. = 189°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, DMSO m.p. = 18.45°C)

**[00158]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 26% weight loss starting at 102°, a 64% weight loss starting at 212° followed by complete decomposition.

Example 17—Multi-Component Crystal of Carbamazepine: Carbamazepine/formamide (1:1 stoichiometry)

**[00159]** 10 mg (0.0423 mmol) carbamazepine was dissolved in a mixture of approximately 1 mL formamide/1 mL THF or 1 mL formamide/1 mL methanol. Slow evaporation of the solvent mixture produced an average yield of clear needles of a 1:1 carbamazepine/formamide co-crystal, as shown in Figure 21B.

**[00160]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{15}N_3O_2$, M=281.31, triclinic P-1; a=5.1077(11), b=16.057(3), c=17.752(4) Å,α=73.711(3)°, β=89.350(3)°, γ=88.636(3)°, V=1397.1(5) $Å^3$, T=100° K, Z=4, μ(MO-Kα)=0.091 $mm^{-1}$, $D_c$=1.337 $Mg/m^3$, λ=0.71073$Å^3$ , F(000)592, $2\theta_{max}$=28.33°. 11132 reflections measured, 6272 unique ($R_{int}$=0.1916). Final residuals for 379 parameters were $R_1$=0.0766 and $wR_2$=0.1633 for I>2σ(I).

**[00161]** Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide homodimers between two carbamazepine moieties and carboxylic acid homodimers between two formamide moieties. Infinite chains are formed by the homodimers linked side by side, with every other set of CBZ molecules attached on the sides of the chain but not bonded to form a dimer.

**[00162]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3392 $cm^{-1}$, (N-H stretch, 1° amine, CBZ); 2875 $cm^{-1}$, (C-H stretch, alkene); 1653 $cm^{-1}$, (C=O); 1590 $cm^{-1}$ , (C=C).

**[00163]** Melting Point: 142-144°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formamide m.p. = -94°C).

**[00164]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 27% weight loss starting at 138°, a 67% weight loss starting at 195° followed by complete decomposition.

Example 18—Multi-Component Crystal of Carbamazepine: Carbamazepine/formic acid (1:1 stoichiometry)

**[00165]** 40 mg (0.1693 mmol) carbamazepine was dissolved in approximately 2 mL formic acid. Slow evaporation of the solvent yielded off-white starbursts of a 1:1 carbamazepine/formic acid co-crystal, as shown in Figure 22B.

**[00166]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{14}N_2O_3$, M=282.29, monoclinic P21/c; a=5.2031(9), b=14.741(2), c=17.882(3) Å,$\alpha$=90°, $\beta$=98.132(3)°, $\gamma$=90°, V=1357.7(4)Å$^3$, T= 100 K, Z=4, $\mu$(MO-K$\alpha$)=0.097 mm$^{-1}$, $D_c$=1.381 Mg/m$^3$, $\lambda$=0.71073Å$^3$ , F(000)592, $2\theta_{max}$=28.3. 9402 reflections measured, 3191 unique ($R_{int}$=0.111). Final residuals for 190 parameters were $R_1$=0.0533 and $wR_2$=0.1268 for I>2$\sigma$(I).

**[00167]** Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid-amine heterodimers arranged in centrosymmetric tetramers.

**[00168]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm$^{-1}$, (1° amine stretch,CBZ); 3026 cm$^{-1}$ (C-H stretch, CBZ); 1692 cm$^{-1}$, (1° amide, C=O stretch).

**[00169]** Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formic acid m.p. = 8.4°C).

**[00170]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 14.60% weight loss starting at 123° and a 68.91% weight loss starting at 196° followed by complete decomposition.

Example 19—Multi-Component Crystal of Carbamazepine: Carbamazepine/trimesic acid (1:1 stoichiometry)

**[00171]** 36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2mL dichloromethane.

Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine/trimesic acid co-crystal, as shown in Figure 23B.

**[00172]** Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å,$\alpha$=90°, $\beta$=98.191(3)°, $\gamma$=90°, V=4099.39(37) Å$^3$, T=-173 K, Z=8, $\mu$(MO-K$\alpha$)=0.110 mm$^{-1}$, $D_c$=1.439 Mg/m$^3$, $\lambda$=0.71073Å$^3$, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique ($R_{int}$=0.0611). Final residuals for 2777 parameters were $R_1$=0.1563, $wR_2$=0.1887 for I>2$\sigma$(I), and $R_1$=0.1441, $wR_2$=0.1204 for all 3601 data.

**[00173]** Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

**[00174]** Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm$^{-1}$(N-H stretch, 1° amine, CBZ); 1688 cm$^{-1}$ (C=O, 1° amide stretch, CBZ); 1602 cm$^{-1}$ (C=C, CBZ).

**[00175]** Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273°C (endotherm). m.p. = NA, decomposes at 278°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, trimesic acid m.p. = 380°C)

**[00176]** Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253° and a 30.20% weight loss starting at 278° followed by complete decomposition.

**[00177]** X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuK$\alpha$ ($\lambda$=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

**[00178]** All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

**[00179]** It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will

be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

Claims

1. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between two or more independent molecular entities, wherein at least one of said two or more independent molecular entities is a pharmaceutical molecule.

2. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a discrete supramolecular entity.

3. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a polymeric structure.

4. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is sustained by a supramolecular homosynthon when said pharmaceutical molecule is in its pure phase.

5. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical property or chemical property that is different from that of said pharmaceutical when said pharmaceutical molecule is in its pure phase.

6. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical or chemical property that is the same as that of said pharmaceutical molecule when said pharmaceutical molecule is in its pure phase.

7. The multiple-component phase composition of claim 5, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

8. The multiple-component phase composition of claim 6, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

9. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is selected from the group consisting of aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

10. The multiple-component phase composition of claim 1, wherein said two or more independent molecular entities are selected from the group consisting of: acetaminophen, 4,4'-bipyridine, and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofen and 4,4'-bipyridine; flurbiprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis (4-pyridyl) ethylene; carbamazepine, *p*-phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5-nitroisophthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7,-adamantanetetracarboxylic acid; carbamazepine and benzoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl sulfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

11. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are selected from the group consisting of hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

12. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are between complementary chemical functionalities on said two or more independent molecular entities.

13. The multiple-component phase composition of claim 15, wherein said complementary chemical functionalities include at least one chemical functionality selected from

the group consisting of acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

14. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are the same.

15. The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are acids.

16. The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are amides.

17. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are not the same.

18. The multiple-component phase composition of claim 17, wherein said complementary chemical functionalities on said two or more independent molecular entities are selected from the group consisting of acids and amides; pyridines and amides; and alcohols and amines.

19. The multiple-component phase composition of claim 1, wherein two or more of said independent molecular entities is a pharmaceutical molecule.

20. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between aspirin and at least one independent molecular entity.

21. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between acetaminophen and at least one independent molecular entity.

22. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between a profen and at least one independent molecular entity.

23. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between phenytoin and at least one independent molecular entity.

24. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between carbamazepine and at least one independent molecular entity.

25. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;

(c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

26. The method of claim 25, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

27. The method of claim 26, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

28. The method of claim 26, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

29. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

30. The method of claim 29, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase

composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

31. The method of claim 30, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

32. The method of claim 30, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

33. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with different molecules;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

34. The method of claim 33, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

35. The method of claim 34, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

36. The method of claim 34, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

Abstract

The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon. The subject invention also pertains to multiple-component phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions.

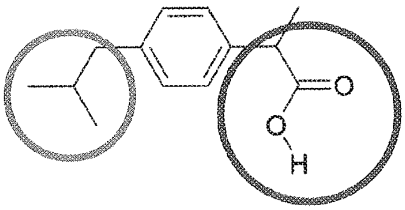



FIG. 1



FIG. 2

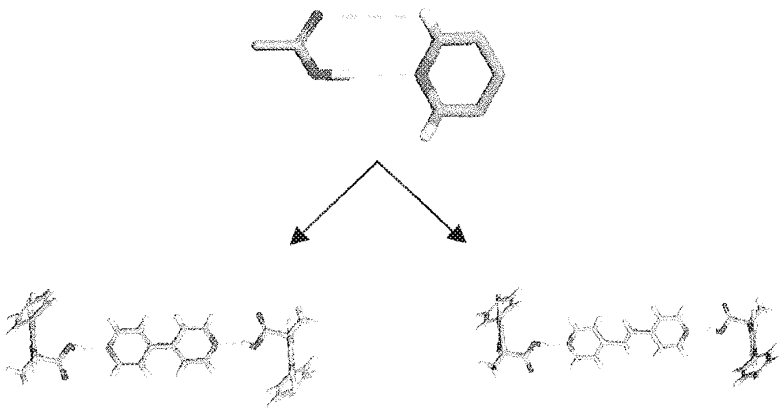


FIG. 3

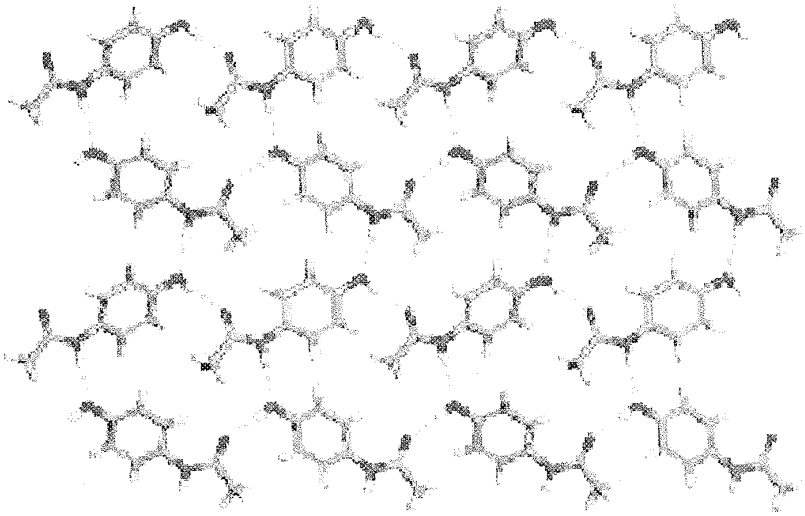


FIG. 4A

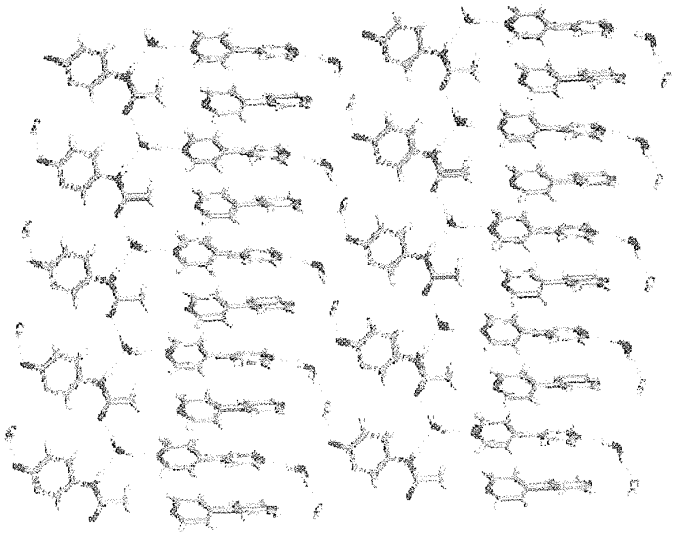


FIG. 4B

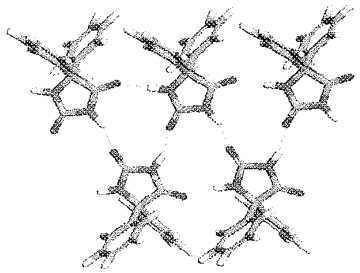


FIG. 5A

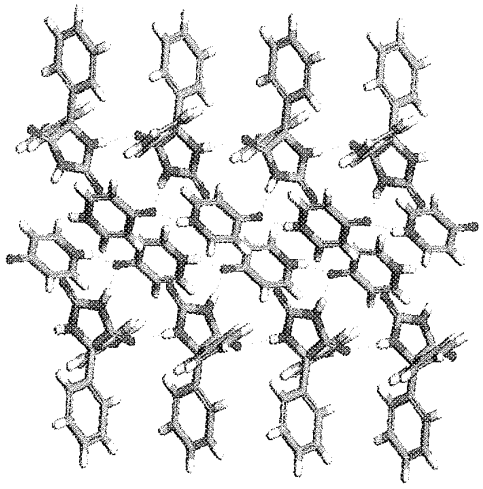


FIG. 5B

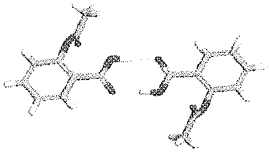


FIG. 6A



FIG. 6C

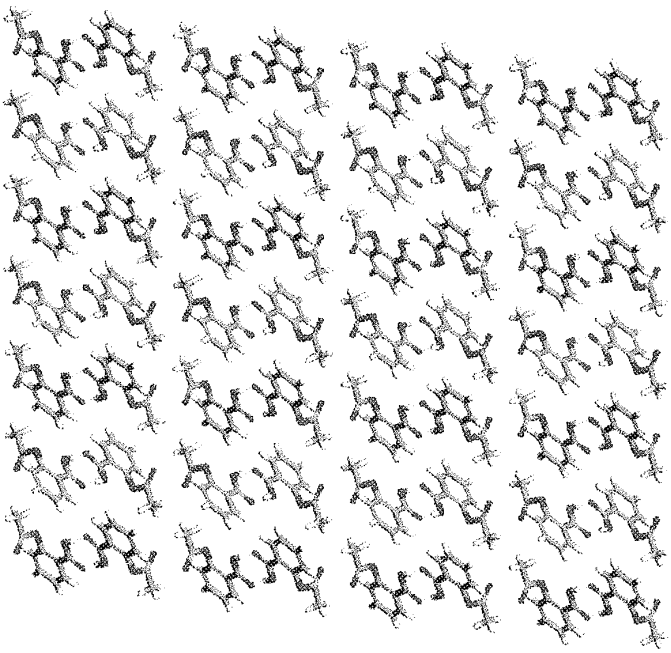


FIG. 6B

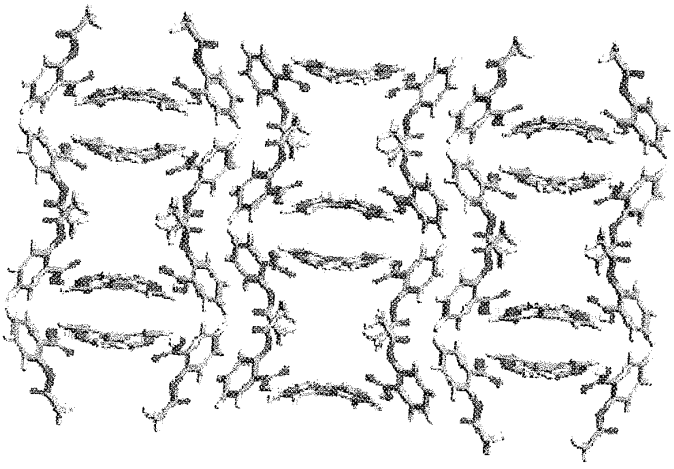


FIG. 6D

FIG. 7A

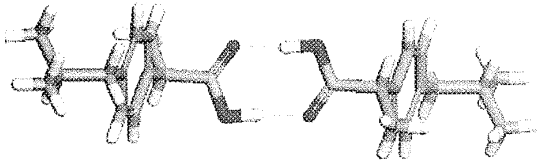
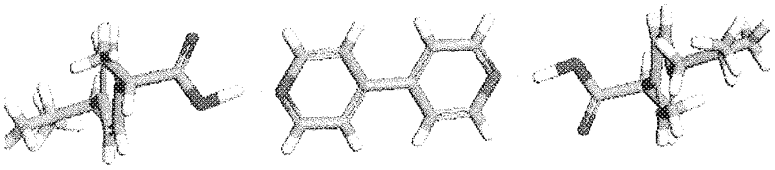


FIG. 7C



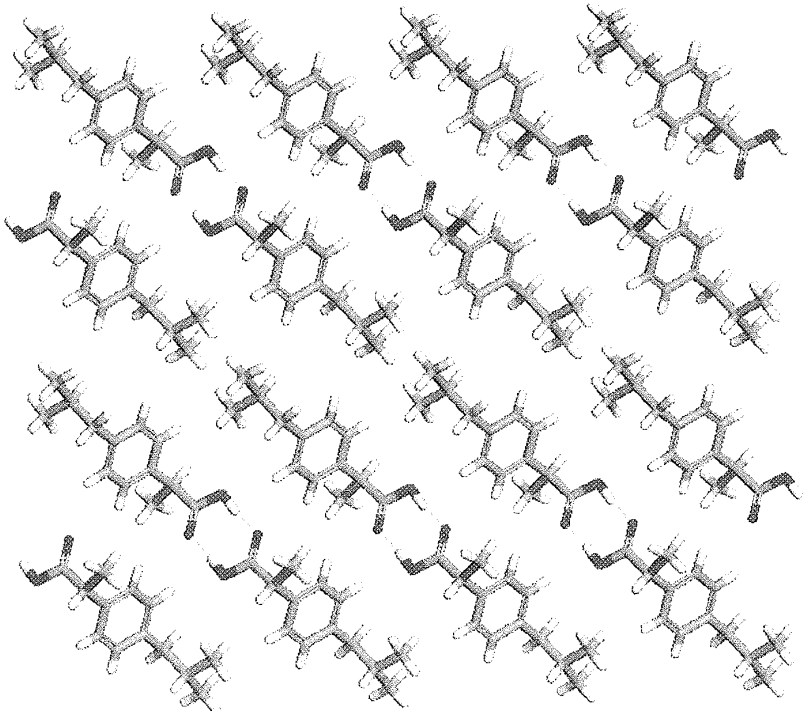


FIG. 7B

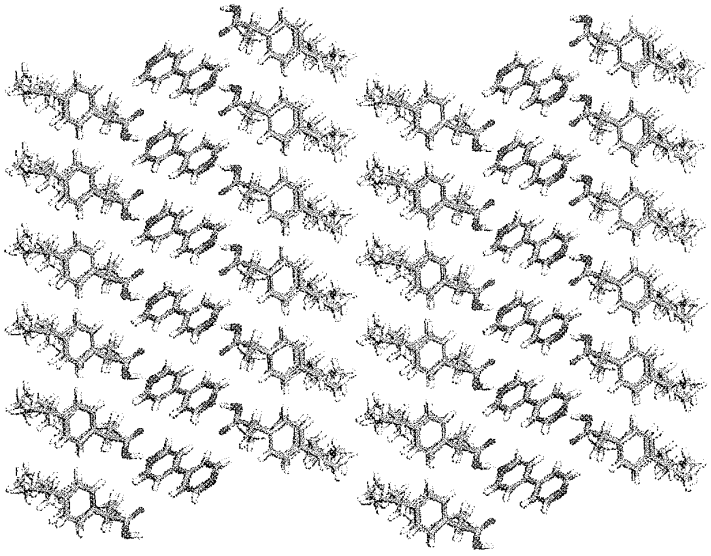


FIG. 7D

FIG. 8A

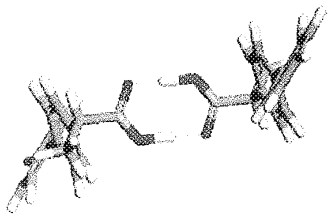
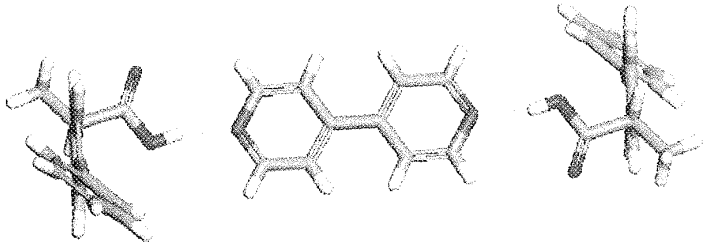


FIG. 8C



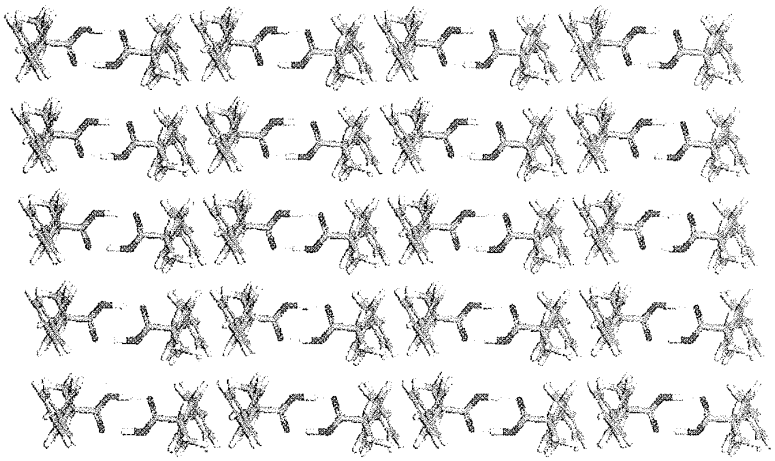


FIG. 8B

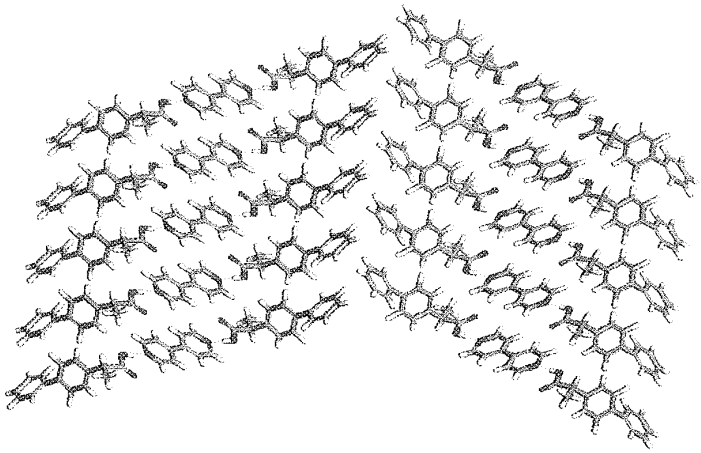


FIG. 8D

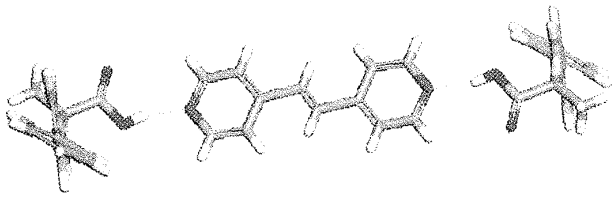


FIG. 9A

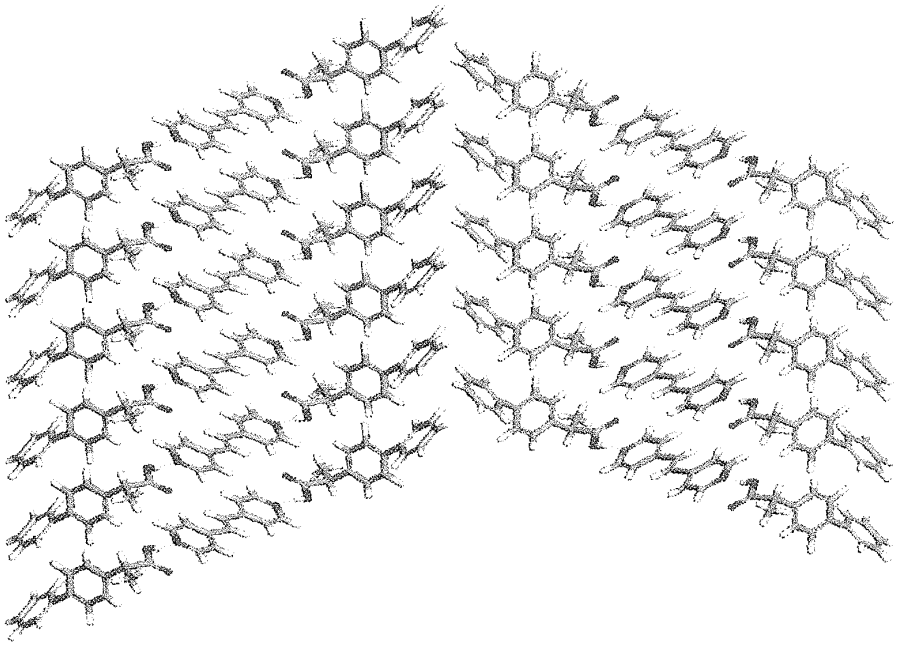


FIG. 9B

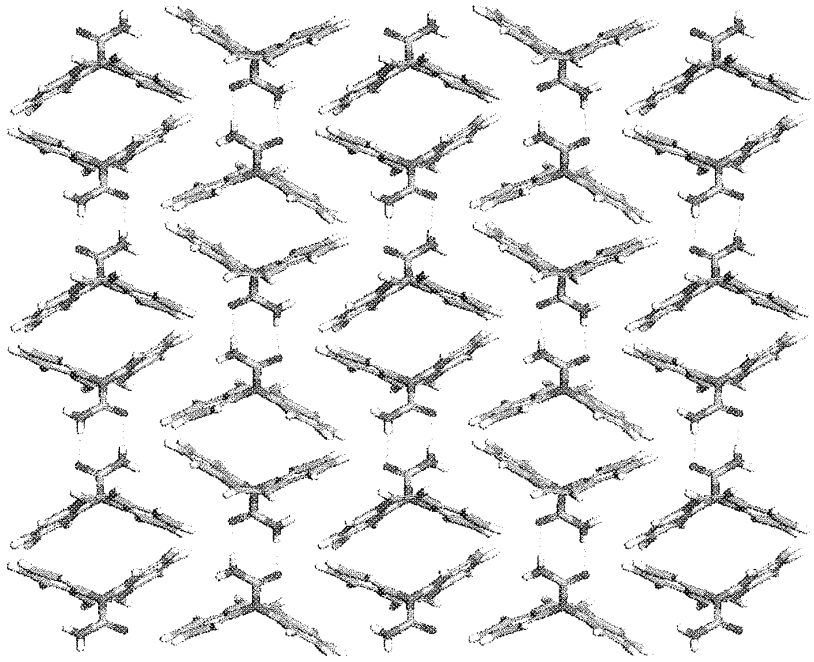


FIG. 10A

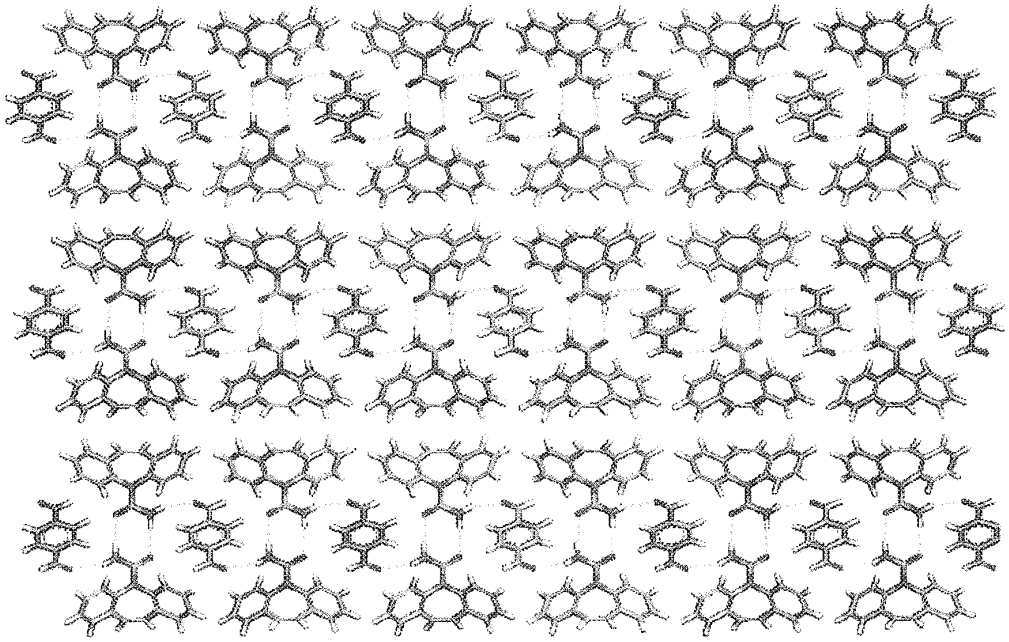


FIG. 10B

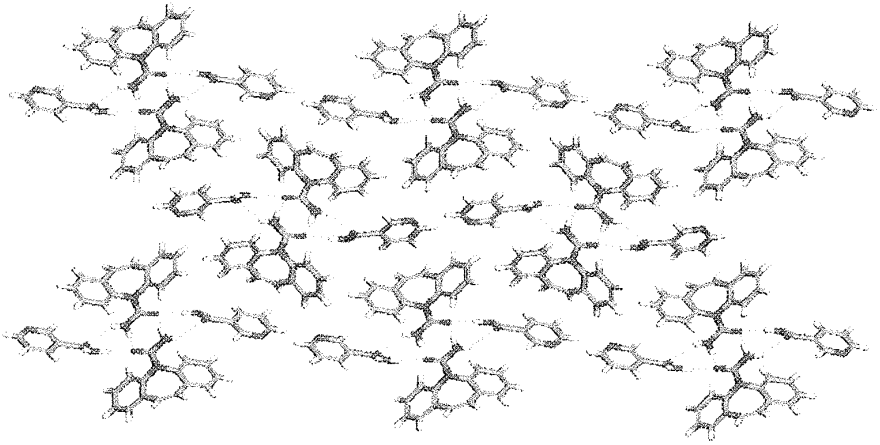


FIG. 11

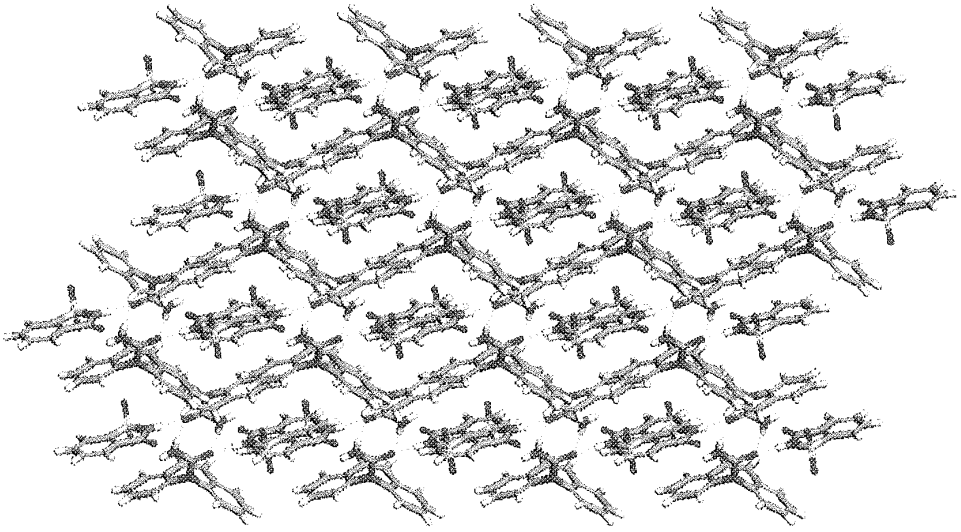


FIG. 12

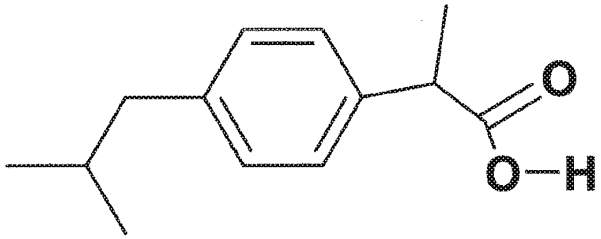



FIG. 13A

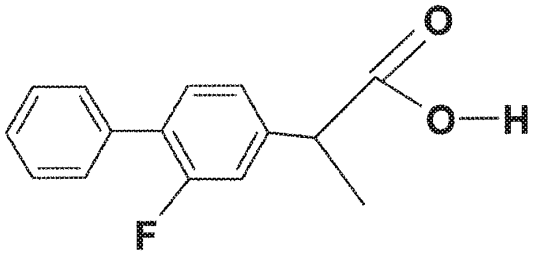



FIG. 13B

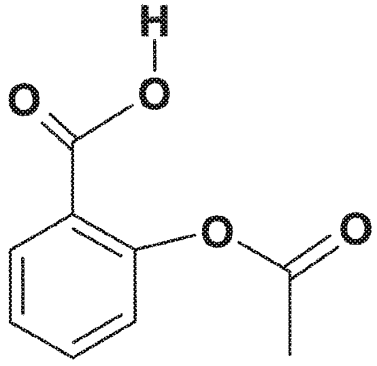



FIG. 13C

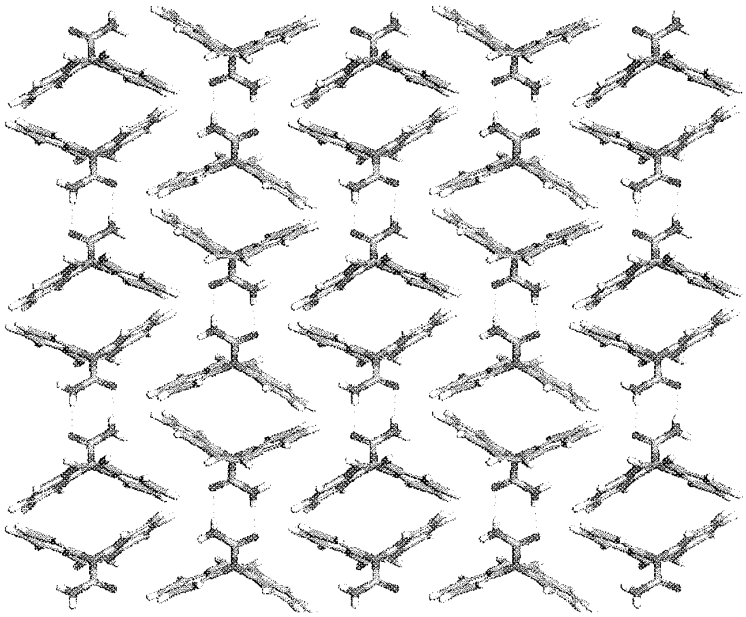


FIG. 14A

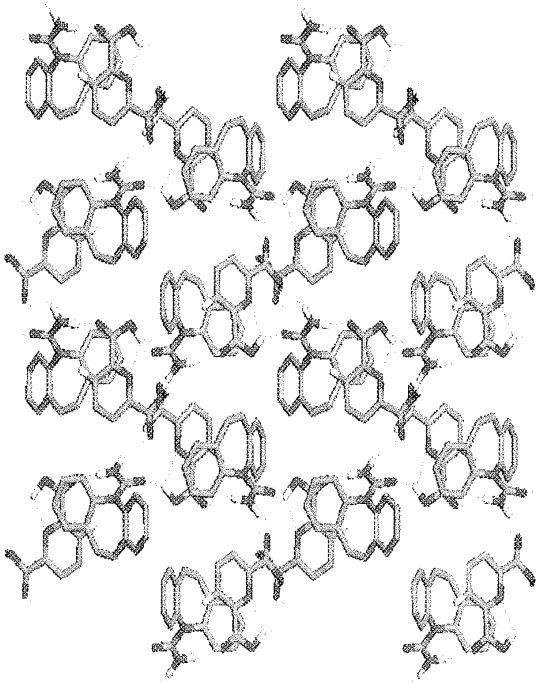


FIG. 14B

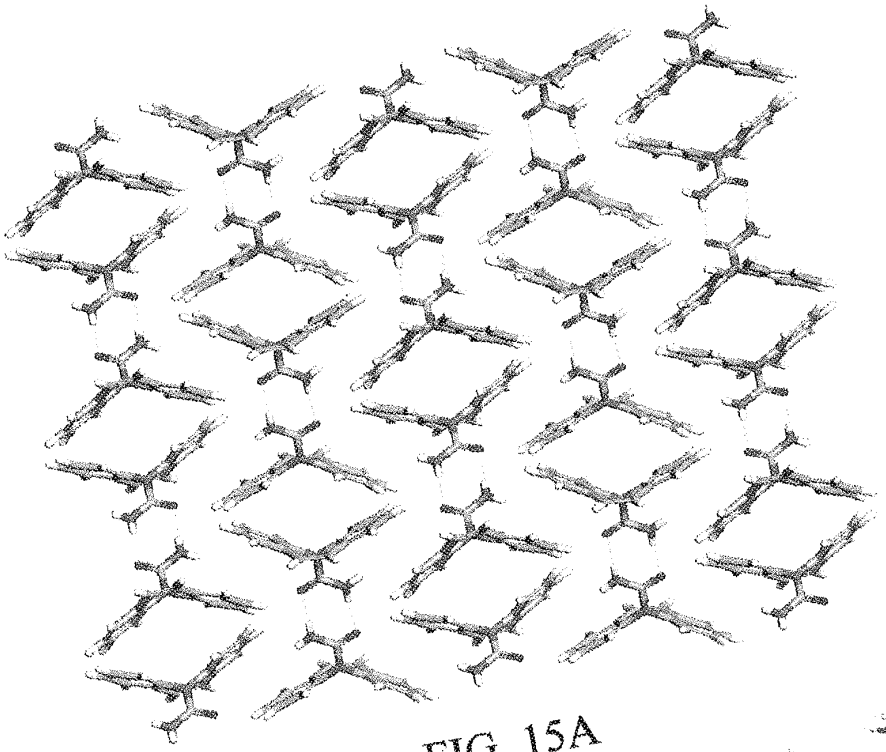


FIG. 15A

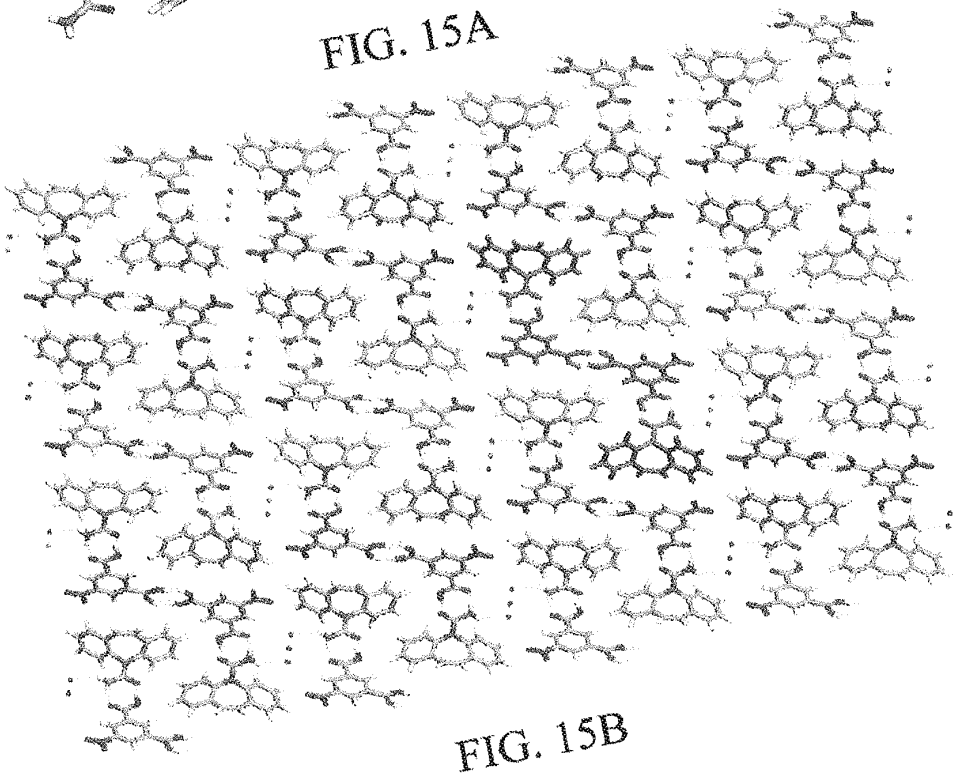


FIG. 15B

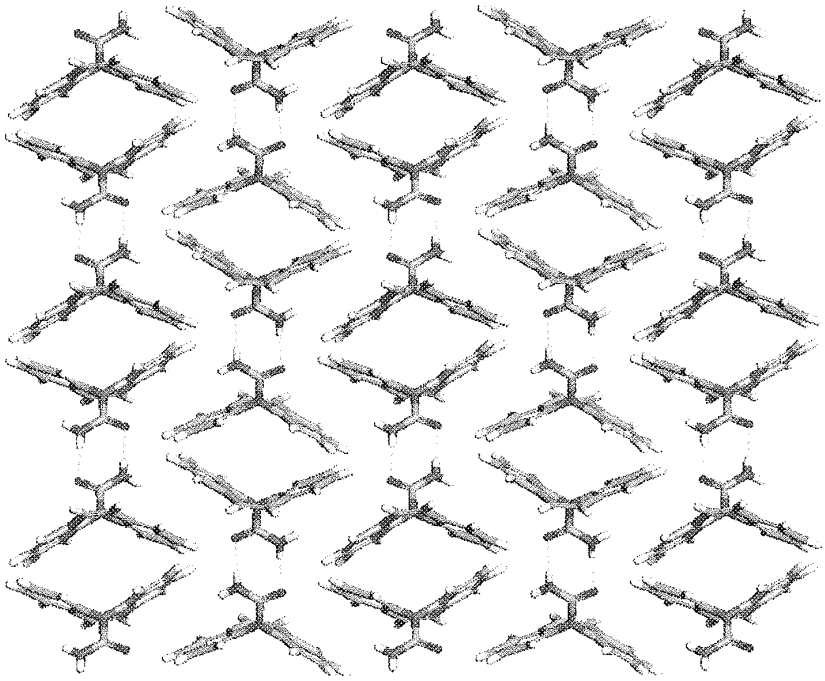


FIG. 16A

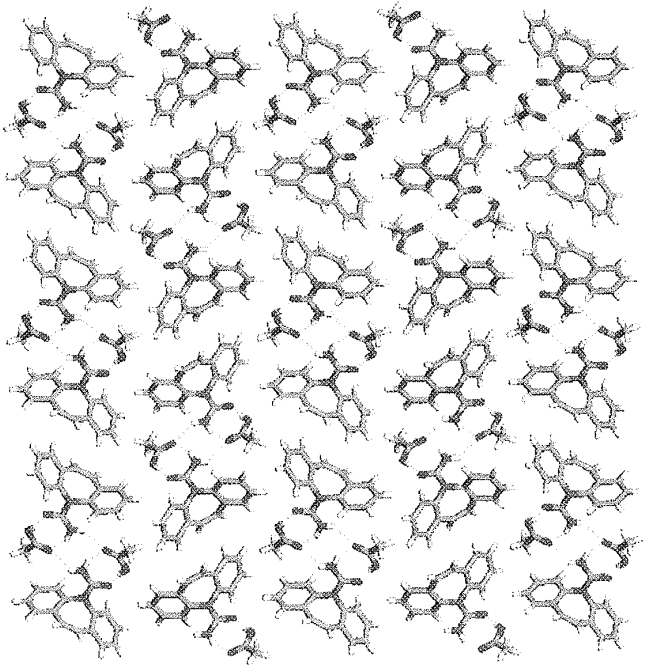


FIG. 16B

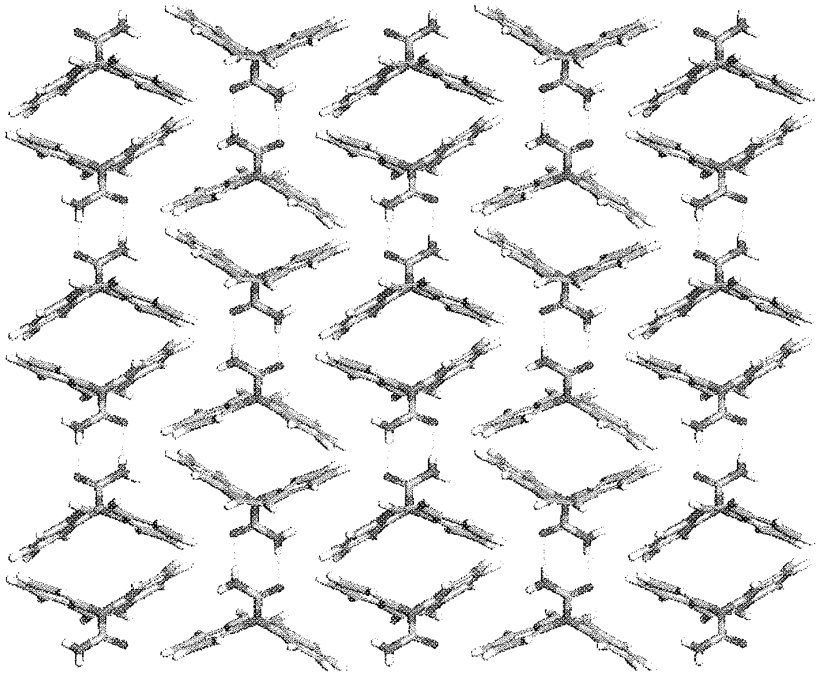


FIG. 17A

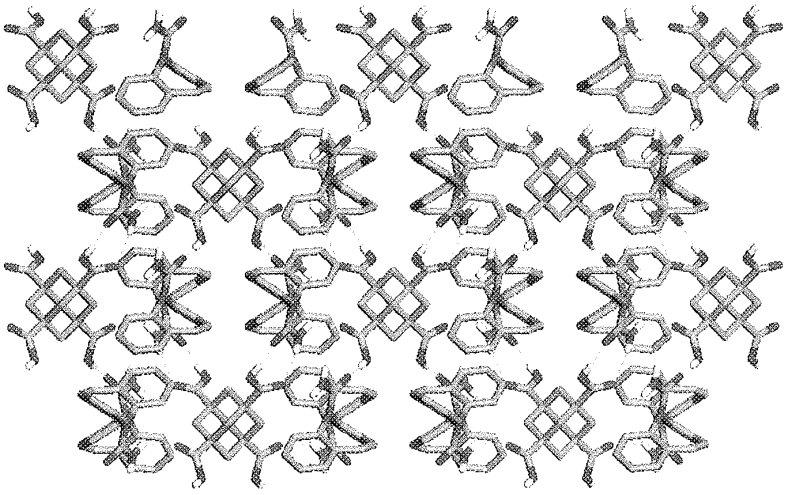


FIG. 17B

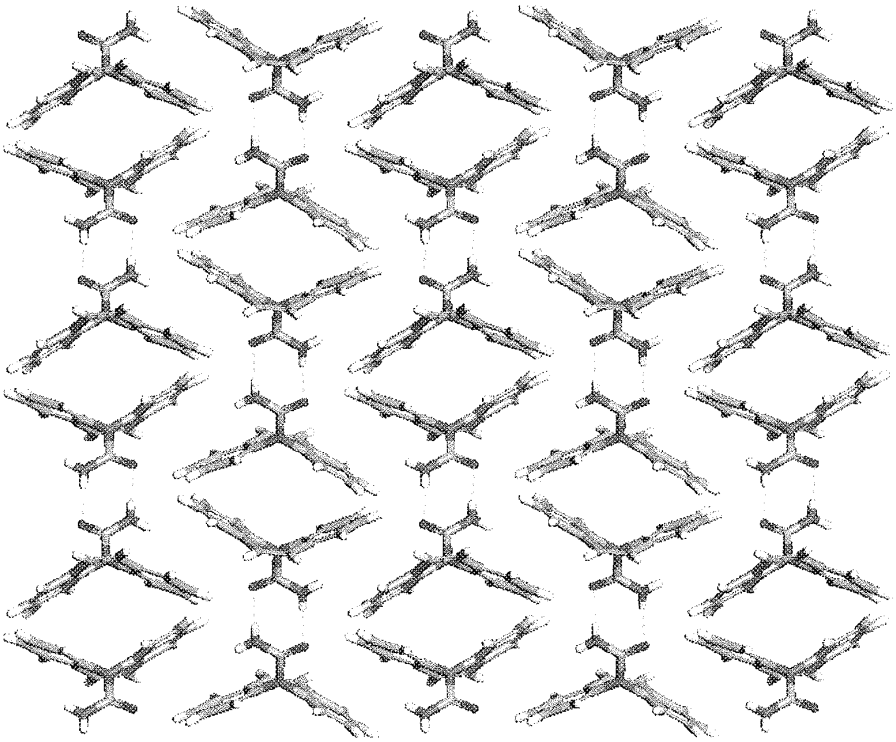


FIG. 18A

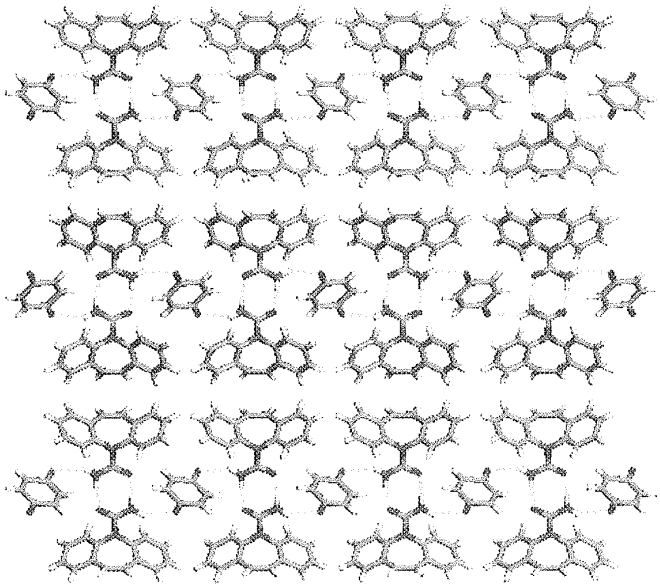


FIG. 18B

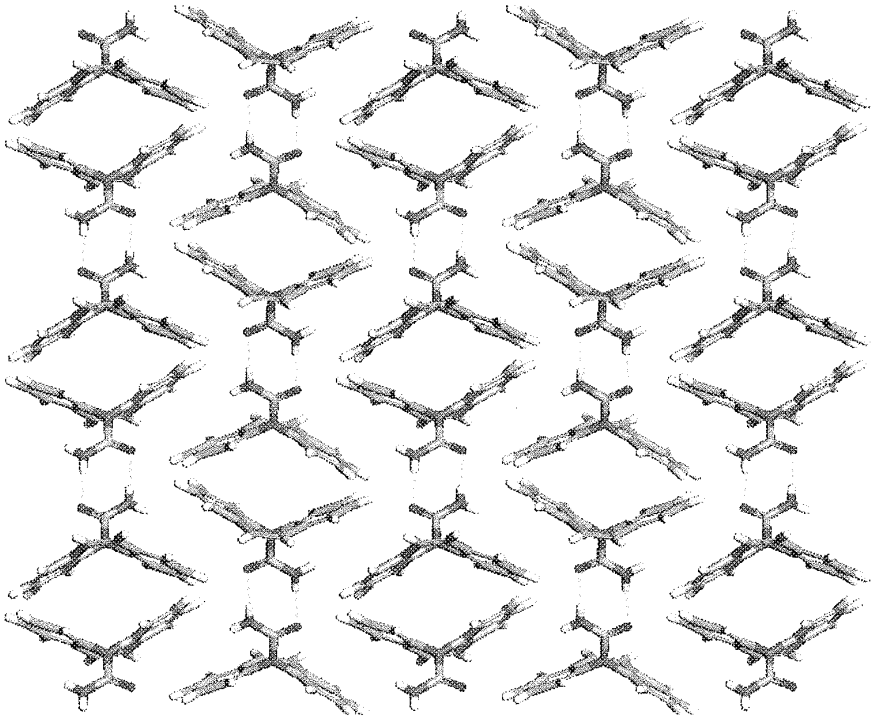


FIG. 19A

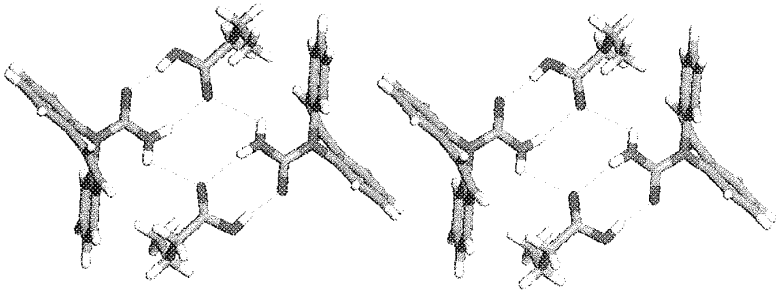


FIG. 19B

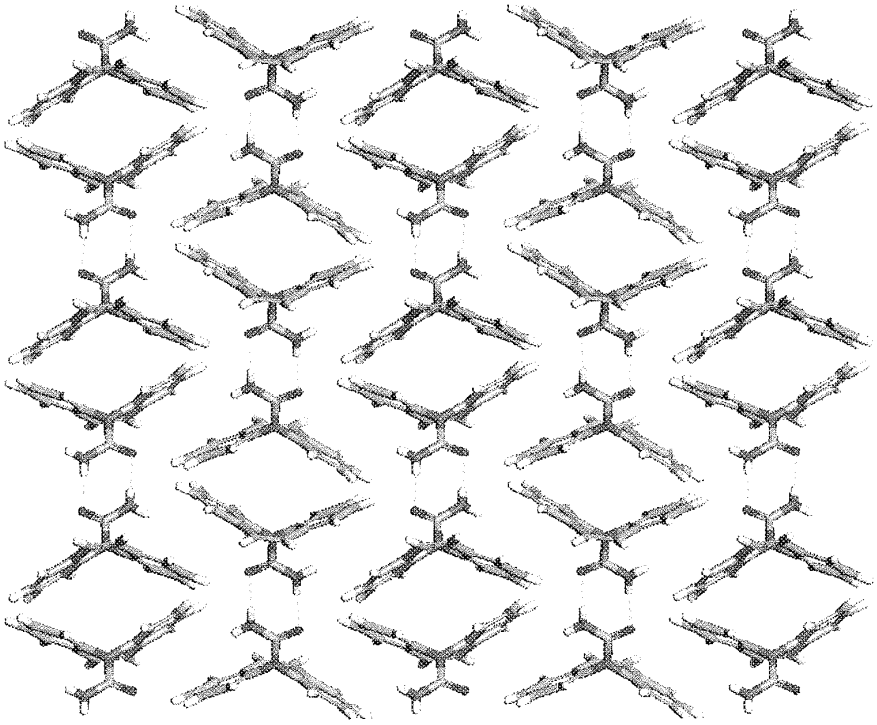


FIG. 20A

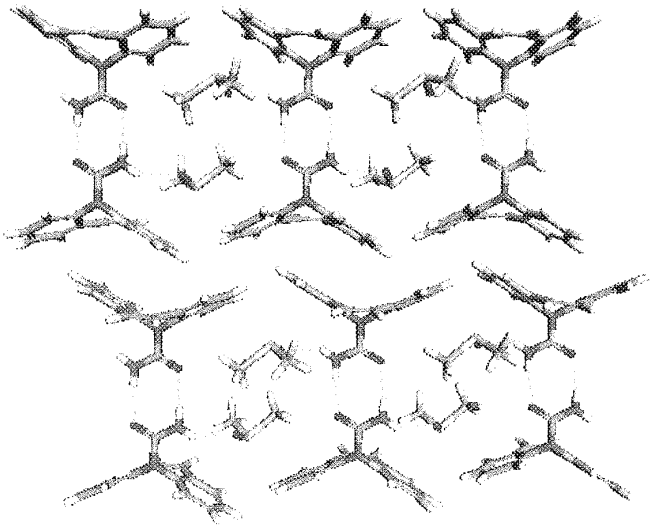


FIG. 20B

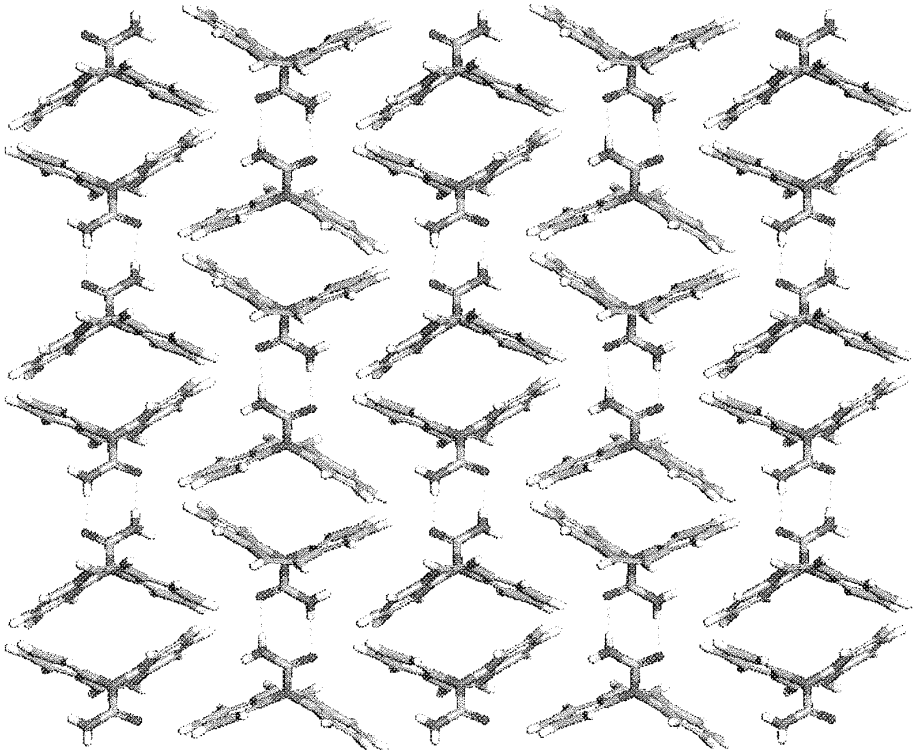


FIG. 21A

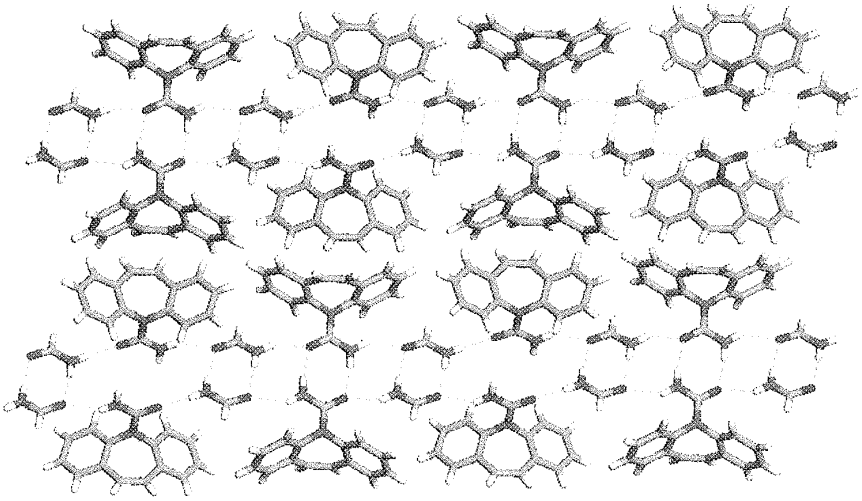


FIG. 21B

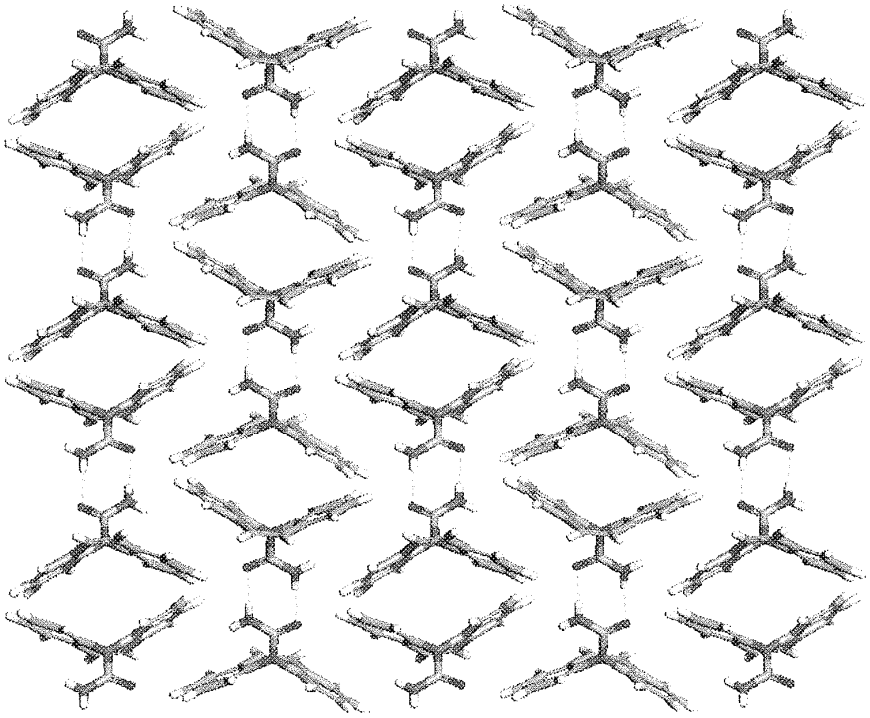


FIG. 22A

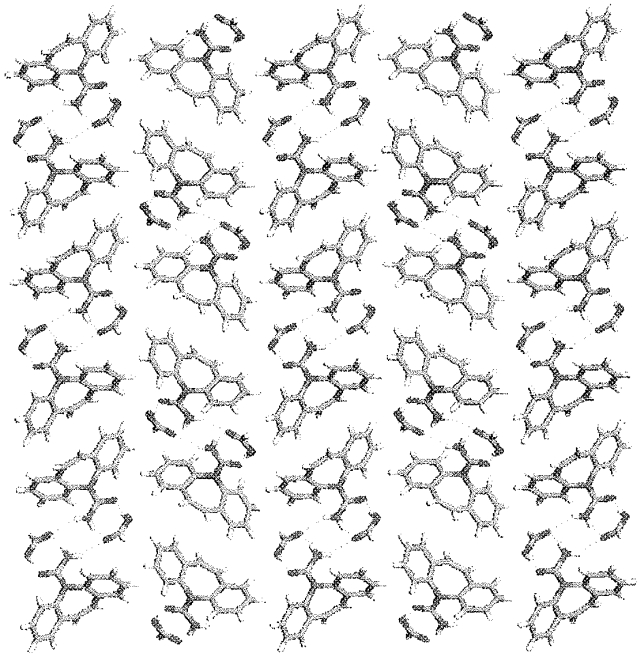


FIG. 22B

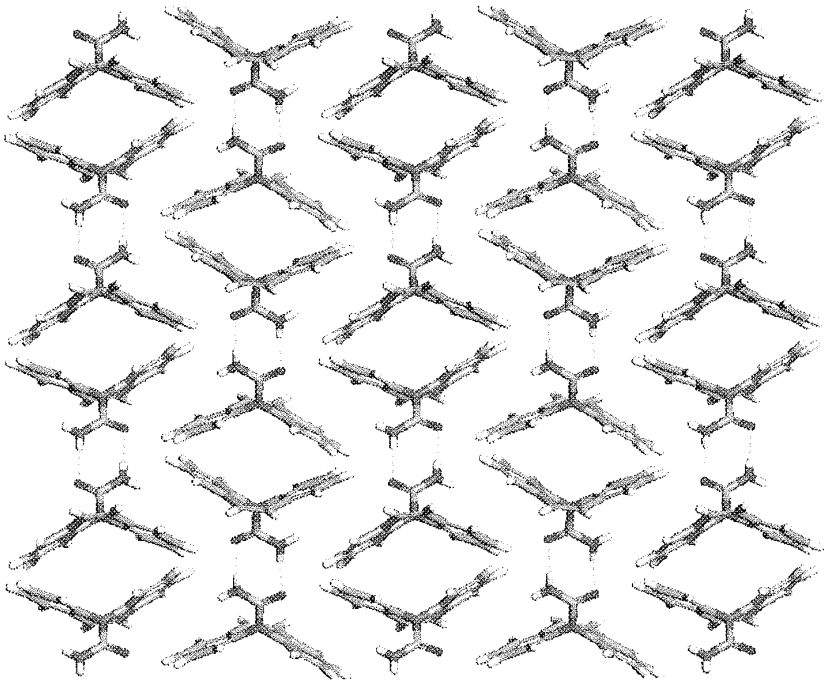


FIG. 23A

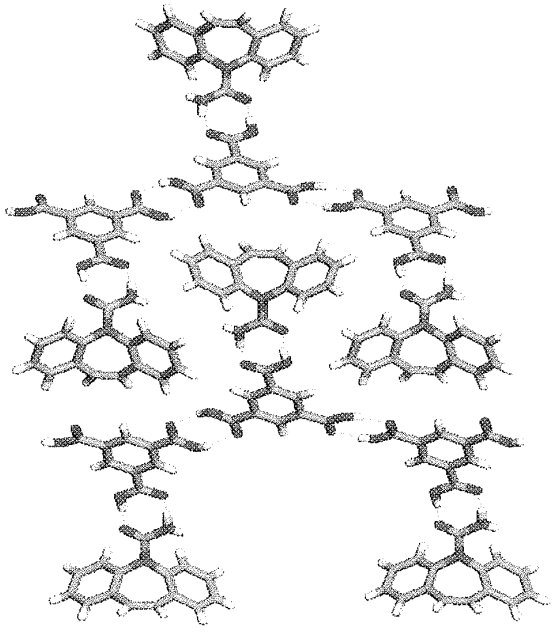


FIG. 23B

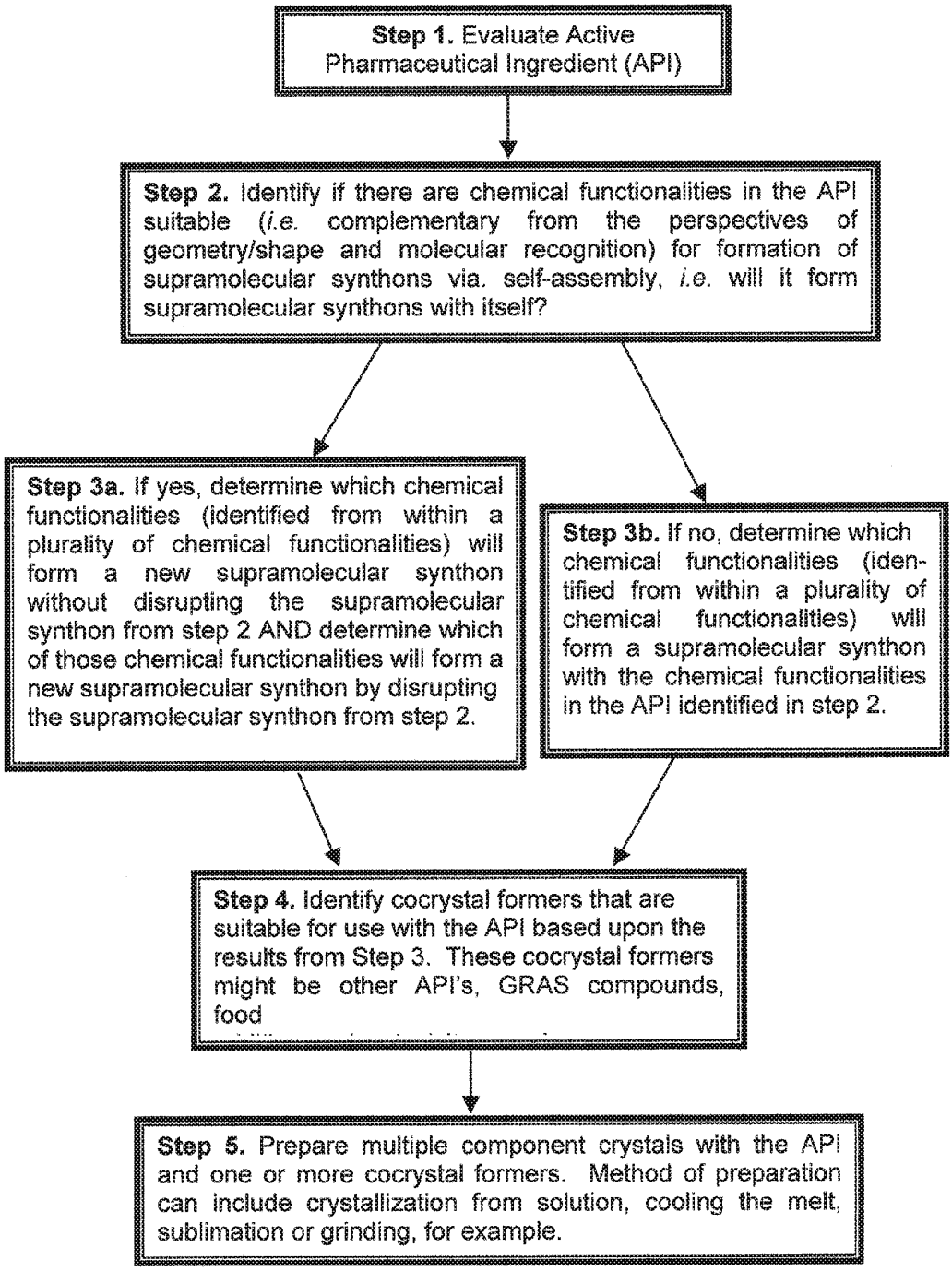

**Step 1.** Evaluate Active Pharmaceutical Ingredient (API)
**Step 2.** Identify if there are chemical functionalities in the API suitable (*i.e.* complementary from the perspectives of geometry/shape and molecular recognition) for formation of supramolecular synthons via. self-assembly, *i.e.* will it form supramolecular synthons with itself?
**Step 3a.** If yes, determine which chemical functionalities (identified from within a plurality of chemical functionalities) will form a new supramolecular synthon without disrupting the supramolecular synthon from step 2 AND determine which of those chemical functionalities will form a new supramolecular synthon by disrupting the supramolecular synthon from step 2.
**Step 3b.** If no, determine which chemical functionalities (identified from within a plurality of chemical functionalities) will form a supramolecular synthon with the chemical functionalities in the API identified in step 2.
**Step 4.** Identify cocrystal formers that are suitable for use with the API based upon the results from Step 3. These cocrystal formers might be other API's, GRAS compounds, food
**Step 5.** Prepare multiple component crystals with the API and one or more cocrystal formers. Method of preparation can include crystallization from solution, cooling the melt, sublimation or grinding, for example.

FIG. 24

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 29667101 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | Edward R. Gates/Nicole Forgrave |
| **Filer Authorized By:** | Edward R. Gates |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 30-JUN-2017 |
| **Filing Date:** | |
| **Time Stamp:** | 14:54:12 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal of New Application | U015770023US03-TRN-ERG.pdf | 32113<br>ce92b40e2f46a38a6f145840e543d52ae47976fe | no | 1 |
| **Warnings:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 2 | Application Data Sheet | U015770023US03-ADS-ERG.pdf | 30345<br>2a9857acc3352c0341ad793acdf934685b9cbe06 | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied ADS fillable form | | | | | |
| 3 | Oath or Declaration filed | U015770023US03-DEC-ERG.pdf | 418895<br>1e7e9c3bec720f1bf8e89d359b11ba9ed2e8527e | no | 3 |
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| **Information:** | | | | | |
| 4 | | U015770023US03-PAMN-ERG.pdf | 28906<br>a9d8e6cc10ccae486a57cbd9a615795e78f9ed26 | yes | 3 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Preliminary Amendment | 1 | 1 |
| | Specification | 2 | 2 |
| | Applicant Arguments/Remarks Made in an Amendment | 3 | 3 |

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| | Specification | 1 | 34 |
| | Claims | 35 | 41 |
| | Abstract | 42 | 42 |

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| 6 | Drawings-only black and white line drawings | U015770023US03-DRW-ERG.pdf | 3813052<br>2e6e1ef04a006c1c742c9098e4f49be7e0cdc75c | no | 22 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 10829183 | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/639,223

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | 70 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 300 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 36 minus 20 = | * 16 | x 40 = | 640 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 9 minus 3 = | * 6 | x 210 = | 1260 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 2630 | | TOTAL | |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE($) | ADDITIONAL FEE($) | OR | RATE($) | ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 |

**CONFIRMATION NO. 8089**

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

**FORMALITIES LETTER**

*OC000000092638587*

Date Mailed: 07/11/2017

# NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

**FILED UNDER 37 CFR 1.53(b)**

***Filing Date Granted***

**Items Required To Avoid Abandonment:**

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of $ **1900** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

**SUMMARY OF FEES DUE:**

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **70** basic filing fee.
- $ **70** surcharge.
- $ **300** search fee.
- $ **360** examination fee.
- $ **1260** for **6** independent claims over 3.
- $ **640** for **16** total claims over 20.

- $( **0**) previous unapplied payment amount.
- $ **2700** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/kgebremichael/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | 2631 | 0.00 | U0157.70023US03 | 36 | 9 |

**CONFIRMATION NO. 8089**

**FILING RECEIPT**

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

OC000000092638586

Date Mailed: 07/11/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

**Applicant(s)**

University of South Florida, Tampa, FL;
The Regents of the University of Michigan, Ann Arbor, MI;

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a CON of 10/378,956 03/03/2003 ABN
which claims benefit of 60/360,768 03/01/2002

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 07/10/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/639,223**

**Projected Publication Date:** To Be Determined - pending completion of Missing Parts

**Non-Publication Request:** No

**Early Publication Request:** No
**** SMALL ENTITY ****
**Title**

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

**Preliminary Class**

375

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | Not Yet Assigned |
| Art Unit: | 2631 |

**Certificate of Electronic Filing under 37 CFR § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 11, 2017 Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

**RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION**

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Notice to File Missing Parts of Nonprovisional Application, mailed July 11, 2017, Applicant submits herewith payment of the filing fee, search fee, examination fee, excess claim fee, and the surcharge for late payment of the filing fees. Applicant also submits herewith a Preliminary Amendment to reduce excess claim fees due. Applicant requests that the excess claim fees be calculated after entrance of the Preliminary Amendment being filed herewith.

Please charge our credit card in the amount of $1,010.00 to cover the fees listed above.

The deadline for responding to the Notification is September 11, 2017. Applicant thus submits that the present Response is timely submitted on Monday, September 11, 2017.

Please charge any deficiency in the fees due, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. U0157.70023US03, from which the undersigned is authorized to draw.

Dated: September 11, 2017

Respectfully submitted,

By /David F. Cauble/
David F. Cauble
Registration Number: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 89 of 415

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
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| Examiner: | Not Yet Assigned |
| Art Unit: | 2631 |

**Certificate of Electronic Filing under 37 CFR § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 11, 2017 Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

## PRELIMINARY AMENDMENT

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Prior to examination on the merits, please amend the above-referenced U.S. Patent Application as follows:

**Amendments to the Claims** are reflected in the Listing of Claims, which begins on page 2 of this paper.

**Remarks** begin on page 7 of this paper.

## AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1. (Original) A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between two or more independent molecular entities, wherein at least one of said two or more independent molecular entities is a pharmaceutical molecule.

2. (Currently Amended) The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a discrete supramolecular entity or a polymeric structure.

3. (Canceled)

4. (Original) The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is sustained by a supramolecular homosynthon when said pharmaceutical molecule is in its pure phase.

5. (Currently Amended) The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical property or chemical property that is different from that of said pharmaceutical when said pharmaceutical molecule is in its pure phase, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

6-8. (Canceled)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 91 of 415

9. (Original) The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is selected from the group consisting of aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

10. (Original) The multiple-component phase composition of claim 1, wherein said two or more independent molecular entities are selected from the group consisting of: acetaminophen, 4,4'-bipyridine, and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofen and 4,4'- . bipyridine; flurbiprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis (4-pyridyl) ethylene; carbamazepine, p-phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5- nitroisophthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7,- adamantanetetracarboxylic acid; carbamazepine and benzoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl stilfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

11. (Original) The multiple-component phase composition of claim 1, wherein said intermolecular interactions are selected from the group consisting of hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

12. (Original) The multiple-component phase composition of claim 1, wherein said intermolecular interactions are between complementary chemical functionalities on said two or more independent molecular entities.

13. (Currently Amended) The multiple-component phase composition of claim 1[[15]], wherein said complementary chemical functionalities include at least one chemical functionality selected from the group consisting of acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 92 of 415

heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

14. (Original) The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are the same.

15. (Original) The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are acids.

16. (Original) The multiple-component phase composition of -.claim 14, wherein said complementary chemical functionalities are amides.

17. (Original) The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are not the same.

18. (Original) The multiple-component phase composition of claim 17, wherein said complementary chemical functionalities on said two or more independent molecular entities are selected from the group consisting of acids and amides; pyridines and amides; and alcohols and amines.

19-24. (Canceled)

25. (Original) A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 93 of 415

(c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

26. (Original) The method of claim 25, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

27-28. (Canceled)

29. (Original) A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 94 of 415

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

30. (Original) The method of claim 29, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

31-32. (Canceled)

33. (Original) A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with different molecules;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

34. (Original) The method of claim 33, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

35-36. (Canceled)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 95 of 415

## REMARKS

Applicant requests entrance of this Preliminary Amendment to reduce the number of claims pending in this Application. After entrance of the present Amendment, four (4) independent claims, twenty (20) total claims, and no multiply dependent claims will be pending in this case. Claim(s) 3, 6-8, 19-24, 27-28, 31-32 and 35-36 have been canceled.

Claim 2 has been amended to further recite the element of claim 3. Claim 5 has been amended to further recite the elements of claim 7. Claim 13 has been amended to depend from claim 1.

Applicant reserves the right to pursue subject matter canceled from the claims in future applications claiming priority to the present Application. Applicant submits that no new matter is added to the Application by this Preliminary Amendment.

Applicant believes all fees due are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. U0157.70023US03, from which the undersigned is authorized to draw.

Dated: September 11, 2017

Respectfully submitted,

By_____/David F. Cauble/_____
David F. Cauble
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 96 of 415

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Chelsea Dowling |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| UTILITY FILING FEE (ELECTRONIC FILING) | 4011 | 1 | 70 | 70 |
| UTILITY SEARCH FEE | 2111 | 1 | 300 | 300 |
| UTILITY EXAMINATION FEE | 2311 | 1 | 360 | 360 |
| **Pages:** | | | | |
| **Claims:** | | | | |
| INDEPENDENT CLAIMS IN EXCESS OF 3 | 2201 | 1 | 210 | 210 |
| **Miscellaneous-Filing:** | | | | |
| LATE FILING FEE FOR OATH OR DECLARATION | 2051 | 1 | 70 | 70 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1010** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 30325826 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Chelsea Dowling |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 11-SEP-2017 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:56:12 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $1010 |
| RAM confirmation Number | 091217INTEFSW15574100 |
| Deposit Account | 232825 |
| Authorized User | Wolf Greenfield |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.16 (National application filing, search, and examination fees) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | U015770023US03-TRN-DFC.pdf | 25132<br>e8549b89dc09da6d11a8310d3b5f07a87c2821c9 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 31467<br>57a52de894825f91590dbd086204c116362ec9cd | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Applicant Response to Pre-Exam Formalities Notice | U015770023US03-RTMP-DFC.pdf | 24196<br>fb676ac5e6771269580cb47c2191ad04b0aaa08e | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | | U015770023US03-PAMN-DFC.pdf | 37336<br>2a3a216ea4b726950cafb71a723ed8ae3d28967c | yes | 7 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Preliminary Amendment | 1 | 1 |
| Claims | 2 | 6 |
| Applicant Arguments/Remarks Made in an Amendment | 7 | 7 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 38711<br>c642b1153843c4e884e35506410cad9115e11100 | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 156842 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

| **TRANSMITTAL FORM** *(to be used for all correspondence after initial filing)* | | | |
|---|---|---|---|
| | | Application Number | 15/639,223-Conf. #8089 |
| | | Filing Date | June 30, 2017 |
| | | First Named Inventor | Michael J. Zaworotko |
| | | Art Unit | 2631 |
| | | Examiner Name | Not Yet Assigned |
| Total Number of Pages in This Submission | | Attorney Docket Number | U0157.70023US03 |

**ENCLOSURES (*Check all that apply*)**

| | | |
|---|---|---|
| [X] Fee Transmittal Form | [ ] Drawing(s) | [ ] After Allowance Communication to TC |
| [ ] Fee Attached | [ ] Licensing-related Papers | [ ] Appeal Communication to Board of Appeals and Interferences |
| [X] Amendment/Reply | [ ] Petition | [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)** |
| [ ] After Final | [ ] Petition to Convert to a Provisional Application | [ ] Proprietary Information |
| [ ] Affidavits/declaration(s) | [ ] Power of Attorney, Revocation Change of Correspondence Address | [ ] Status Letter |
| [ ] Extension of Time Request | [ ] Terminal Disclaimer | [ ] Other Enclosure(s) (please Identify below): |
| [ ] Express Abandonment Request | [ ] Request for Refund | |
| [ ] Information Disclosure Statement | [ ] CD, Number of CD(s) _____ | |
| [ ] Certified Copy of Priority Document(s) | [ ] Landscape Table on CD | |
| [X] Reply to Missing Parts/ Incomplete Application | Remarks | |
| [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53 | | |

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble | | |
| Date | September 11, 2017 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 CFR § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 11, 2017 Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

**5730928.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | Not Yet Assigned |
| Art Unit | 2631 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)1,010.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[ ] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below [ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 [X] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 280 | 140* | 70 | 600 | 300 | 150 | 720 | 360 | 180 | 730.00 |
| Design | 180 | 90 | 45 | 120 | 60 | 30 | 460 | 230 | 115 | |
| Plant | 180 | 90 | 45 | 380 | 190 | 95 | 580 | 290 | 145 | |
| Reissue | 280 | 140 | 70 | 600 | 300 | 150 | 2,160 | 1,080 | 540 | |
| Provisional | 260 | 130 | 65 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $140 small entity status filing fee for a utility application is further reduced to $70 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 80 | 40 | 20 |
| Each independent claim over 3 (including Reissues) | 420 | 210 | 105 |
| Multiple dependent claims | 780 | 390 | 195 |

| **Total Claims** | | **Extra Claims** | | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|---|
| _____ | - 20 or HP = | _____ | x | _____ | = | _____ |

HP = highest number of total claims paid for, if greater than 20.

**Multiple Dependent Claims**

| **Fee ($)** | **Fee Paid ($)** |
|---|---|
| | |

| **Indep. Claims** | | **Extra Claims** | | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|---|
| 4 | - 3 or HP = | 1 | x | 210.00 | = | 210.00 |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | | **Extra Sheets** | | **Number of each additional 50 or fraction thereof** | | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|---|---|---|
| _____ | - 100 = | _____ | /50 = | _____ | (round **up** to a whole number) x | _____ | = | _____ |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2051 Surcharge - Late filing fee | 70.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble | | | Date | September 11, 2017 |

**Certificate of Electronic Filing under 37 CFR § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 11, 2017 Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

**5730927.1**

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/639,223

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | 70 | | N/A | |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | 300 | | N/A | |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | 360 | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 20 minus 20 = | * | x 40 = | 0.00 | OR | | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 4 minus 3 = | * 1 | x 210 = | 210 | | | |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | 0.00 | | | |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | 0.00 | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | 940 | | TOTAL | |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE($) | ADDITIONAL FEE($) | OR | RATE($) | ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | 2631 | 1010 | U0157.70023US03 | 20 | 4 |

**CONFIRMATION NO. 8089**

**UPDATED FILING RECEIPT**

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

OC000000094027358

Date Mailed: 09/14/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

**Applicant(s)**

University of South Florida, Tampa, FL;
The Regents of the University of Michigan, Ann Arbor, MI;

**Power of Attorney:** None

**Domestic Priority data as claimed by applicant**

This application is a CON of 10/378,956 03/03/2003 ABN
which claims benefit of 60/360,768 03/01/2002

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

**Permission to Access Application via Priority Document Exchange:** Yes

**Permission to Access Search Results:** Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

**If Required, Foreign Filing License Granted:** 07/10/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/639,223**

**Projected Publication Date:** 12/21/2017

**Non-Publication Request:** No

**Early Publication Request:** No
**** SMALL ENTITY ****
**Title**

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

**Preliminary Class**

375

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**NOT GRANTED**

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 |

**CONFIRMATION NO. 8089**

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

**PUBLICATION NOTICE**

*OC000000096240740*

**Title:**MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

**Publication No.**US-2017-0362182-A1
**Publication Date:**12/21/2017

## NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 05/08/2018

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MASSACHUSETTS 02210-2206
UNITED STATES OF AMERICA

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/08/2018 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1625 | **AIA Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 11 September 2017.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 1-2,4-5,9-18,25-26,29-30 and 33-34 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 1-2,4-5,9-18,25-26,29-30 and 33-34 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***DETAILED ACTION***

***Election/Restriction***

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2, 4, 5, and 9-18, drawn to a multiple component phase composition comprising a solid phase that is sustained by intermolecular interactions between two or more molecular entities wherein as least one of the molecular entities is a pharmaceutical molecule, classified in C07D213/02.

II. Claims 25 and 26, drawn to a method of identifying complementary chemical functionalities on order to form a supramolecular synthon in which one step is identifying a chemical functionality that is not capable of disrupting non-covalent bonding within the supramolecular synthon, classified in C07D213/02.

III. Claims 29 and 30, drawn to a method of identifying complementary chemical functionalities on order to form a supramolecular synthon in which one step is identifying a chemical functionality that is capable of disrupting non-covalent bonding within the supramolecular synthon, classified in C07D213/02.

IV. Claims 33 and 34, drawn to a method of identifying complementary chemical functionalities in order to form a supramolecular synthon, classified in C07D213/02.

The inventions are independent or distinct, each from the other because:

Inventions I-IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are multiply divergent. Whereas invention I is drawn to a multiple component composition, inventions II-IV are drawn to different methods. Inventions II and III are different due to the following difference: in group II, the

chemical functionality **is not capable of disrupting non-covalent bonding** within the supramolecular synthon; and in group III, the chemical functionality **is capable of disrupting non-covalent bonding** within the supramolecular synthon. Invention IV is drawn to method of identifying complementary functionalities (which is not co-extensive with an invention of group II or III).

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

--the inventions require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search strategies or search queries).

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner

finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

This application contains claims directed to the following patentably distinct species at least two species of which one is a pharmaceutical molecule. The species are independent or distinct because claim 10 describes groups of compounds which are different in structure and function. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 2, 4, 5, 9-18, 24, 25, 29, 30, 33, and 34 are generic. In the election, a group of compounds meeting the metes and bounds of claim 1, 24, 29, or 33 must be elected.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

--the inventions require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search strategies or search queries).

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely

traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 8:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-372-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available

through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1625

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 8, 2018 Signature: /Taryn Bollers/ (Taryn Bollers)

## AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Restriction/Election of Species Requirement, dated May 8, 2018, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action was July 8, 2018. A four-month extension of time from July 8, 2018, up to and including November 8, 2018, is hereby respectfully requested, and the extension fee is being paid using the credit card payment option of the USPTO's Electronic Filing System. Applicant thus submits that the present Response is timely submitted on Thursday, November 8, 2018.

Please amend the above-identified U.S. patent application as follows:

**Amendments to the Claims** are reflected in the Listing of Claims, which begins on page 2 of this paper.

**Remarks** begin on page 5 of this paper.

## AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1 – 36. (Canceled)

37. (New) 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-crystal 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-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

38. (New) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

39. (New) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 118 of 415

40. (New) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and one co-crystal former.

41. (New) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of one active pharmaceutical ingredient (API) and one co-crystal former.

42. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a group selected from acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, and nitro groups.

43. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an acid.

44. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amine.

45. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amide.

46. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an alcohol.

47. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 119 of 415

48. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a heterosynthon.

49. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon and a heterosynthon.

50. (New) The pharmaceutical composition of claim 48, wherein the heterosynthon comprises an alcohol/amine interaction.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 120 of 415

## REMARKS

Claims 1-2, 4-5, 9-18, 25-26, 29-30, and 33-34 were pending and under consideration by the Examiner. By this amendment, claims 1-36 are canceled and new claims 37-50 are entered. Support for new claims 37-50 can be found throughout the Application as originally filed. No new matter is added to the Application by the present Amendment.

The Restriction/Election Requirement set forth in the Office Action of May 8, 2018 is moot in view of the foregoing amendments. Applicant submits that new claims 37-50 are drawn to a single invention.

Applicant believes all fees due with this Response are being paid by credit card. However, if any additional fees are due, please charge them, or credit any overpayment, to our Deposit Account No. 23/2825, under Docket No. U0157.70023US03, from which the undersigned is authorized to draw.

Dated: November 8, 2018

Respectfully submitted,

By____/David F. Cauble/___
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1625 |
| Practitioner Docket No. | U0157.70023US03 |

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)1,100.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 300 | 150* | 75 | 660 | 330 | 165 | 760 | 380 | 190 | |
| Design | 200 | 100 | 50 | 160 | 80 | 40 | 600 | 300 | 150 | |
| Plant | 200 | 100 | 50 | 420 | 210 | 105 | 620 | 310 | 155 | |
| Reissue | 300 | 150 | 75 | 660 | 330 | 165 | 2,200 | 1,100 | 550 | |
| Provisional | 280 | 140 | 70 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 460 | 230 | 115 |
| Multiple dependent claims | 820 | 410 | 205 |

| **Total Claims** | | **Extra Claims** | **Fee ($)** | | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|---|---|
| | - or HP = | | x | = | | **Fee ($)** | **Fee Paid ($)** |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | | **Extra Claims** | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|
| | - or HP = | | x | = | |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | | **Extra Sheets** | | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|---|---|
| | - 100 = | | /50 = | (round **up** to a whole number) x | | = |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2254 Extension for response within fourth month | 1,100.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | November 8, 2018 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 8, 2018 Signature: /Taryn Bollers/ (Taryn Bollers)

**6751023.1**

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) U0157.70023US03 |
|---|---|
| Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| Art Unit 1625 | Examiner N. E. Jarrell |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|---|
| ☐ | One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☐ | Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ |
| ☐ | Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☒ | Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ 1,100.00 |
| ☐ | Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. ~~Form PTO-2038 is attached.~~

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

☐ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 73,490 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

| /David F. Cauble/ | November 8, 2018 |
|---|---|
| Signature | Date |
| David F. Cauble, PhD, JD | 617.646.8000 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

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Dated: November 8, 2018 Signature: /Taryn Bollers/ (Taryn Bollers)

**6751027.1**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Taryn Bollers |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 4 months with $0 paid | 2254 | 1 | 1100 | 1100 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1100** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 34252236 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Taryn Bollers |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 08-NOV-2018 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:00:22 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $1100 |
| RAM confirmation Number | 110918INTEFSW15020000 |
| Deposit Account | 232825 |
| Authorized User | Wolf Greenfield |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.21 (Miscellaneous fees and charges) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | U015770023US03-TRN-DFC.pdf | 26448<br>bcc607dec3224176570e7f620729df195ee964e9 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | | U015770023US03-ERRRAMN-DFC.pdf | 32537<br>21be657227afde2b7e072888794 3a6df9b2447c3 | yes | 5 |
| | **Multipart Description/PDF files in .zip description** | | | | |
| | **Document Description** | | **Start** | **End** | |
| | Response to Election / Restriction Filed | | 1 | 1 | |
| | Claims | | 2 | 4 | |
| | Applicant Arguments/Remarks Made in an Amendment | | 5 | 5 | |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 32550<br>8ccfa08e7bc7d0c93da7d52e80b922284fbf523a | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Extension of Time | U015770023US03-EXT-DFC.pdf | 24620<br>00b5079b5a4a5fcf7f4cbc5bacfcc7c5010edc66 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 30939<br>157ce3bbd43f3e11529bbcad960183e7073ebf61 | no | 2 |

| Warnings: | |
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| Information: | |
| Total Files Size (in bytes): | 147094 |

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
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**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

| **TRANSMITTAL FORM** *(to be used for all correspondence after initial filing)* | | | |
|---|---|---|---|
| | | Application Number | 15/639,223-Conf. #8089 |
| | | Filing Date | June 30, 2017 |
| | | First Named Inventor | Michael J. Zaworotko |
| | | Art Unit | 1625 |
| | | Examiner Name | N. E. Jarrell |
| Total Number of Pages in This Submission | | Attorney Docket Number | U0157.70023US03 |

**ENCLOSURES (*Check all that apply*)**

| | | |
|---|---|---|
| [X] Fee Transmittal Form | [ ] Drawing(s) | [ ] After Allowance Communication to TC |
| [ ] Fee Attached | [ ] Licensing-related Papers | [ ] Appeal Communication to Board of Appeals and Interferences |
| [ ] Amendment/Reply | [ ] Petition | [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)** |
| [ ] After Final | [ ] Petition to Convert to a Provisional Application | [ ] Proprietary Information |
| [ ] Affidavits/declaration(s) | [ ] Power of Attorney, Revocation Change of Correspondence Address | [ ] Status Letter |
| [X] Extension of Time Request | [ ] Terminal Disclaimer | [X] Other Enclosure(s) (please Identify below): |
| [ ] Express Abandonment Request | [ ] Request for Refund | Amendment and Response to Restriction/Election Requirement |
| [ ] Information Disclosure Statement | [ ] CD, Number of CD(s) _____ | |
| [ ] Certified Copy of Priority Document(s) | [ ] Landscape Table on CD | |
| [ ] Reply to Missing Parts/ Incomplete Application | Remarks | |
| [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53 | | |

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | November 8, 2018 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

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Dated: November 8, 2018 Signature: /Taryn Bollers/ (Taryn Bollers)

**6751025.1**

| FORM PTO-1449/A and B (modified PTO/SB/08) | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 1 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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| Examiner's Initials # | Cite No. | U.S. Patent Document | | Name of Patentee or Applicant of Cited Document | Date of Publication or Issue of Cited Document MM-DD-YYYY |
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*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378956 , filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

| FORM PTO-1449/A and B (modified PTO/SB/08)<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 2 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 3 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 4 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 5 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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|---|---|
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| FORM PTO-1449/A and B (modified PTO/SB/08) | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet 6 of 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
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| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
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| EXAMINER: | DATE CONSIDERED: |
|---|---|
| | |

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378956 , filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

| FORM PTO-1449/A and B (modified PTO/SB/08)<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 30 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

| | | | |
|---|---|---|---|
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| EXAMINER: | DATE CONSIDERED: |
|---|---|
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# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378956 , filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 34253019 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Chelsie Bailey |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 08-NOV-2018 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:33:19 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| Submitted with Payment | no |
|---|---|

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Foreign Reference | CA1148020A1.pdf | 1069724<br>63d21f07e46a9e6b5155f030b13a1e9212b5a14f | no | 29 |
| **Warnings:** | | | | | |

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|---|---|---|---|---|---|
| **Information:** | | | | | |
| 2 | Other Reference-Patent/App/Search documents | U015770023WO00_ISR_mailed_10-24-2003_QC.pdf | 322961<br>670b5740aa18e0f8aeca9e68a6db7a782bcbe326 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Non Patent Literature | The_Merck_Index_12th_ed_1996_Entries_5683_9094_QC.pdf | 835931<br>e1eadff9e41f657b41af609497c359a81ebfb6c7 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Non Patent Literature | Ito_et_al_Tetrahedron_2000_v56_p6833_QC.PDF | 749913<br>0849a9d3ede60fc6395e7d6725f72fa47ae4590f | no | 12 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Non Patent Literature | Iwamoto_et_al_Acta_Cryst_1989_vC45_p1110_QC.PDF | 226687<br>aecef3be960afc2318ea5de13ba39a3772056dc6 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | Jiang_et_al_Anti_Cancer_Drugs_2000_v11_p49_QC.pdf | 131612<br>40fcf2a53ba8adc161936d35ab131d475309ba6b | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | Non Patent Literature | Smith_et_al_J_Phys_Chem_B_2001_v105_p5818_QC.pdf | 357514<br>ae64037c687307745d3745db337f903ef99fef76 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | Miscellaneous Incoming Letter | U015770023US03-TRN-DFC.pdf | 26275<br>d568ff74609eccf71fac4c9c103f1c6e97e26a9b | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

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| 9 | Transmittal Letter | U015770023US03-IDSBODY-DFC.pdf | 31149<br>95e840f3d2f8196732c86b582bd3ce25908abeae | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | Information Disclosure Statement (IDS) Form (SB08) | U015770023US03-IDS1449-DFC.pdf | 300166<br>9b90f04e3fa7ef0639ffac421f5b09e733618edd | no | 30 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 11 | Other Reference-Patent/App/Search documents | U015770023EP00_ESR_mailed_11-22-2006_QC.pdf | 516809<br>d76f239178f9c8ff9ecaf1b3ea62fb31d0300fe5 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 4568741 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**<u>New Applications Under 35 U.S.C. 111</u>**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/06662

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/25 C07C69/86 C07D233/74 C07C57/30 C07C57/58
C07D223/26 C07D213/22 C07D213/16 C07C47/544 C07D213/82
C07D275/06 C07D213/80 C07C53/08 C07C61/125 C07C50/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | BAILEY WALSH ET AL.: "Crystal engineering of the composition of pharmaceutical phases" CHEM. COMMUN., 2003, pages 186-187, XP002248827 the whole document | 1-20,22 |
| P,X | OSWALD, I.D.H. ET AL.: "The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors" ACTA CRYST., vol. B58, 2002, pages 1057-1066, XP009014505 the whole document | 1-9, 11-19,21 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 July 2003 | 24. 10. 03 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Johnson, C. |

Form PCT/ISA/210 (second sheet) (July 1992)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 163 of 415

## INTERNATIONAL SEARCH REPORT

International Application No
PCT/ 03/06662

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EL-NAHHAS S A: "PHYSICO-CHEMICAL CHARACTERISTICS OF CARBAMAZEPINE-BETA-CYCLODEXTRININ CLUSION COMPOUNDS AND CARBAMAZEPINE-PEG SOLID DISPERSIONS" PHARMAZIE, VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, DD, vol. 51, no. 12, 1 December 1996 (1996-12-01), pages 960-963, XP000633833 ISSN: 0031-7144 paragraph [3.2.4.3] | 1-9, 11-19,24 |
| X | JAMES E. F. REYNOLDS, EDITOR: "Martindale. The extra pharmacopoeia" 1993, THE PHARMACEUTICAL PRESS , LONDON , XP002248828 page 1431 (e.g. acetaminophen, aspirin, and caffeine tablets), page 1465 (e.g. Aspirin plus C), page 1521 (Codafen Continus), page 1610 (Gaboril Complex) | 1-9, 11-23 |
| X | GB 1 297 261 A (E.R. SQUIBB & SONS INC.) 22 November 1972 (1972-11-22) the whole document | 1-9, 11-19,21 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 164 of 415

# INTERNATIONAL SEARCH REPORT

In ional application No.
PCT/US 03/06662

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25,29,33
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iii) PCT - Scheme, rules and method for performing mental acts
The methods of independent claims 25, 29 and 33 comprise 4 purely intellectual steps and therefore constitute methods for performing mental acts, for which no search is necessary.

2. [X] Claims Nos.: 1-9,11-24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

10, 26-28, 30-32, 34-36 (all part)

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 165 of 415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 25,29,33

Rule 39.1(iii) PCT - Scheme, rules and method for performing mental acts

The methods of independent claims 25, 29 and 33 comprise 4 purely intellectual steps and therefore constitute methods for performing mental acts, for which no search is necessary.

---

Continuation of Box I.2

Claims Nos.: 1-9,11-24

The technical features of claim 1 are: i) a solid composition ii) having at least 2 components iii) at least one of which is a pharmaceutical molecule.

Pharmaceuticals which are administered in a solid form (e.g. as tablets) rarely contain 100% pharmaceutical - in the majority of cases other components such as fillers are present. All such pharmaceutical compositions fall within the scope of claim 1. None of the features of dependent claims 2-9 appear to add any characteristic that would distinguish the subject matter of these claims from the vast majority of solid pharmaceutical compositions currently on the market. An extract of "Martindale" has been cited to illustrate examples of compositions falling within the scope of claim 9 (see e.g. acetaminophen, aspirin and caffeine tablets, acetaminophen and codeine tablets, aspirin and ascorbic acid). Pharmazie 51 (1996) 12 960-963 is cited to illustrate an example of a carbamazepine composition falling within present claim 9. The dependent claims 11-24 also do not contain any feature that would distinguish their subject matter from well-known pharmaceutical preparations such as those cited in the documents mentioned above.

In view of the huge number of pharmaceutical compositions that fall within the scope of present claims 1-9 and 11-24, of which the compositions cited above form only an arbitrary selection, it is not possible to perform any meaningful search of these claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 166 of 415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 167 of 415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are acetaminophen, 4,4'-bipyridine and water, and its method of preparation.

---

2. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are phenytoin and pyridine, and its method of preparation.

---

3. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are aspirin and 4,4'-bipyridine, and its method of preparation.

---

4. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are ibuprofen and 4,4'-bipyridine, and its method of preparation.

---

5. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are flurbiprofen and 4,4'-bipyridine, and its method of preparation.

---

6. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are flurbiprofen and trans-1,2-bis(4-pyridyl)ethylene, and its method of preparation.

---

7. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and p-phthalaldehyde, and its method of preparation.

---

8. claims: 10, 26-28, 30-32, 34-36 (all part)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 168 of 415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Composition according to claim 1 wherein the two or more components are carbamazepine and nicotinamide, and its method of preparation.

---

9. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and saccharin, and its method of preparation.

---

10. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 2,6-pyridinedicarboxylic acid, and its method of preparation.

---

11. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 5-nitroisophthalic acid, and its method of preparation.

---

12. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and acetic acid, and its method of preparation.

---

13. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid, and its method of preparation.

---

14. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and benzoquinone, and its method of preparation.

---

15. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and butyric acid, and its method of preparation.

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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 169 of 415

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

16. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and dimethyl sulfoxide, and its method of preparation.

---

17. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and formamide, and its method of preparation.

---

18. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and formic acid, and its method of preparation.

---

19. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and trimesic acid, and its method of preparation.

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## INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No
PCT/US 03/06662

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| GB 1297261 A | 22-11-1972 | CA 948642 A1 | 04-06-1974 |
| | | CH 507253 A | 15-05-1971 |
| | | DE 2000210 A1 | 23-07-1970 |
| | | FR 2034467 A1 | 11-12-1970 |

Form PCT/ISA/210 (patent family annex) (July 1992)

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1625 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

  Form PTO-1449

  Copies of cited references

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | November 8, 2018 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 CFR § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 8, 2018 Electronic Signature for Chelsie Bailey: /Chelsie Bailey/

**6224460.1**

DOCKET NO.: U0157.70023US03

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

**Certificate of Electronic Filing under 37 CFR §1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 8, 2018 Electronic Signature for Chelsie Bailey: /Chelsie Bailey/

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed before the mailing of a first Office Action on the merits in the above-identified case.

No fee or certification is required.

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

| Serial No. | Filing Date | Inventor(s) | Docket No. |
|---|---|---|---|
| *10/378,956 | March 3, 2003 | Zaworotko et al. | U0157.70023US01 |
| *14/179,862 | February 13, 2014 | Zaworotko et al. | U0157.70023US02 |

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Private PAIR .

The undersigned would like to bring to the Examiner's attention the enclosed search report or other communication from a corresponding or related International or Foreign National Application:

| Serial No. | Date of Mailing | Type(s) of Communication | Docket No. |
|---|---|---|---|
| EP 03711407.1 | 11-22-2006 | European Search Report | U0157.70023EP00 |
| PCT/US2003/06662 | 10-24-2003 | International Search Report | U0157.70023WO00 |

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /David F. Cauble/
David F. Cauble, PhD, JD, Reg. No. 73,490
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US03
Date: November 8, 2018

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>15/639,223 | Filing Date<br>06/30/2017 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY**: ☐ LARGE ☒ SMALL ☐ MICRO

## APPLICATION AS FILED – PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | RATE ($) | FEE ($) |
|---|---|---|---|---|
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | **11/08/2018** | | | | | | |
| | Total (37 CFR 1.16(i)) | * 14 | Minus | ** 36 | = 0 | X $50 = | 0 |
| | Independent (37 CFR 1.16(h)) | * 1 | Minus | ***9 | = 0 | X $230 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | **0** |

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * | Minus | ** | = | X $ = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | X $ = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | |
| | | | | | | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
SHARON M. WEST

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 02/26/2019

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/26/2019 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1625 | **AIA Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 08 November 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 30 June 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 8 November 2018.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Election/Restrictions***

Applicant's election without traverse of a cocrystal of an active pharmaceutical ingredient and a conformer in the reply filed on 8 November 2018 is acknowledged.

***Information Disclosure Statement***

The information disclosure statements filed 8 November 2018 are acknowledged and considered.

***Claim Rejections - 35 USC § 112***

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

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-50 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for preparation of cocrystals of examples 1-17 in specification, does not reasonably provide enablement for preparation of the scope of cocrystals claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some

> experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

*The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a stoichiometric cocrystal of an active pharmaceutical ingredient and a coformer. Thus, the claims taken together with the specification imply a stoichiometric cocrystal can be formed.

*The state of the prior art and (4) the predictability or unpredictability of the art:*

KUMAR (*Indian Journal of Pharmaceutical Sciences*, **2017**, *79(6)*, 858-71) describes that many steps are required to make a cocrystal (page 862, column 2, paragraph 3 to page 865, column 1, paragraph 1). Additionally, different methods of making cocrystalas are known (page 865, column 1, paragraph 2 to page 866, column 1, paragraph 4). The formation of cocrystals has challenges: selection of a suitable conformer and stability in the presence of excipients (page 867, column 2, paragraph 2 to page 868, column 1, paragraph 2). Development, screening, and evaluation of a new cocrystals of drugs require lot of time due to the steps required for each part.

*The relative skill of those in the art:*

While the artisan generally would have an advanced degree in cocrystal formation and analysis, their high level of skill and knowledge is insufficient to overcome the lack of understanding as to how cocrystal formation occurs.

*The amount of direction or guidance presented and the presence or absence of working examples:*

The specification has provided guidance for preparation of the following cocrystals (examples 1-17 in specification):acetaminophen: 4,4'-bipyridine:water (1:1:1); phenytoin/pyridine (1:1); aspirin and 4,4'-bipyridine (2:1); ibuprogen and 4,4'-bipyridine (2:1); flurbiprofen and [4,4'-bipyridine or trans-1,2-bis(4-pyridyl)ethylene] (2:1); carbamazepine and [one of *p*-phthalaldehyde, nicotinamide, saccharin, 5-nitroisophthalic acid, acetic acid, 1,3,5,7-adamantanetetracarboxylic acid, benzoquinone, butyric acid, DMSO, or formamide] (1:1); carbamazepine and 2,6-pyridinecarboxylic acid (2:3)

However, the specification does not provide guidance for the scope of stoichiometric cocrystals claimed.

*The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to cocrystal formation and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

***Claim Rejections - 35 USC § 102***

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 37-42, 45, 46, and 48 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by HSU (*Acta Crystallographica*, **1974**, *B30*, 843-846, cited in IDS). Hsu describes a 1:1 cocrystal of salicylamide and 5-ethyl-5-isoamylbarbituric acid (title and abstract). Hydrogen bonding is used to bind the compounds together (abstract; page 845, column 2 to page 846, column 1, paragraph 1).

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application,

or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37and 45 of copending Application No. 14/179862 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 14/179862. Claim 37 of '862 overlaps with instant claims 37 and 39. Claim 45 of '862 is embraced by instant claims 37 and 40.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Conclusion***

Claims 37-50 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 8:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-372-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1625

| Notice of References Cited | Application/Control No. 15/639,223 | Applicant(s)/Patent Under Reexamination Zaworotko et al. | |
|---|---|---|---|
| | Examiner NOBLE E JARRELL | Art Unit 1625 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | | | | | |
| | B | | | | | |
| | C | | | | | |
| | D | | | | | |
| | E | | | | | |
| | F | | | | | |
| | G | | | | | |
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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 185 of 415

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
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| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1625 |

| CPC - Searched* | | |
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| Symbol | Date | Examiner |
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| Symbol | Date | Examiner |
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| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |
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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 186 of 415

| FORM PTO-1449/A and B (modified PTO/SB/08) | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet 1 of 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
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| | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
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| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
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| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
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| FORM PTO-1449/A and B (modified PTO/SB/08) **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
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| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 30 | of | 30 | GROUP ART UNIT:1625 | EXAMINER: Not Yet Assigned |

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|---|---|---|---|
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| EXAMINER: | DATE CONSIDERED: |
|---|---|
| /NOBLE E JARRELL/ | 02/19/2019 |

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378956 , filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

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# BIB DATA SHEET

**CONFIRMATION NO. 8089**

| SERIAL NUMBER | FILING or 371(c) DATE<br>RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | 424 | 1625 | U0157.70023US03 |

**APPLICANTS**

University of South Florida, Tampa, FL;
The Regents of the University of Michigan, Ann Arbor, MI;

**INVENTORS**

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

**** CONTINUING DATA ***************************

This application is a CON of 10/378,956 03/03/2003 ABN
which claims benefit of 60/360,768 03/01/2002

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
07/10/2017

| Foreign Priority claimed ❑ Yes ☑ No<br>35 USC 119(a-d) conditions met ❑ Yes ☑ No<br>Verified and Acknowledged /NOBLE E JARRELL/ Examiner's Signature | ❑ Met after Allowance<br>Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | FL | 22 | 20 | 4 |

**ADDRESS**

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206
UNITED STATES

**TITLE**

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

| FILING FEE RECEIVED | | |
|---|---|---|
| 1010 | FEES: Authority has been given in Paper<br>No._____ to charge/credit DEPOSIT ACCOUNT<br>No._____ for following: | ❑ All Fees<br>❑ 1.16 Fees (Filing)<br>❑ 1.17 Fees (Processing Ext. of time)<br>❑ 1.18 Fees (Issue)<br>❑ Other _____<br>❑ Credit |

DOCKET NO.: U0157.70023US03

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

**Certificate of Electronic Filing under 37 CFR §1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 8, 2018 Electronic Signature for Chelsie Bailey: /Chelsie Bailey/

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed before the mailing of a first Office Action on the merits in the above-identified case.

No fee or certification is required.

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.



ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

| Serial No. | Filing Date | Inventor(s) | Docket No. |
|---|---|---|---|
| *10/378,956 | March 3, 2003 | Zaworotko et al. | U0157.70023US01 |
| *14/179,862 | February 13, 2014 | Zaworotko et al. | U0157.70023US02 |

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Private PAIR .

The undersigned would like to bring to the Examiner's attention the enclosed search report or other communication from a corresponding or related International or Foreign National Application:

| Serial No. | Date of Mailing | Type(s) of Communication | Docket No. |
|---|---|---|---|
| EP 03711407.1 | 11-22-2006 | European Search Report | U0157.70023EP00 |
| PCT/US2003/06662 | 10-24-2003 | International Search Report | U0157.70023WO00 |

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

/NOBLE E JARRELL/ 02/20/2019

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /David F. Cauble/
David F. Cauble, PhD, JD, Reg. No. 73,490
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US03
Date: November 8, 2018

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

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                 E CRYSTALLIZATION/CT
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L3               QUE SPE=ON  ABB=ON  PLU=ON  CRYSTALLINITY+OLD/CT
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                 E E3+ALL
L4               QUE SPE=ON  ABB=ON  PLU=ON  "CRYSTAL STRUCTURE"+PFT,NT/CT
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                 E E3+ALL
L5               QUE SPE=ON  ABB=ON  PLU=ON  "CRYSTAL STRUCTURE"+PFT,NT/CT
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                 E E2
                 E E3+OLD,NT1
L6               QUE SPE=ON  ABB=ON  PLU=ON  DRUGS+PFT,NT1/CT
L7         16288 SEA SPE=ON  ABB=ON  PLU=ON  L6 AND (L2 OR L3 OR L4 OR L5)
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L9               QUE SPE=ON  ABB=ON  PLU=ON  PD<=20010301
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L11         1160 SEA SPE=ON  ABB=ON  PLU=ON  L7 AND (L8 OR L9 OR L10)
L12            0 SEA SPE=ON  ABB=ON  PLU=ON  L11 AND L1
L13            4 SEA SPE=ON  ABB=ON  PLU=ON  L11 AND L6 (L) (COCRYSTAL? OR CO
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| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 12384 | (Zaworotko rodriguez (2a) hornedo moulton).in. | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:38 |
| L2 | 128 | c07d223/26.cpc. | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:38 |
| L3 | 5 | l1 and l2 | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:39 |
| L4 | 9 | l2 and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:44 |
| L5 | 5 | l4 and l3 | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:44 |
| L6 | 4 | l4 not l5 | US-PGPUB; USPAT | OR | OFF | 2019/02/19 17:45 |

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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

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Dated: July 23, 2019 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

## RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

In response to the Office Action dated February 26, 2019, the time being extended to the present by the attached Petition for Extension of Time, Applicant respectfully requests entrance of the following Amendments and consideration of the following Remarks.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks/Arguments** begin on page 5 of this paper.

## AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1 – 36. (Canceled)

37. (Previously presented) 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-crystal 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-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

38. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

39. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 225 of 415

40. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and one co-crystal former.

41. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of one active pharmaceutical ingredient (API) and one co-crystal former.

42. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a group selected from acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, and nitro groups.

43. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an acid.

44. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amine.

45. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amide.

46. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an alcohol.

47. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 226 of 415

48. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a heterosynthon.

49. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon and a heterosynthon.

50. (Previously presented) The pharmaceutical composition of claim 48, wherein the heterosynthon comprises an alcohol/amine interaction.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 227 of 415

## REMARKS

Prior to entry of the instant amendments, claims 37-50 were pending in the Application. No claims have been amended in this response. Each of the rejections levied by the Examiner is addressed in turn below.

*Claim Rejections under 35 U.S.C. § 112*

Claims 37-50 are rejected under 35 U.S.C. 112(a), first paragraph, because the specification, while being enabling for the preparation of co-crystals of examples 1-17 in the specification, allegedly does not enable preparation of the scope of co-crystals as claimed. Applicant respectfully disagrees, and as a preliminary matter notes that the Application discloses 19 working examples.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (*United States v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed. Cir. 1988)) This standard is satisfied by the present application.

In paragraph [0043], the present application discloses a method of preparing a multiple-component solid phase composition composed of an API and at least one co-crystal former involving techniques such as such as crystallization from solution, cooling the melt, sublimation and grinding. A "multiple-component phase" is defined in paragraph [0047] as any solid material (phase) that is sustained by intermolecular interactions between at least two independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. "Pharmaceutical entities" are defined in paragraph [0048] and numerous examples of chemical functional groups that are capable of forming supramolecular synthons are provided.

Paragraphs [0040]-[0042] disclose methods for identifying complementary chemical functional groups with which to form the desired supramolecular synthons. The methods involve

- evaluating the structure of an API, which can include determining its crystal structure;



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 228 of 415

- determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules;
- identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthons with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and
- identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

In paragraphs [0057]-[0178], the Applicant discloses the application of the preceding method to the discovery of 19 different co-crystals. MPEP 2164.02(III) states that:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art…would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus ***only where adequate reasons are advanced*** by the examiner ***to establish that a person skilled in the art could not use the genus as a whole without undue experimentation***. (Emphasis added)

In the Office Action, no adequate reasons have been advanced to support the rejection of the claimed genus. For example, page 3 of the Office Action references Kumar et al. for allegedly teaching that "many steps are required to make a cocrystal…and that different methods of making cocrystals are known…" Applicant respectfully notes that the present Application itself discloses a method having several steps, and discloses different methods of making cocrystals. In this regard, Kumar et al. merely reiterates the teachings of the present Application. Kumar et al. allegedly teaches that "the formation of cocrystals has challenges: selection of a suitable conformer…" In this regard, Applicant notes that the present Application discloses a method of selecting a suitable conformer on the basis of complementary chemical functionality. Kumar et al. neither teaches nor suggests the inoperability of the methods disclosed in the present Application. Kumar et al. allegedly teaches that the "development, screening, and evaluation of new cocrystals of drugs [requires a] lot of time due to the steps required…" Even assuming, arguendo, that this statement is



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 229 of 415

accurate, it is not evidence that undue experimentation is required to make and use the claimed invention. MPEP 2164.01 states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." In fact, Kumar et al. itself discloses that the art engages in such experimentation, as described below.

Page 3 of the Office Action states that although the relative skill of those in the art is high, "their…skill and knowledge is insufficient to overcome the lack of understanding as to how cocrystal formation occurs." Applicant disagrees. The Office has not identified any teaching of Kuman et al. that indicates a lack of understanding. In fact, Kuman et al. makes no such statement.

Page 4 of the Office Action states that the "specification does not provide guidance for the scope of the stoichiometric crystals claimed." In response, Applicant refers the Office to MPEP 2164.02(III), quoted above, and maintains that no adequate reasons have been advanced to support the rejection of the claimed genus.

On page 4, the Office Action refers to "the high unpredictability" evidenced by Kumar et al, and the "lack of guidance" provided by the specification. As discussed above, the specification provides abundant guidance, and there is no evidence that the guidance provided is insufficient to enable the full scope of the claimed invention. Furthermore, Applicant notes that nowhere in Kumar et al. is there a teaching that cocrystal formation is unpredictable. To the contrary, Kumar et al. teaches that:

- "A ***prediction can be made*** by ΔpKa value whether cocrystals are formed or not." (page 859, second column, first paragraph);
- "***Cocrystals…formation can be predicted*** by proton transfer between acid and base. The formation of…cocrystals can be predicted by determining the ΔpKa=[pKa (base)-pKa (acid)]" (page 863, first column, third paragraph);
- "The miscibility of the components in the solid state ***could predict the cocrystal formation***." (page 863, second column, fourth paragraph); and
- "FTIR spectroscopy is ***used to predict*** the intermolecular interactions and compatibility study between drug and coformers." (page 866, first column, fifth paragraph)

At least for the foregoing reasons, Applicant requests withdrawal of the rejection of the claims under 35 U.S.C. 112(a), first paragraph.

*Claim Rejections under 35 U.S.C. § 102*

Claims 37-42, 45, 46, and 48 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Hsu (*Acta Crystallographica*, 1974, B30, 843-846, cited in IDS), hereinafter referred to as "Hsu". Applicant respectfully traverses this rejection.

Hsu allegedly teaches a 1:1 cocrystal of salicylamide and 5-ethyl-5-isoamylbarbituric acid. However, Hsu does not teach a pharmaceutical composition, as claimed. As such, Hsu does not teach all elements of claim 37, and therefore does not anticipate claim 37, or claims depending therefrom. Accordingly, Applicant requests withdrawal of this rejection.

*Double Patenting*

Claims 37-50 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 45 of copending Application No. 14/179862. Applicant requests that the Examiner hold this rejection in abeyance until the claims are otherwise held to be in condition for allowance.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 231 of 415

## CONCLUSION

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

All fees due in connection with the filing of this paper are being paid by credit card. However, if additional fees are due with this filing, please charge our Deposit Account No. 23/2825, under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: July 23, 2019

Respectfully submitted,

By /David F. Cauble/_____
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 232 of 415

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 2 months with $0 paid | 2252 | 1 | 300 | 300 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **300** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 36667043 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 23-JUL-2019 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 16:10:14 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $300 |
| RAM confirmation Number | 072419INTEFSW16104700 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26316<br>b5814897e69d7bb05a3f89423ea21d4bb0c5dd66 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 32833<br>02eb296b0ee01e6aac8197b8673719200190e773 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Extension of Time | U015770023US03-EXT-DFC.pdf | 25045<br>4194c8df8ed07aaf003c2ed3d4a396c3bc7941f2 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | | U015770023US03-AMN-DFC.pdf | 65365<br>71b704dab0a5ab9579222eb07b2a82e4dfd868f6 | yes | 9 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Amendment/Req. Reconsideration-After Non-Final Reject | 1 | 1 |
| Claims | 2 | 4 |
| Applicant Arguments/Remarks Made in an Amendment | 5 | 9 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 30758<br>f4d54997a41da37b931e05ae082e89412bc8151a | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 180317 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) U0157.70023US03 |
|---|---|
| Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| Art Unit 1625 | Examiner N. E. Jarrell |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☒ Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ 300.00 |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. ~~Form PTO-2038 is attached~~.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 73,490 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

| /David F. Cauble/ | July 23, 2019 |
|---|---|
| Signature | Date |
| David F. Cauble, PhD, JD | 617.646.8000 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 23, 2019 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**7399581.1**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1625 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | July 23, 2019 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 23, 2019 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**7399576.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1625 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)300.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 300 | 150* | 75 | 660 | 330 | 165 | 760 | 380 | 190 | |
| Design | 200 | 100 | 50 | 160 | 80 | 40 | 600 | 300 | 150 | |
| Plant | 200 | 100 | 50 | 420 | 210 | 105 | 620 | 310 | 155 | |
| Reissue | 300 | 150 | 75 | 660 | 330 | 165 | 2,200 | 1,100 | 550 | |
| Provisional | 280 | 140 | 70 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 460 | 230 | 115 |
| Multiple dependent claims | 820 | 410 | 205 |

| **Total Claims** | | **Extra Claims** | | **Fee ($)** | | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|---|---|---|
| 20 | - or HP = | | x | | = | | **Fee ($)** | **Fee Paid ($)** |
| | | | | | | | | |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | | **Extra Claims** | | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|---|
| | - or HP = | | x | | = | |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | | **Extra Sheets** | | **Number of each additional 50 or fraction thereof** | | **Fee ($)** | | **Fee Paid ($)** |
|---|---|---|---|---|---|---|---|---|
| | - 100 = | | /50 = | | (round **up** to a whole number) x | | = | |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2252 Extension for response within second month | 300.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | July 23, 2019 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 23, 2019 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**7399574.1**

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>15/639,223 | Filing Date<br>06/30/2017 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☐ LARGE ☑ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $40 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $210 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 07/23/2019 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 14 | Minus | ** 36 | = 0 | | x $50 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 1 | Minus | *** 9 | = 0 | | x $230 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /TINA J BARDEN/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 11/05/2019

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1625 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/05/2019 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1625 | **AIA (FITF) Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 23 July 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

**DETAILED ACTION**

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Response to Amendment***

The rejections of 26 February 2019 are overcome by the amendment filed 23 July 2019.

***Priority***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, 365(c), or 386(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of pre-AIA 35 U.S.C. 112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994)

The disclosure of the prior-filed application, Application No. 10/378956 fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application. Application 10/378956 does not disclose pharmaceutical composition comprising a co-crystal. Original claims of 3 March 2003 recite a multiple-component phase composition of with no mention of a pharmaceutically acceptable carrier. The specification provides no discussion of a pharmaceutical composition win a co-crystal. Examples 1-19 (page 17, paragraph [0056] to page 33, paragraph [00177]) describe co-crystals only. There is no discussion of a pharmaceutical composition comprising a co-crystal and a separate pharmaceutical acceptable carrier. Example 1 of 10/378956 is drawn to a crystalline complex of acetaminoiphen, 4,4'-bipyidine, and water. This co-crystal has no additional pharmaceutically acceptable carrier which is required by the instant claims set. Based on this analysis the effective filing of the instant application is 30 April 2017.

***Claim Rejections - 35 USC § 112***

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

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-50 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for preparation of cocrystals of examples 1-17 in specification, does not reasonably provide enablement for preparation of the scope of cocrystals claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

*The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a stoichiometric cocrystal of an active pharmaceutical ingredient and a co-former. Thus, the claims taken together with the specification imply a stoichiometric cocrystal can be formed.

*The state of the prior art and (4) the predictability or unpredictability of the art:*

MIRSOSHNYK (*Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341) describes that translational challenges are present in cocrystal design (page 334, section 2; sections 3 and 4, pages 337-340). The challenges include the following: stability of an active pharmacological ingredient; seeing studies that follow the development cycle all the way to the end product; systematically investigating the applicability of agglomeration techniques; and regulatory issues.

*The relative skill of those in the art:*

While the artisan generally would have an advanced degree in cocrystal formation and analysis, their high level of skill and knowledge is insufficient to overcome the lack of understanding as to how cocrystal formation occurs.

*The amount of direction or guidance presented and the presence or absence of working examples:*

The specification has provided guidance for preparation of the following cocrystals (examples 1-17 in specification):acetaminophen: 4,4'-bipyridine:water (1:1:1); phenytoin/pyridine (1:1); aspirin and 4,4'-bipyridine (2:1); ibuprofen and 4,4'-bipyridine (2:1); flurbiprofen and [4,4'-bipyridine or trans-1,2-bis(4-pyridyl)ethylene] (2:1); carbamazepine and [one of *p*-phthalaldehyde, nicotinamide, saccharin, 5-nitroisophthalic acid, acetic acid, 1,3,5,7-adamantanetetracarboxylic acid, benzoquinone, butyric acid, DMSO, or formamide] (1:1); carbamazepine and 2,6-pyridinecarboxylic acid (2:3)

The specification does not provide guidance for the scope of stoichiometric cocrystals claimed.

*The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to cocrystal formation and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

***Response to Arguments***

This rejection is maintained because the art shows that pharmaceutical cocrystal deign presently has challenges that need to be overcome. Applicants argue that the MPEP 21264.10 states that although experimentation may be complex, it is not considered undue. In light of Mirshnyk, these challenges still need to be overcome.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 37-49 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by MCMAHON (WO2006007448, published 19 January 2006). McMahon describes co-crystals of examples 1-11 (page 55, paragraph [00189] to page 63, paragraph [00235]). In these co-crystals, hydrogen bonding is used to bond the compounds of the co-crystals (pages 27-34, paragraph [00110]; page 57, table XXI). Different method of making the co-crystals are described (page 49, paragraph [00159] to page 52, paragraph [00174]). Pharmaceutical compositions comprising these co-crystals are described (page 35, paragraph [00113] to page 48, paragraph [00157]).

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-

processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37and 45 of copending Application No. 14/179862 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 14/179862. Claim 37 of '862 overlaps with instant claims 37 and 39. Claim 45 of '862 is embraced by instant claims 37 and 40.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Response to Arguments***

This rejection is maintained because applicants have decided to keep this rejection in abeyance.

***Conclusion***

Claims 37-50 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 9:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Kosar can be reached on 571-372-0913. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1625

| Notice of References Cited | Application/Control No. 15/639,223 | Applicant(s)/Patent Under Reexamination Zaworotko et al. | |
|---|---|---|---|
| | Examiner NOBLE E JARRELL | Art Unit 1625 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | | | | | |
| | B | | | | | |
| | C | | | | | |
| | D | | | | | |
| | E | | | | | |
| | F | | | | | |
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| | J | | | | | |
| | K | | | | | |
| | L | | | | | |
| | M | | | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | MIRSOSHNYK. Expert Opinion in Drug Delivery, 2009, 6(4), 333-341 (Year: 2009) |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 250 of 415

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1625 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| c07d223/26.cpc. and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | 02/19/2019 | NJ |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| Search Notes | Date | Examiner |
| c07d223/26.cpc. and (cocrystal co NEAR crystalcocrystals co near crystals).clm. | 02/19/2019 | NJ |
| stn registry and hcaplus | 02/19/2019 | NJ |
| inventor search in PALM and EAST | 02/19/2019 | NJ |
| stn registry and hcaplus | 10/30/2019 | NJ |

| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| C07D | 223/26 | 02/19/2019 | NJ |

| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |
|---|---|



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 251 of 415

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     FILE 'HCAPLUS' ENTERED AT 12:50:10 ON 30 OCT 2019
L1             4 SEA SPE=ON  ABB=ON  PLU=ON  US20170362182 /PN
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                 E E3+ALL
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                 E E26+ALL
L3               QUE SPE=ON  ABB=ON  PLU=ON  "MOLECULAR ASSOCIATION"+NT/CT
                 E SELF-ASSEMBLY/CT
                 E E3+ALL
L4               QUE SPE=ON  ABB=ON  PLU=ON  SELF-ASSEMBLY+OLD,NT/CT
                 E SUPRAMOLECULAR STRUCTURE/CT
                 E E3+ALL
L5               QUE SPE=ON  ABB=ON  PLU=ON  "SUPRAMOLECULAR STRUCTURE"+OLD/CT
L6           475 SEA SPE=ON  ABB=ON  PLU=ON  (L2 OR L3 OR L4 OR L5) (L)
                 (COCRSYTAL? OR CO (1A) CRYSTAL?)
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                 D SCA
                 E DRUG DELIVERY SYSTEMS/CT
                 E E3+ALL
L8               QUE SPE=ON  ABB=ON  PLU=ON  "DRUG DELIVERY SYSTEMS"+OLD,NT/CT
L9            29 SEA SPE=ON  ABB=ON  PLU=ON  L6 AND L8
                 E COCRYSTALLIZATION/CT
                 E E3+ALL
                 E E6+ALL
L10              QUE SPE=ON  ABB=ON  PLU=ON  CRYSTALLIZATION+NT/CT
L11          249 SEA SPE=ON  ABB=ON  PLU=ON  L6 AND L10
L12           25 SEA SPE=ON  ABB=ON  PLU=ON  L9 AND L11

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     FILE 'HCAPLUS' ENTERED AT 13:02:06 ON 30 OCT 2019
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L14            4 SEA SPE=ON  ABB=ON  PLU=ON  L12 NOT L13
L15           25 SEA SPE=ON  ABB=ON  PLU=ON  (L13 OR L14)

     FILE HOME

     FILE HCAPLUS

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     FILE COVERS 1907 - 30 Oct 2019 VOL 171 ISS 20
     FILE LAST UPDATED: 29 Oct 2019 (20191029/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015
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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 252 of 415

HCAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct 11, 2019 (20191011/UP).

FILE HCA

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FILE COVERS 1907 - 24 Oct 2019 VOL 171 ISS 20
FILE LAST UPDATED: 24 Oct 2019 (20191024/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

HCA now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>15/639,223 | Filing Date<br>06/30/2017 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☐ LARGE ☑ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $40 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $210 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 04/03/2020 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 14 | Minus | ** 36 | = 0 | | x $50 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 1 | Minus | *** 9 | = 0 | | x $230 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /CHRISTINE V MOORE/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated:April 3, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

## RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

In response to the Office Action dated November 5, 2019, the time for response being extended by the attached Petition for Extension of Time, please amend the above-identified U.S. patent application as follows:

**Listing of the Claims** begins on page 2 of this paper.

**Remarks/Arguments** begin on page 5 of this paper.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 2 months with $0 paid | 2252 | 1 | 300 | 300 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **300** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 39059413 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 03-APR-2020 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:35:35 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $300 |
| RAM confirmation Number | E202043F36016860 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26171<br>8c2704835642f9f979c157d9cc9da6e10418c891 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 32968<br>167cbd3c3b3ccbbfaf73b5f467b715d75e5279e8 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Extension of Time | U015770023US03-EXT-DFC.pdf | 24988<br>e4c9ad809c051b1fecdbdb05323380b4eacd3d81 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | | U015770023US03-RESP-DFC.pdf | 57424<br>2bf918cca95e87ccb5b8acf5b010e4bf19b6a7a2 | yes | 9 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Applicant Arguments/Remarks Made in an Amendment | 5 | 9 |
| Claims | 2 | 4 |
| Amendment/Req. Reconsideration-After Non-Final Reject | 1 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 30756<br>686cdcdbc7065564925f67558b013797319ca298 | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 172307 |

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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

PTO/AIA/22 (03-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) U0157.70023US03 |
|---|---|
| Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| Art Unit 1625 | Examiner N. E. Jarrell |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $200 | $100 | $50 | $ |
| ☒ Two months (37 CFR 1.17(a)(2)) | $600 | $300 | $150 | $ 300.00 |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1,400 | $700 | $350 | $ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,200 | $1,100 | $550 | $ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $3,000 | $1,500 | $750 | $ |

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. ~~Form PTO-2038 is attached~~.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 73,490 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

| /David F. Cauble/ | April 3, 2020 |
|---|---|
| Signature | Date |
| David F. Cauble, PhD, JD | 617.646.8000 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**8096340.1**

## REMARKS

Prior to entry of the instant amendments, claims 37-50 were pending in the Application. No claims have been amended.

## PRIORITY

The office action states that U.S. Patent Application No. 10/378,956 (the '956 application) fails to provide adequate support or enablement for one or more claims of the application but it allegedly does not disclose a pharmaceutical composition comprising a co-crystal, stating "Original claims of 3 March 2003 recite a multiple-component phase composition [with] no mention of a pharmaceutically acceptable carrier. The specification provides no discussion of a pharmaceutical composition [with] a co-crystal." Applicant disagrees.

In the '956 application as filed, paragraph [0037] discloses that "Figure 24 shows an exemplified scheme for preparing ***multiple-component phase compositions*** of the subject invention." Figure 24 describes the preparation of "***multiple-component crystals***" from an API and one or more co-crystal formers. Examples 1-19 describe "***Multi-component crystals***" and refer to each such crystal as a "***co-crystal***." Accordingly, it is clear that the applicant of the '956 application equates the term "multiple-component phase compositions" with the term "multiple component crystals" and that the latter term is equivalent to the term "co-crystal." As such, the term "multiple-component phase composition" is equivalent to the term "co-crystal."

Paragraph [0049] discloses that "[t]he ***multiple-component phase compositions*** can be formulated according to known methods for preparing pharmaceutically useful compositions," that "[s]uch ***pharmaceutical compositions*** can be adapted for various forms of administration…" and that "the pharmaceutical compositions can include a ***pharmaceutically acceptable carrier*** or diluent." Accordingly, it is clear that the '956 application contemplates the preparation of pharmaceutical compositions comprising co-crystals, and that such pharmaceutical compositions may comprise a pharmaceutically acceptable carrier.

As such, the instant application has a valid claim of priority to the '956 application, which was filed on March 3, 2003.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 262 of 415

## CLAIM REJECTIONS – 35 USC § 112

Claims 37-50 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for preparation of cocrystals of examples 1-17 in the specification, allegedly does not reasonably provide enablement for preparation of the scope of cocrystals claimed. Applicant disagrees.

As a preliminary matter, Applicant notes that the previous office action (non-final rejection dated February 26, 2019) included a rejection of claims 37-50 under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, which was supported by a single publication (Kumar et al.) This rejection was overcome by Applicant's response under 37 CFR § 1.111, dated July 23, 2019. The present rejection is also supported by a single publication (Miroshnyk et al.), and therefore the Applicant traverses the rejection for the reasons stated in its response of July 23, 2019, with further remarks specifically in response to the Office's characterization of Miroshnyk et al.

On page 4 of the present non-final rejection, the Office states that "This rejection is maintained because the art shows that pharmaceutical cocrystal [design] presently has challenges that need to be overcome… In light of [Miroshnyk], these challenges still need to be overcome." On page 3 of the non-final rejection, the Office states that those challenges include:

1. stability of an active pharmacological ingredient;
2. seeing studies that follow the development cycle all the way to the end product;
3. systematically investigating the applicability of agglomeration techniques; and
4. regulatory issues.

These alleged challenges are addressed in turn below:

(1) Miroshnyk et al. does not characterize "stability of an active pharmaceutical ingredient" as a challenge to pharmaceutical co-crystal design. To the contrary, Miroshnyk et al. teaches that pharmaceutical co-crystals are a ***solution*** to the problem of poor API stability:

> *The stability of a solid API when exposed a wide range of relative humidities is another essential property… It is often the case that moisture promotes unwanted solid-phase transformation of an API…One approach proposed to inhibit such moisture-induced phase transformations is rational co-former selection for a specific formulation. In this context,* ***co-crystallization of an API with a co-former***

> ***can be thought as a more-radical strategy to address the poor physical stability of moisture-sensitive pharmaceutical materials***. *For instance, caffeine/oxalic acid co-crystals have been demonstrated to be superior to caffeine anhydrate in terms of physical stability to humidity.* (Page 338, left column, last paragraph; emphasis added)

(2) Miroshnyk et al. does not characterize "seeing studies that follow the development cycle all the way to the end product" as a challenge to pharmaceutical co-crystal design. Miroshnyk et al. states that it "would be desirable" to see such studies, but in no way suggests that this is a "challenge to pharmaceutical co-crystal design," as stated on page 4 of the office action. The fact that Miroshnyk is not aware of any such studies, or the fact that such studies may not have been published, cannot be understood to mean that such studies have not taken place, or that the skilled person is not capable of performing such studies without undue experimentation. To the contrary, the fact that such studies have taken place can be inferred from the regulatory approval in Japan of the ipragliflozin/L-proline co-crystal Suglat (see, e.g., Astellas press release dated December 21, 2018, made of record in the IDS submitted concurrently herewith). Here, Applicant notes MPEP 2164.01, which states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." As evidenced, at least, by the regulatory approval described above, the art does engage in such experimentation, i.e., studies that follow the development cycle of a co-crystalline drug product all the way to the end product.

(3) Miroshnyk et al. states that "there is a need for studies that systematically investigate the applicability of agglomeration techniques…" but goes on to say that such studies "***could*** provide valuable information for ***commercial-scale manufacture*** of co-crystal systems." (Page 338, right column, third paragraph; emphasis added) Miroshnyk et al.'s statement regarding studies related to ***commercial-scale manufacture*** does not teach or suggest that the skilled person would be unable to make and use the claimed pharmaceutical compositions. Even, arguendo, if the statement were understood to represent such a teaching, the regulatory approval and commercial availability of Suglat tablets, discussed above, proves that the art is equipped to engage in experimentation required to commercially manufacture solid formulations of pharmaceutical co-crystals.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 264 of 415

(4) Miroshnyk et al. states that "Regulatory issues are also of ***great interest***," for example, "whether a new co-crystal of a marketed API is eligible for regulatory approval via the abbreviated new drug approval mechanism…" These statements of Miroshnyk et al. clearly relate to commercial considerations, and are irrelevant to the question of enablement.

At least for the foregoing reasons, Applicant requests withdrawal of the rejection of the claims under 35 U.S.C. 112(a), first paragraph.

## CLAIM REJECTIONS – 35 USC § 102

Claims 37-49 are rejected under pre AIA 35 U.S.C. 102(b) as being anticipated by McMahon (WO2006007448), hereinafter referred to as "McMahon". Applicant disagrees. As described above, instant application has a valid claim of priority to U.S. Patent Application No. 10/378,956, which was filed on March 3, 2003. McMahon claims priority to June 17, 2004. Accordingly, the instant application is not anticipated by McMahon, and Applicant requests withdrawal of the rejection of the claims under 35 U.S.C. 102(b).

## DOUBLE PATENTING

Claims 37-50 are provisionally rejected on the ground of non-statutory double patenting as being unpatentable over claims 37 and 45 of co-pending Application No. 14/179,862. Applicant requests that the Examiner hold this rejection in abeyance until the claims are otherwise held to be in condition for allowance.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 265 of 415

## CONCLUSION

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

All fees due in connection with this filing are being paid by Credit Card. However, should additional fees be due with this filing, please charge our Deposit Account No. 23/2825, under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: April 3, 2020

Respectfully submitted,

By /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 266 of 415

## LISTING OF THE CLAIMS

1 – 36. (Canceled)

37. (Previously presented) 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-crystal 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-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

38. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

39. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.

40. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and one co-crystal former.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 267 of 415

41. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of one active pharmaceutical ingredient (API) and one co-crystal former.

42. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a group selected from acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, and nitro groups.

43. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an acid.

44. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amine.

45. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amide.

46. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an alcohol.

47. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon.

48. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a heterosynthon.

49. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon and a heterosynthon.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 268 of 415

50. (Previously presented) The pharmaceutical composition of claim 48, wherein the heterosynthon comprises an alcohol/amine interaction.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 269 of 415

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1625 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | April 3, 2020 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**8096339.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1625 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)300.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

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**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 300 | 150* | 75 | 660 | 330 | 165 | 760 | 380 | 190 | |
| Design | 200 | 100 | 50 | 160 | 80 | 40 | 600 | 300 | 150 | |
| Plant | 200 | 100 | 50 | 420 | 210 | 105 | 620 | 310 | 155 | |
| Reissue | 300 | 150 | 75 | 660 | 330 | 165 | 2,200 | 1,100 | 550 | |
| Provisional | 280 | 140 | 70 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 460 | 230 | 115 |
| Multiple dependent claims | 820 | 410 | 205 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| _____ - or HP = | _____ x | _____ = | _____ |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| _____ - or HP = | _____ x | _____ = | _____ |

HP = highest number of independent claims paid for, if greater than 3.

| **Multiple Dependent Claims** | |
|---|---|
| **Fee ($)** | **Fee Paid ($)** |
| _____ | _____ |

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| _____ - 100 = | _____ /50 = | _____ (round **up** to a whole number) x | _____ = | _____ |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2252 Extension for response within second month | 300.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | April 3, 2020 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

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Dated: April 3, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

8096338.1

| FORM PTO-1449/A and B (modified PTO/SB/08) | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet 1 of 1 | GROUP ART UNIT: 1699 | EXAMINER: N. E. Jarrell |

**U.S. PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | U.S. Patent Document | | Name of Patentee or Applicant of Cited Document | Date of Publication or Issue of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| | | Number | Kind Code | | |
| | | 2019-0169130 | A1 | Zaworotko et al. | 06-06-2019 |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | Foreign Patent Document | | | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY | Translation (Y/N) |
|---|---|---|---|---|---|---|---|
| | | Office/ Country | Number | Kind Code | | | |
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**OTHER ART – NON PATENT LITERATURE DOCUMENTS**

| Examiner's Initials # | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | Translation (Y/N) |
|---|---|---|---|
| | | [NO AUTHOR LISTED], Approval of Suglat Tablets, Selective SGLT2 Inhibitor, for Additional Indication of type 1 diabetes mellitus and Additional dosage and administration in Japan. Astellas Pharma Inc., 12 Dec 2018, https://www.astellas.com/en/news/14481. Accessed 22 Mar 2020. 2 pages. | |
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[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

| EXAMINER: | DATE CONSIDERED: |
|---|---|
| | |

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.**8097831.1**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Katherine Wade |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| SUBMISSION- INFORMATION DISCLOSURE STMT | 2806 | 1 | 120 | 120 |
| | | **Total in USD ($)** | | **120** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 39061362 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Katherine Wade |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 03-APR-2020 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 17:01:17 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $120 |
| RAM confirmation Number | E202043H02268613 |
| Deposit Account | 232825 |
| Authorized User | Katherine Wade |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.17 (Patent application and reexamination processing fees) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | U015770023US03-TRN-DFC.pdf | 26184<br>d8792def09905f79ed90eb55b8986bdfca3e6bfd | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 32819<br>96b464bc3eddb826dc2e264450ecdc5266e708d5 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Transmittal Letter | U015770023US03-IDSBODY-DFC.pdf | 30332<br>75a248a1083d2ea8fbff12676293979dc7c1924c | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Information Disclosure Statement (IDS) Form (SB08) | U015770023US03-IDS1449-DFC.pdf | 23207<br>bd77b0a7ca4e4d645c8e9892798adc7b38521e18 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 5 | Non Patent Literature | Suglat_Approval_Announcement_2018.pdf | 1088637<br>05f60f8c09306a16f6ed343ae56be20468b4d2ee | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Fee Worksheet (SB06) | fee-info.pdf | 30874<br>52fd76847f40b4e8e7b64b5d7ce2e47c72f726b6 | no | 2 |
| **Warnings:** | | | | | |

| Information: | |
|---|---|
| Total Files Size (in bytes): | 1232053 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

DOCKET NO.: U0157.70023US03

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Electronic Signature for Katherine T. Wade: /Katherine T. Wade/

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of a first Office Action, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution in this application.

Please charge our Credit Card in the amount of $120.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

| Serial No. | Filing Date | Inventor(s) | Docket No. |
|---|---|---|---|
| *16/270,981 | 02-08-2019 | Zaworotko et al. | U0157.70023US04 |

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Private PAIR .

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: U0157.70023US03
Date: April 3, 2020

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1699 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Form PTO-1449
Copy of cited reference

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | April 3, 2020 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Electronic Signature for Katherine T. Wade: /Katherine T. Wade/

**8097830.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1699 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)120.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 300 | 150* | 75 | 660 | 330 | 165 | 760 | 380 | 190 | |
| Design | 200 | 100 | 50 | 160 | 80 | 40 | 600 | 300 | 150 | |
| Plant | 200 | 100 | 50 | 420 | 210 | 105 | 620 | 310 | 155 | |
| Reissue | 300 | 150 | 75 | 660 | 330 | 165 | 2,200 | 1,100 | 550 | |
| Provisional | 280 | 140 | 70 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 460 | 230 | 115 |
| Multiple dependent claims | 820 | 410 | 205 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|
| | | | | **Fee ($)** | **Fee Paid ($)** |
| 20 - 20 or HP = | x | = | | | |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| 4 - 4 or HP = | x | = | |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| - 100 = | /50 = | (round **up** to a whole number) x | | = |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement | 120.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | April 3, 2020 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Electronic Signature for Katherine T. Wade: /Katherine T. Wade/

8097829.1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 07/10/2020
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 07/10/2020 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (FITF) Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 03 April 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 3 April 2020.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

## DETAILED ACTION

### *Notice of Pre-AIA or AIA Status*

The present application is being examined under the pre-AIA first to invent provisions.

### *Response to Amendment*

Claims 37-50 are pending and examined on the merits. The rejection under 35 U.S.C. 102 is overcome by the arguments filed 3 April 2020. Based on the priority arguments, the priority date of the instant application is 3 March 2003 (based on paragraph [0049] of the specification).

### *Information Disclosure Statement*

The information disclosure statements filed 3 April 2020 are acknowledged and considered.

### *Claim Rejections - 35 USC § 112*

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

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-50 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for preparation of cocrystals of examples 1-17 in specification, does not reasonably provide enablement for preparation of the scope of cocrystals claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

*The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a stoichiometric cocrystal of an active pharmaceutical ingredient and a co-former. Thus, the claims taken together with the specification imply a stoichiometric cocrystal can be formed.

*The state of the prior art and (4) the predictability or unpredictability of the art:*

MIRSOSHNYK (*Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341) describes that translational challenges are present in cocrystal design (page 334, section 2; sections 3 and 4, pages 337-340). The challenges include the following: stability of an active pharmacological ingredient; seeing studies that follow the development cycle all the way to the end product; systematically investigating the applicability of agglomeration techniques; and regulatory issues.

*The relative skill of those in the art:*

While the artisan generally would have an advanced degree in cocrystal formation and analysis, their high level of skill and knowledge is insufficient to overcome the lack of understanding as to how cocrystal formation occurs.

*The amount of direction or guidance presented and the presence or absence of working examples:*

The specification has provided guidance for preparation of the following cocrystals (examples 1-17 in specification):acetaminophen: 4,4'-bipyridine:water (1:1:1); phenytoin/pyridine (1:1); aspirin and 4,4'-bipyridine (2:1); ibuprofen and 4,4'-bipyridine (2:1); flurbiprofen and [4,4'-bipyridine or trans-1,2-bis(4-pyridyl)ethylene] (2:1); carbamazepine and [one of *p*-phthalaldehyde, nicotinamide, saccharin, 5-nitroisophthalic acid, acetic acid, 1,3,5,7-adamantanetetracarboxylic acid, benzoquinone, butyric acid, DMSO, or formamide] (1:1); carbamazepine and 2,6-pyridinecarboxylic acid (2:3)

The specification does not provide guidance for the scope of stoichiometric cocrystals claimed.

*The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to cocrystal formation and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the

specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

***Response to Arguments***

This rejection is maintained because the state of the art shows that pharmaceutical cocrystal deign presently has challenges that need to be overcome. Applicants argue that the MPEP 21264.10 states that although experimentation may be complex, it is not considered undue. Applicants argues that the reference shows the studies relating to co-crystal can (or should be) done. The reference teaches both that this type of research can be done and more challenges are present that need to be dealt with ("Expert opinion" section, pages 337-338; "Conclusions" section, pages 338-340).

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer

may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 45 of copending Application No. 14/179862 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 14/179862. Claim 37 of '862 overlaps with instant claims 37 and 39. Claim 45 of '862 is embraced by instant claims 37 and 40.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 37, 38 and 42 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37, 38, and 42 of copending Application No. 16/270981 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 16/270981. Claims 37, 38, and 42 of '981 overlap with instant claims 37, 38, and 42. Example 1 (page 16, paragraph [0056] to page 17, paragraph [0059]) shows a co-crystal of acetaminophen, bipyridine, and water.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Response to Arguments***

This double patenting rejection against 14/179682 is maintained because applicants have decided to keep this rejection in abeyance.

***Conclusion***

Claims 37-50 are not allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 3 April 2020 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and

the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 9:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1699

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1699 |

| CPC - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| c07d223/26.cpc. and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | 02/19/2019 | NJ |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| Search Notes | Date | Examiner |
| c07d223/26.cpc. and (cocrystal co NEAR crystalcocrystals co near crystals).clm. | 02/19/2019 | NJ |
| stn registry and hcaplus | 02/19/2019 | NJ |
| inventor search in PALM and EAST | 02/19/2019 | NJ |
| stn registry and hcaplus | 10/30/2019 | NJ |

| Interference Search | | | |
|---|---|---|---|
| US Class/CPC Symbol | US Subclass/CPC Group | Date | Examiner |
| C07D | 223/26 | 02/19/2019 | NJ |

| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |
|---|---|



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 290 of 415

DOCKET NO.: U0157.70023US03

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 3, 2020 Electronic Signature for Katherine T. Wade: /Katherine T. Wade/

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of a first Office Action, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution in this application.

Please charge our Credit Card in the amount of $120.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

8097832.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

| Serial No. | Filing Date | Inventor(s) | Docket No. |
|---|---|---|---|
| *16/270,981 | 02-08-2019 | Zaworotko et al. | U0157.70023US04 |

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Private PAIR .

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

/NOBLE E JARRELL/ 07/06/2020

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: U0157.70023US03
Date: April 3, 2020

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

| FORM PTO-1449/A and B (modified PTO/SB/08) **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 1 | of | 1 | GROUP ART UNIT: 1699 | EXAMINER: N. E. Jarrell |

**U.S. PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | U.S. Patent Document Number | U.S. Patent Document Kind Code | Name of Patentee or Applicant of Cited Document | Date of Publication or Issue of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| | | 2019-0169130 | A1 | Zaworotko et al. | 06-06-2019 |
| | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | Foreign Patent Document Office/ Country | Foreign Patent Document Number | Foreign Patent Document Kind Code | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY | Translation (Y/N) |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
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**OTHER ART – NON PATENT LITERATURE DOCUMENTS**

| Examiner's Initials # | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | Translation (Y/N) |
|---|---|---|---|
| | | [NO AUTHOR LISTED], Approval of Suglat Tablets, Selective SGLT2 Inhibitor, for Additional Indication of type 1 diabetes mellitus and Additional dosage and administration in Japan. Astellas Pharma Inc., 12 Dec 2018, https://www.astellas.com/en/news/14481. Accessed 22 Mar 2020. 2 pages. | |
| | | | |
| | | | |

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

| EXAMINER: /NOBLE E JARRELL/ | DATE CONSIDERED: 07/06/2020 |
|---|---|

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.**8097831.1**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

PTO/AIA/25 (04-13)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION** | Docket Number (Optional) U0157.70023US03 |
|---|---|

In re Application of: Michael J. Zaworotko et al.

Application No.: 15/639,223-Conf. #8089

Filed: June 30, 2017

For: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

The applicant, University of South Florida and The Regents of the University of Michigan, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 16/270,981, filed, Feb. 8, 2019, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent granted on the pending **reference** application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 73,490

/David F. Cauble/ — Signature
October 8, 2020 — Date

David F. Cauble, PhD, JD — Typed or printed name

Attorney for Applicant(s) — Title
617.646.8000 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

**8598925.1**

| TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT | Docket Number (Optional) U0157.70023US03 |
|---|---|

In re Application of: Michael J. Zaworotko et al.

Application No.: 15/639,223-Conf. #8089

Filed: June 30, 2017

For: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

The applicant, University of South Florida and The Regents of the University of Michigan, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 10,633,344 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 73,490

/David F. Cauble/ — Signature

October 8, 2020 — Date

David F. Cauble, PhD, JD — Typed or printed name

Attorney for Applicant(s) — Title

617.646.8000 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| NOTICE OF APPEAL | 2401 | 1 | 420 | 420 |
| **Post-Allowance-and-Post-Issuance:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| STATUTORY OR TERMINAL DISCLAIMER | 2814 | 2 | 170 | 340 |
| | | **Total in USD ($)** | | **760** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 40791820 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 08-OCT-2020 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 12:18:43 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $760 |
| RAM confirmation Number | E202008C19041470 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26479<br>e90e0663671254a03cd3c449e11b2d7563e96a34 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 37480<br>27bb0a4ad74b407ae185c2376eadcfe5ac171ebd | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Notice of Appeal Filed | U015770023US03-NAPL-DFC.pdf | 20977<br>e7edc3ab75a8423e5a69832a761a5b6313d3bd2b | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Pre-Brief Conference request | U015770023US03-PABRF-DFC.pdf | 20346<br>1ebb38240ffd78f3a705232096eb5469eb5e767c | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Miscellaneous Incoming Letter | U015770023US03-PABRF-ARG-DFC.pdf | 50882<br>387c090b76d3a07e889c7350cbf483cfbc32783f | no | 5 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Terminal Disclaimer Filed | U015770023US03-TD-APL-DFC.pdf | 20890<br>e01e650af520b9bd5f1a2ea334d4124be35f9c53 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 7 | Terminal Disclaimer Filed | U015770023US03-TD-PAT-DFC.pdf | 19561<br>044441d81d41886f9ca799aafa7b1e93cd4dcbe6 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | Fee Worksheet (SB06) | fee-info.pdf | 32423<br>866ea3ab9c12bc27d2cd1b1db594606450c1c930 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 229038 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

| **TRANSMITTAL FORM** *(to be used for all correspondence after initial filing)* | | | |
|---|---|---|---|
| | | Application Number | 15/639,223-Conf. #8089 |
| | | Filing Date | June 30, 2017 |
| | | First Named Inventor | Michael J. Zaworotko |
| | | Art Unit | 1699 |
| | | Examiner Name | N. E. Jarrell |
| Total Number of Pages in This Submission | | Attorney Docket Number | U0157.70023US03 |

**ENCLOSURES (*Check all that apply*)**

| | | |
|---|---|---|
| [x] Fee Transmittal Form | [ ] Drawing(s) | [ ] After Allowance Communication to TC |
| [ ] Fee Attached | [ ] Licensing-related Papers | [ ] Appeal Communication to Board of Appeals and Interferences |
| [ ] Amendment/Reply | [ ] Petition | [x] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)** |
| [ ] After Final | [ ] Petition to Convert to a Provisional Application | [ ] Proprietary Information |
| [ ] Affidavits/declaration(s) | [ ] Power of Attorney, Revocation Change of Correspondence Address | [ ] Status Letter |
| [ ] Extension of Time Request | [x] Terminal Disclaimer (2) | [x] Other Enclosure(s) (please Identify below): |
| [ ] Express Abandonment Request | [ ] Request for Refund | Pre-Appeal Brief Request For Review Form (PTO/AIA/33); Pre-Appeal Brief Request For Review |
| [ ] Information Disclosure Statement | [ ] CD, Number of CD(s) _____ | |
| [ ] Certified Copy of Priority Document(s) | [ ] Landscape Table on CD | |
| [ ] Reply to Missing Parts/ Incomplete Application | Remarks | |
| [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53 | | |

**SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT**

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | October 8, 2020 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 7, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**8600687.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1699 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)760.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 320 | 160* | 80 | 700 | 350 | 175 | 800 | 400 | 200 | |
| Design | 220 | 110 | 55 | 160 | 80 | 40 | 640 | 320 | 160 | |
| Plant | 220 | 110 | 55 | 440 | 220 | 110 | 660 | 330 | 165 | |
| Reissue | 320 | 160 | 80 | 700 | 350 | 175 | 2,320 | 1,160 | 580 | |
| Provisional | 300 | 150 | 75 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $160 small entity status filing fee for a utility application is further reduced to $80 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 480 | 240 | 120 |
| Multiple dependent claims | 860 | 430 | 215 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|
| | | | | **Fee ($)** | **Fee Paid ($)** |
| _____ - 20 or HP = | _____ x | _____ = | _____ | _____ | _____ |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| _____ - 4 or HP = | _____ x | _____ = | _____ |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| _____ - 100 = | _____ /50 = | _____ (round **up** to a whole number) x | _____ = | _____ |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2814 Statutory disclaimer, including terminal ... | 340.00 |
| 2401 Notice of appeal | 420.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | October 8, 2020 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 7, 2020 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

8600797.1

| **NOTICE OF APPEAL** FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD | Docket Number (Optional) U0157.70023US03 |
|---|---|

| | | |
|---|---|---|
| | In re Application of Michael J. Zaworotko et al. | |
| | Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| | For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| | Art Unit 1699 | Examiner N. E. Jarrell |

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 840.00

[x] Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ 420.00

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____

Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[x] Payment by credit card. ~~Form PTO-2038 is attached~~.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 23/2825.

[x] Payment made via EFS-Web.

[ ] A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed. For extensions of time in reexamination proceedings, see 37 CFR 1.550.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

[ ] applicant [x] attorney or agent of record Registration number 73,490 [ ] attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /David F. Cauble/

Typed or printed name David F. Cauble, PhD, JD

Telephone Number 617.646.8000

Date October 8, 2020

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

Doc Code: AP.PRE.REQ

PTO/AIA/33 (03-13)
Approved for use through 11/30/2020
OMB 0651-0031 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PRE-APPEAL BRIEF REQUEST FOR REVIEW** | Docket Number (Optional) U0157.70023US03 | |
|---|---|---|
| I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on October 7, 2020. Signature /Cathy Nicholson/ Typed or printed name Cathy Nicholson | Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| | First Named Inventor Michael J. Zaworotko et al. | |
| | Art Unit 1699 | Examiner N. E. Jarrell |

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant.

☒ attorney or agent of record.
Registration number 73,490.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/David F. Cauble/
Signature

David F. Cauble, PhD, JD
Typed or printed name

617.646.8000
Telephone number

Date

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 7, 2020 Signature: /Cathy Nicholson (Cathy Nicholson)

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby requests review of the rejection of claims 37-50 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. As a preliminary matter, Applicant notes that the outstanding rejections on grounds of non-statutory double patenting over claims 37 and 45 of Application Number 14/179,862 (now issued as US Patent Number 10,633,344) and claims 37, 38, and 42 of co-pending Application 16/270,981 are moot in view of the terminal disclaimer filed over both of these publications.

The rejection under 35 U.S.C. § 112, first paragraph has been maintained following Applicant's response of April 3, 2020. On page 4 of the Final Rejection dated July 10, 2020, the Office explains that "[t]his rejection has been maintained because the state of the art shows that pharmaceutical co-crystal [design] presently has challenges that need to be overcome." The Office bases this view on the publication of Miroshnyk et al., *Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341 ("Miroshnyk"), noting specifically the "Expert Opinion" section, pages 337-338; and the "Conclusions" section, pages 338-340.

With regard to the *Wands* factor related to "the state of the prior art and the predictability of unpredictability in the art," Applicant notes as a preliminary matter that the publication of Miroshnyk is not prior art. Nevertheless, the Office maintains that Miroshnyk provides evidence of "high unpredictability in the art" in view of alleged "translational challenges [that] are present in cocrystal design…" (page 3). Such challenges allegedly include:

1. Stability of an active pharmacological ingredient;
2. Seeing studies that follow the development cycle all the way to the end product;
3. Systematically investigating the applicability of agglomeration techniques; and
4. Regulatory issues.

The publication of Miroshnyk does not demonstrate high unpredictability in the art as it pertains to the manufacture and use of the ***claimed invention***, and Applicant submits that the teachings of Miroshnyk have been mischaracterized by the Office. The four alleged teachings of Miroshnyk, listed above, are addressed in turn below.

(1) Miroshnyk does not characterize "stability of an active pharmaceutical ingredient" as a challenge to pharmaceutical co-crystal design. To the contrary, Miroshnyk teaches that pharmaceutical co-crystals are a ***solution*** to the problem of poor API stability:

> *The stability of a solid API when exposed a wide range of relative humidities is another essential property… It is often the case that moisture promotes unwanted solid-phase transformation of an API…One approach proposed to inhibit such moisture-induced phase transformations is rational co-former selection for a specific formulation. In this context,* ***co-crystallization of an API with a co-former can be thought as a more-radical strategy to address the poor physical stability of moisture-sensitive pharmaceutical materials****. For instance, caffeine/oxalic acid co-crystals have been demonstrated to be superior to caffeine anhydrate in terms of physical stability to humidity.* (Page 338, left column, last paragraph; emphasis added).

(2) Miroshnyk does not characterize "seeing studies that follow the development cycle all the way to the end product" as a challenge to pharmaceutical co-crystal design. Miroshnyk states that it "would be desirable" to see such studies, but in no way suggests that this is a "challenge to pharmaceutical co-crystal design," as stated on page 4 of the Non-final Rejection dated November 5, 2019. The fact that Miroshnyk is not aware of any such studies, or the fact that such studies may



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 307 of 415

not have been published, cannot be understood to mean that such studies have not taken place, or that the skilled person is not capable of performing such studies without undue experimentation. To the contrary, the fact that such studies have taken place can be inferred from the regulatory approval in Japan of the ipragliflozin/L-proline co-crystal Suglat (see, *e.g.*, Astellas press release dated December 21, 2018, made of record in the IDS submitted on April 3, 2020). Here, Applicant notes MPEP 2164.01, which states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." As evidenced, at least, by the regulatory approval described above, the art does engage in such experimentation, *i.e.*, studies that follow the development cycle of a co-crystalline drug product all the way to the end product.

(3) Miroshnyk states that "there is a need for studies that systematically investigate the applicability of agglomeration techniques…" but goes on to say that such studies "***could*** provide valuable information for ***commercial-scale manufacture*** of co-crystal systems." (page 338, right column, third paragraph; emphasis added) Miroshnyk's statement regarding studies related to ***commercial-scale manufacture*** does not teach or suggest that the skilled person would be unable to make and use the claimed pharmaceutical compositions. Even assuming, *arguendo*, that the statement were understood to represent such a teaching, the regulatory approval and commercial availability of Suglat tablets, discussed above, proves that the art is equipped to engage in experimentation required to commercially manufacture solid formulations of pharmaceutical co-crystals.

(4) Miroshnyk states that "Regulatory issues are also of ***great interest***," for example, "whether a new co-crystal of a marketed API is eligible for regulatory approval via the abbreviated new drug approval mechanism…" These statements of Miroshnyk clearly relate to considerations that are irrelevant to the manufacture and use of the claimed invention, and therefore are irrelevant to the question of enablement.

With regard to the *Wands* factor related to "the relative skill of those in the art," the Office alleges that "the artisan generally would have an advanced degree in cocrystal formation and analysis, [but that] their high level of skill and knowledge is insufficient to overcome the lack of understanding as to how cocrystal formation occurs." Applicant submits that Miroshnyk does not teach or suggest that there is a lack of understanding as to how cocrystal formation occurs. On the contrary, Miroshnyk describes in detail the "General aspects of co-crystal formation" (pages 334-



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 308 of 415

337) and even discloses a "Schematic of steps for co-crystal design" (Figure 2). There is no other evidence of record which supports the presumption of a lack of understanding as to how cocrystal formation occurs, nor is there any evidence of record that the knowledge of a person having ordinary skill in the art (*i.e.*, having an advanced degree in cocrystal formation and analysis) would be insufficient to overcome any lack of understanding.

With regard to the *Wands* factor related to "the quantity of experimentation necessary," the Office refers to the "state of the prior art as discussed by the references above" (*i.e.*, the publication of Miroshnyk). For the reasons described above, Applicant submits that there is no teaching of Miroshnyk which indicates that undue experimentation would be required to make or use the claimed invention, and consequently that there is no evidence of record to support the Office's statements in this regard.

With regard to the *Wands* factor related to "the amount of direction or guidance presented and the presence of absence of working examples," the Office acknowledges the working examples of examples 1-17 but does not acknowledge the considerable guidance provided in addition to these examples. For example, in paragraph [0043], the application discloses a method of preparing a multiple-component solid phase composition composed of an API and at least one co-crystal former involving techniques such as such as crystallization from solution, cooling the melt, sublimation and grinding. A "multiple-component phase" is defined in paragraph [0047] as any solid material (phase) that is sustained by intermolecular interactions between at least two independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. "Pharmaceutical entities" are defined in paragraph [0048] and numerous examples of chemical functional groups that are capable of forming supramolecular synthons are provided. Paragraphs [0040]-[0042] disclose methods for identifying complementary chemical functional groups with which to form the desired supramolecular synthons. The methods involve:

- evaluating the structure of an API, which can include determining its crystal structure;
- determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules;
- identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 309 of 415

synthons with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and

- identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

In paragraphs [0057] through [0178], the methods described above are applied to the preparation of 19 different, exemplary co-crystals. In this regard, Applicant notes that MPEP 2164.02(III) states:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art…would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus ***only where adequate reasons are advanced*** by the examiner ***to establish that a person skilled in the art could not use the genus as a whole without undue experimentation***. (Emphasis added)

The Office has not advanced any reasons or evidence supporting a conclusion that a skilled person would not be able to make and use the claimed genus without undue experimentation.

At least for the foregoing reasons, the Office has not adequately supported the rejection of 37-50 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Accordingly, reversal of this rejection is respectfully requested.

A Notice of Appeal (and associated fees) are submitted herewith. If a further fee is due with this Pre-Appeal Brief Request, please charge our Deposit Account No. 23/2825, under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: October 8, 2020

Respectfully submitted,

By /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 310 of 415

| *Application Number* | Application/Control No. | Applicant(s)/Patent under Reexamination | |
|---|---|---|---|
| * 15/639,223 * | 15/639,223 | Zaworotko et al. | |
| | **Examiner** | **Art Unit** | |
| | JARRELL, NOBLE E | 1699 | |

| **Document Code - DISQ** | **Internal Document - DO NOT MAIL** |
|---|---|

| **TERMINAL DISCLAIMER** | ☐ APPROVED | ☑ DISAPPROVED |
|---|---|---|
| **Date Filed:** **08 October 2020** | **This patent is subject to a Terminal Disclaimer** | |

## Approved/Disapproved by:

/CHARRISSA S BROWN/

**Technology Center: PLRC**

**Telephone: (571)272-1558**

2 TD'S Disapproved.
The person who signed the terminal disclaimer is not the applicant, patentee or an attorney or agent of record. 37 CFR 1.321(a) and (b). (See FP 14.26.08)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 311 of 415

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 11/17/2020
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/17/2020 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| Notice of Panel Decision from Pre-Appeal Brief Review | Application No. | Applicant(s) | |
|---|---|---|---|
| | 15/639,223 | Zaworotko et al. | |
| | Examiner | Art Unit | AIA (FITF) Status |
| | Andrew D Kosar | 1625 | No |

This is in response to the Pre-Appeal Brief Request for Review filed 08 October 2020 .

1. ☐ **Improper Request** - The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: _____ .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☐ **Proceed to Board of Patent Appeals and Interferences** - A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☐ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____ .
Claim(s) objected to: _____ .
Claim(s) rejected: _____ .
Claim(s) withdrawn from consideration: _____ .

3. ☐ **Allowable application** - A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☑ **Reopen Prosecution** - A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

| | |
|---|---|
| (1) ANDREW D KOSAR . | (3) Lora Driscoll . |
| (2) Noble Jarrell . | (4) _____ . |

| | | |
|---|---|---|
| /Andrew D Kosar/<br>Supervisory Patent Examiner, Art Unit 1625 | | |

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 02/05/2021
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/05/2021 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (FITF) Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 08 October 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

**DETAILED ACTION**

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Response to Amendment***

This action is in response to the notice of appeal filed 8 October 2020 and pre-appeal brief conference decision of 17 November 2020. Prosecution is being re-opened. The 35 U.S.C. 112 (a) scope of enablement rejection is dropped.

***Claim Rejections - 35 USC § 112***

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons. Each synthon is formed from a stoichiometric amount of at least one active pharmaceutical ingredient (API) and at least one co-crystal former. The synthons are associated together through non-covalent hydrogen bonding. The universe of pharmaceutical compositions comprising an API and co-crystal former includes any co-crystal comprising an API and co-crystal bound together by noncovalent H-bonding.

(1) Level of skill and knowledge in the art:

HSU (*Acta Crystallographica*, **1974**, *B30*, 843-846, cited in IDS) describes a 1:1 cocrystal of salicylamide and 5-ethylisoamylbarbituric acid (title and abstract). Hydrogen bonding is used to bind the compounds together (abstract; page 845, column 2 to page 846, column 1, paragraph 1).

MIROSHNYK (*Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341, cited previously) describes how cocrystals are bound together and examples of the same (table 1, page 336; table 2, page 339).

(2) Partial structure:

A partial structure encompasses a pharmaceutical composition comprising a cocrystal of an API and a co-crystal former bound together by non-covalent H-bonding.

(3) Physical and/or chemical properties and (4) Functional characteristics:

Examples 1-18 (page 16, paragraph [0056]) to page 33, paragraph [00177]) describe different properties of the compositions selected from crystal data, IR spectroscopy, DSC, TGA, and XRPD. The examples provide a wide range of solid phases having properties such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability.

(5) Method of making the claimed invention:

Example 1 shows a representative method of making a pharmaceutical composition where 50 mg of acetaminophen and 52 mg of 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation lead to colorless needles of 1:1:1 acetaminophen:4,4'-bipyridine:water co-crystal (figure 4B).

The MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 37-50 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any a pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of examples 1-18 and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention

will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

The concept of a "GRAS compound" (page 12, paragraph [0046]) is unclear because the metes and bounds of what is regarded as safe and requires more guidance (KNUDSEN, *Regulatory Toxicology and Pharmacology*, **1995**, *21*, 365-369).

Claims 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the required structural components of an API and a co-crystal former and the functional groups that are used for non-covalent hydrogen bonding. None of claims 37-49 fully define the required structural elements of the API or the cocrystal former. Rather, an API and cocrystal former are defined by their properties. Hsu (same reference as above) prepares a complex of salicylamide and 5-ethylisoamylbarbituric acid. Miroshnyk (same reference as above) describes three broad methods of non-covalent H-bonding interactions and various combinations of seven different API's with various cocrystal formers.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference

claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 45 of U.S. Patent No. 10633344 (hereinafter '344). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of '344. Claim 37 of '344 overlaps with instant claims 37 and 39. Claim 45 of '344 is embraced by instant claims 37 and 40.

Claims 37, 38 and 42 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37, 38, and 42 of copending Application No. 16/270981 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 16/270981. Claims 37, 38, and 42 of '981 overlap with instant claims 37, 38, and 42. Example 1 (page 16, paragraph [0056] to page 17, paragraph [0059]) shows a co-crystal of acetaminophen, bipyridine, and water.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Response to Amendment***

The terminal disclaimers filed 9 October 2020 are not approved because the person who signed the terminal disclaimer is not the applicant, patentee, or an attorney or agent of record (see 37 CFR 1.321 (a) and (b) and FP 14.26.08). Consequently the double patenting rejections are maintained.

***Conclusion***

Claims 37-50 are not allowable presently.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 9:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1699

| Notice of References Cited | Application/Control No. 15/639,223 | Applicant(s)/Patent Under Reexamination Zaworotko et al. | |
|---|---|---|---|
| | Examiner NOBLE E JARRELL | Art Unit 1699 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| * | A | US-10633344-B2 | 04-2020 | Zaworotko; Michael J. | A61P29/00 | 1/1 |
| | B | | | | | |
| | C | | | | | |
| | D | | | | | |
| | E | | | | | |
| | F | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
|---|---|---|---|---|---|---|
| | N | | | | | |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1699 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| c07d223/26.cpc. and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | 02/19/2019 | NJ |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| c07d223/26.cpc. and (cocrystal co NEAR crystalcocrystals co near crystals).clm. | 02/19/2019 | NJ |
| stn registry and hcaplus | 02/19/2019 | NJ |
| inventor search in PALM and EAST | 02/19/2019 | NJ |
| stn registry and hcaplus | 10/30/2019 | NJ |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| C07D | 223/26 | 02/19/2019 | NJ |

| | |
|---|---|
| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 322 of 415

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PATENT APPLICATION FEE DETERMINATION RECORD**<br>Substitute for Form PTO-875 | Application or Docket Number<br>15/639,223 | Filing Date<br>06/30/2017 | ☐ To be Mailed |
|---|---|---|---|

**ENTITY:** ☐ LARGE ☑ SMALL ☐ MICRO

## APPLICATION AS FILED - PART I

| FOR | (Column 1)<br>NUMBER FILED | (Column 2)<br>NUMBER EXTRA | | RATE ($) | FEE ($) |
|---|---|---|---|---|---|
| ☐ BASIC FEE<br>(37 CFR 1.16(a), (b), or (c)) | N/A | N/A | | N/A | |
| ☐ SEARCH FEE<br>(37 CFR 1.16(k), (i), or (m)) | N/A | N/A | | N/A | |
| ☐ EXAMINATION FEE<br>(37 CFR 1.16(o), (p), or (q)) | N/A | N/A | | N/A | |
| TOTAL CLAIMS<br>(37 CFR 1.16(i)) | minus 20 = | * | | x $40 = | |
| INDEPENDENT CLAIMS<br>(37 CFR 1.16(h)) | minus 3 = | * | | x $210 = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | |
| ☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | | TOTAL | |

## APPLICATION AS AMENDED - PART II

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 05/27/2021 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * 14 | Minus | ** 36 | = 0 | | x $50 = | 0 |
| | Independent<br>(37 CFR 1.16(h)) | * 1 | Minus | *** 9 | = 0 | | x $240 = | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | 0 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | |
|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | | RATE ($) | ADDITIONAL FEE ($) |
| | Total<br>(37 CFR 1.16(i)) | * | Minus | ** | = | | x $0 = | |
| | Independent<br>(37 CFR 1.16(h)) | * | Minus | *** | = | | x $0 = | |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | |
| | ☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | |
| | | | | | | | TOTAL ADD'L FEE | |

| | |
|---|---|
| * If the entry in column 1 is less than the entry in column 2, write "0" in column 3. | LIE |
| ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". | /CHRISTINE V MOORE/ |
| *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". | |
| The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1. | |

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1625 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 27, 2021 Signature: /Cathy Nicholson / (Cathy Nicholson)

**RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

In response to the Office Action dated February 5, 2021, the time being extended to the present by the attached Petition for Extension of Time, please amend the above-identified U.S. patent application as follows:

**Listing of the Claims** begins on page 2 of this paper.

**Remarks** begin on page 5 of this paper.

## LISTING OF THE CLAIMS

1 – 36. (Canceled)

37. (Previously presented) 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-crystal 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-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein supramolecular synthons comprise non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

38. (Currently amended) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, ~~a GRAS compound,~~ a food additive, a low toxicity organic, and a metal-organic complex.

39. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.

40. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and one co-crystal former.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 325 of 415

41. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of one active pharmaceutical ingredient (API) and one co-crystal former.

42. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a group selected from acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, and nitro groups.

43. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an acid.

44. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amine.

45. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amide.

46. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an alcohol.

47. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon.

48. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a heterosynthon.

49. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon and a heterosynthon.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 326 of 415

50. (Previously presented) The pharmaceutical composition of claim 48, wherein the heterosynthon comprises an alcohol/amine interaction.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 327 of 415

## REMARKS

Prior to entry of the instant amendments, claims 37-50 were pending in the Application. Claim 38 has been amended. No new matter is added. Upon entry of the amendments, claims 37-50 will be pending.

***CLAIM REJECTIONS – 35 USC § 112***

Page 4 of the Office Action states that "it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s)…had possession of the entire scope of the invention." The Office further takes the position that "although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples of the specification."

Applicants respectfully disagree. MPEP 2163 states that "[a]n applicant may…show that an invention is complete by disclosure of…complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613 (quoting the Written Description Guidelines, 66 Fed. Reg. at 1106, n. 49, stating that 'if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function'), concluding "[t]hus, ***the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function."*** Emphasis added.

Claim 37 specifies, inter alia, the following structure in relation to the recited co-crystal:

- stoichiometric amounts of an API and a co-crystal former;
- 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; and
- co-crystal former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding.

Claim 37 specifies, inter alia, the function:

- hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-crystal former.

The function recited in claim 37 relates to hydrogen bonding between complimentary functional groups of the API and the co-crystal formula. There is a well-established correlation between structure and function in the context of hydrogen bonding, and the correlation was well-established as of the filing date of the present application. The correlation between structure and function in the context of hydrogen bonding is described in terms of hydrogen bond donors and hydrogen bond acceptors.

The correlation between structure and function, and the associated terminology, is reflected in the Examples and Figures of the instant application. See, e.g., Figure 1 depicts a carboxylic acid moiety comprising a carbonyl (hydrogen bond acceptor) and an acidic hydrogen (hydrogen bond donor). Figure 2 depicts the interaction between hydrogen bond donor and acceptor. Figures 4A-4B depict hydrogen bonding interactions between the H atoms (hydrogen bond donors) of amide moieties and water, with the O and N atoms (hydrogen bond acceptors) of carbonyl moieties, water, and bipyridine. Paragraph [0018] of the application refers to "all hydrogen bonding donors and acceptors interacting" in Figures 4A-4B. Paragraph [0009] of the application refers to certain representative, non-limiting examples of functional groups which may participate in hydrogen bonding: acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (e.g. pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocyles, N-heterocycles (saturated or unsaturated), O-heterocycles, ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

With reference to the bold/italicized text above, the written description requirement is satisfied in connection with the present application by the disclosure of structure and function, both as noted above, together with a well-established correlation between structure and function. Moreover, the application describes adequate exemplary structures and working examples, i.e., each of Examples 1-19. As such, Applicant requests withdrawal of this rejection.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 329 of 415

Claims 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly being indefinite in view of the term "GRAS compound." Applicant respectfully disagrees, and as a preliminary matter notes that independent claim 37, and dependent claims 39-50 do not recite the term "GRAS compound." As such, Applicant understands the rejection to be limited to claim 38. Without conceding the merits of the rejection, and solely to expedite prosecution, claim 38 has been amended to delete the term "GRAS compound." Accordingly, Applicant requests withdrawal of this rejection.

Claims 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements. Specifically, the Office alleges that the claims omit "the required structural components of an API and co-crystal former and the functional groups that are used for non-covalent hydrogen bonding. Applicant respectfully disagrees.

MPEP 2172.01 states that "[a] claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling" and that "[i]f a claim fails to interrelate essential elements of the invention as defined by applicant(s) in the specification, the claim may be rejected under… 35 U.S.C. 112, second paragraph, as indefinite.

The present rejection is under 35 U.S.C. 112 (pre-AIA), second paragraph, and therefore the relevant question is whether the rejected claims "fail to interrelate essential elements of the invention as defined by applicant(s) in the specification." Applicant notes that the specification does not define any subject matter as "essential" in relation to the claimed invention, and the Office has not identified any part of the specification that defines "essential" subject matter. The Office has cited the publications of Hsu and Miroshnyk, but the publications of Hsu and Miroschnyk are not part of the specification, and therefore the Office has not met its threshold burden of specifying which essential elements, ***as defined by the applicant in the specification***, have been omitted, or that the applicant has failed to interrelate. Accordingly, Applicant requests withdrawal of this rejection.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 330 of 415

***DOUBLE PATENTING***

Claims 37-50 are rejected on the ground of non-statutory double patenting as being unpatentable over claims 37 and 45 of U.S. Patent No. 10,633,344.

Claims 37, 38, and 42, are provisionally rejected on the ground of non-statutory double patenting as being unpatentable over claims 37, 38 and 42, of co-pending Application No. 16/270981.

Applicant requests that these rejections be held in abeyance until the claims are held to be in condition for allowance otherwise.

## CONCLUSION

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

All fees due are being paid by Credit Card. However, should additional fees be due with this filing, please charge our Deposit Account No. 23/2825, under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: May 27, 2021

Respectfully submitted,

By /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 331 of 415

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 1 month with $0 paid | 2251 | 1 | 110 | 110 |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **110** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 42839449 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 27-MAY-2021 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:23:36 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $110 |
| RAM confirmation Number | E20215QF23510314 |
| Deposit Account | |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26208<br>e26e4e41e44073d0092da717a532577d1d6b9dd5 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 37423<br>022c6d4e09afc507616a9318c505a7c111f31e84 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Extension of Time | U015770023US03-EXT-DFC.pdf | 25074<br>b0119b2a54f4e15a6e13147a92e8fa22808e5396 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | | U015770023US03-AMN-DFC.pdf | 52303<br>e003a70187ec65359dfea4067dba87335a385b90 | yes | 8 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Amendment/Req. Reconsideration-After Non-Final Reject | 1 | 1 |
| Claims | 2 | 4 |
| Applicant Arguments/Remarks Made in an Amendment | 5 | 8 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 30756<br>af3b35954e44d4d33de9437b3d843263c769be04 | no | 2 |

| Warnings: | |
|---|---|
| Information: | |
| Total Files Size (in bytes): | 171764 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1699 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | May 27, 2021 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: _May 27, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9274873.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1699 |
| Practitioner Docket No. | U0157.70023US03 |

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)110.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

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**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 320 | 160* | 80 | 700 | 350 | 175 | 800 | 400 | 200 | |
| Design | 220 | 110 | 55 | 160 | 80 | 40 | 640 | 320 | 160 | |
| Plant | 220 | 110 | 55 | 440 | 220 | 110 | 660 | 330 | 165 | |
| Reissue | 320 | 160 | 80 | 700 | 350 | 175 | 2,320 | 1,160 | 580 | |
| Provisional | 300 | 150 | 75 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $160 small entity status filing fee for a utility application is further reduced to $80 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 480 | 240 | 120 |
| Multiple dependent claims | 860 | 430 | 215 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|
| | | | | **Fee ($)** | **Fee Paid ($)** |
| 20 - or HP = | | x | = | | |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| - or HP = | | x | = |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| - 100 = | /50 = | (round **up** to a whole number) x | | = |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2251 Extension for response within first month | 110.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | May 27, 2021 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 27, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9274872.1**

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) U0157.70023US03 |
|---|---|
| Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| Art Unit 1699 | Examiner N. E. Jarrell |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| [x] One month (37 CFR 1.17(a)(1)) | $220 | $110 | $55 | $ 110.00 |
| [ ] Two months (37 CFR 1.17(a)(2)) | $640 | $320 | $160 | $ |
| [ ] Three months (37 CFR 1.17(a)(3)) | $1,480 | $740 | $370 | $ |
| [ ] Four months (37 CFR 1.17(a)(4)) | $2,320 | $1,160 | $580 | $ |
| [ ] Five months (37 CFR 1.17(a)(5)) | $3,160 | $1,580 | $790 | $ |

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[x] Payment by credit card. ~~Form PTO-2038 is attached~~.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[x] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

[x] Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

[ ] applicant.

[ ] attorney or agent of record. Registration number _____ .

[x] attorney or agent acting under 37 CFR 1.34. Registration number 73,490 .

| /David F. Cauble/ | May 27, 2021 |
|---|---|
| Signature | Date |
| David F. Cauble, PhD, JD | 617.646.8000 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: May 27, 2021 Signature: /Cathy Nicholson/(Cathy T. Nicholson)

**9274874.1**

| FORM PTO-1449/A and B (modified PTO/SB/08) | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet 1 of 1 | GROUP ART UNIT: 1699 | EXAMINER: N. E. Jarrell |

**U.S. PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | U.S. Patent Document Number | U.S. Patent Document Kind Code | Name of Patentee or Applicant of Cited Document | Date of Publication or Issue of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**FOREIGN PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | Foreign Patent Document Office/ Country | Foreign Patent Document Number | Foreign Patent Document Kind Code | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY | Translation (Y/N) |
|---|---|---|---|---|---|---|---|
| | | WO | 2006/007448 | A2 | Transform Pharmaceuticals, Inc. | 01-19-2006 | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**OTHER ART – NON PATENT LITERATURE DOCUMENTS**

| Examiner's Initials # | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | Translation (Y/N) |
|---|---|---|---|
| | | KOBAYASHI et al., Supramolecular architecture consisting of an enantiopure amine and an achiral carboxylic acid: application to the enantioseparation of racemic alcohols. Org Lett. 2004 Aug 19;6(17):2941-4. doi: 10.1021/ol048948b. | |
| | | KODAMA et al., Two-component supramolecular helical architectures: creation of tunable dissymmetric cavities for the inclusion and chiral recognition of the third components. Chemistry. 2007;13(7):2144-52. doi: 10.1002/chem.200601295. | |
| | | | |

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

| EXAMINER: | DATE CONSIDERED: |
|---|---|
| | |

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

**9372490.1**

| PATENT TERM ADJUSTMENT STATEMENT UNDER 37 CFR 1.704(d) | | |
|---|---|---|
| | Application Number | 15/639,223-Conf. #8089 |
| | Filing Date | June 30, 2017 |
| | First Named Inventor | Michael J. Zaworotko |
| | Art Unit | 1699 |
| | Examiner Name | N. E. Jarrell |
| | Practitioner Docket No. | U0157.70023US03 |

**APPLICANT HEREBY STATES THE FOLLOWING (please review 37 CFR 1.704(d) before filing this form):**

[x] Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in 37 CFR 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

**AND/OR**

[ ] Each item of information contained in the information disclosure statement is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in 37 CFR 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

**INSTRUCTIONS:**

- **This form will not satisfy the requirement of 37 CFR 1.97(e).** The present statement is filed under 37 CFR 1.704(d) and will not substitute for compliance with any of the requirements of 37 CFR 1.97 and 1.98. For an information disclosure statement to comply with 37 CFR 1.97(c) or (d), the information disclosure statement must be accompanied by a statement under 37 CFR 1.97(e) notwithstanding any statement filed under 37 CFR 1.704(d).
- The present form (PTO/SB/133) should be filed concurrently with the information disclosure statement to derive benefit under 37 CFR 1.704(d).

| Signature | /David F. Cauble/ | Date | July 2, 2021 |
|---|---|---|---|
| Typed or printed name | David F. Cauble, PhD, JD | Practitioner Registration Number | 73,490 |

***Note:*** *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

[ ] *Total of 1 forms are submitted.

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 2, 2021 Signature: /Jessica O. Valli/ (Jessica O. Valli)

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Jessica Valli |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| SUBMISSION- INFORMATION DISCLOSURE STMT | 2806 | 1 | 130 | 130 |
| | | **Total in USD ($)** | | **130** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 43159890 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Jessica Valli |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 02-JUL-2021 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 12:38:15 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $130 |
| RAM confirmation Number | E202172C39174342 |
| Deposit Account | 232825 |
| Authorized User | Jessica Valli |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>37 CFR 1.17 (Patent application and reexamination processing fees) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Miscellaneous Incoming Letter | U015770023US03-TRN-DFC.pdf | 26440<br>58e02104c44761da16ce7ea5445c918b5a94dcde | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 32801<br>e5ad306079dac5d0e9bb63440a92ab845e8974bd | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Letter specifying the conditions for filing under 37CFR1.97 | U015770023US03-IDSBODY-DFC.pdf | 28916<br>3fc638454205c545493667861c8ded1bcb585f48 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Information Disclosure Statement (IDS) Form (SB08) | U015770023US03-IDS1449-DFC.pdf | 22847<br>f86b6fecfee542f24de894dc79b6a8b48ae9b3a6 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 5 | Patent Term Adjustment Stmt Under 37CFR1.704(d) | U015770023US03-IDSPTA-DFC.pdf | 62936<br>a4b4c72c72afdb7825889d43f4f053b2998818a2 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Non Patent Literature | Kobayashi_et_al_Org_Lett_2004_v6_p2941.pdf | 476619<br>e6c52cb690cc78f67220df2bd21fe69a77bcbe41 | no | 4 |
| **Warnings:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 7 | Non Patent Literature | Kodama_et_al_Chemistry_2007_v13_p2144.pdf | 746708<br>bafb9e5d56d07ffdac47f2248ce4373466a35273 | no | 9 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | Foreign Reference | WO2006007448A2.pdf | 7168462<br>286d37bb43a17e09a24a1e1baa7a2fbb111ddea4 | no | 149 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | Fee Worksheet (SB06) | fee-info.pdf | 30649<br>0387790e799083cebaf44989e1fd2787d67a374d | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 8596378 | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1699 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):
  - Patent Term Adjustment Statement Under 37 CFR 1.704(d)
  - Form PTO-1449
  - Copies of cited references

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | July 2, 2021 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 2, 2021 Signature: /Jessica O. Valli/ (Jessica O. Valli)

**9372487.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1699 |
| Practitioner Docket No. | U0157.70023US03 |

[x] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)130.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [x] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[x] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[x] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[x] Credit any overpayment of fee(s)

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 320 | 160* | 80 | 700 | 350 | 175 | 800 | 400 | 200 | |
| Design | 220 | 110 | 55 | 160 | 80 | 40 | 640 | 320 | 160 | |
| Plant | 220 | 110 | 55 | 440 | 220 | 110 | 660 | 330 | 165 | |
| Reissue | 320 | 160 | 80 | 700 | 350 | 175 | 2,320 | 1,160 | 580 | |
| Provisional | 300 | 150 | 75 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $160 small entity status filing fee for a utility application is further reduced to $80 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 480 | 240 | 120 |
| Multiple dependent claims | 860 | 430 | 215 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|
| | | | | **Fee ($)** | **Fee Paid ($)** |
| 20 - 20 or HP = | x | = | | | |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| 4 - 4 or HP = | x | = | |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| - 100 = | /50 = | (round **up** to a whole number) x | | = |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement | 130.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | July 2, 2021 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: July 2, 2021 Signature: /Jessica O. Valli/ (Jessica O. Valli)

**9372592.1**

DOCKET NO.: U0157.70023US03

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

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Dated: July 2, 2021 Signature: /Jessica O. Valli/ (Jessica O. Valli)

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of a first Office Action, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution in this application.

Please charge our Credit Card in the amount of $130.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

PART II: Compliance with 37 C.F.R. § 1.704(d)

Each item of information contained in this Information Disclosure Statement

(i) was first cited in any communication from a patent office in a counterpart foreign or international application or from the United States Patent and Trademark Office, and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty (30) days prior to the filing of the Information Disclosure Statement; or

(ii) is a communication that was issued by a patent office in a counterpart foreign or international application or by the United States Patent and Trademark Office, and this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty (30) days prior to the filing of the Information Disclosure Statement.

PART III: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;

2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;

3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102, or an admission by Applicant as prior art.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Docket No.: U0157.70023US03
Date: July 2, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 08/11/2021

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 08/11/2021 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (FITF) Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 27 May 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 2 July 2021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

**DETAILED ACTION**

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Response to Amendment***

The amendment filed 27 May 2021 overcomes the 35 U.S.C. 112 (b) rejection regarding "GRAS compounds". The other rejections of 5 February 2021 under 35 U.S.C. 112 and double patenting are maintained for the reasons stated below.

***Information Disclosure Statement***

The information disclosure statement filed 2 July 2021 is acknowledged and considered.

***Claim Rejections - 35 USC § 112***

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him.

Claim(s) 37-50 is/are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph due to lack of written description.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons. Each synthon is formed from a stoichiometric amount of at least one active pharmaceutical ingredient (API) and at least one co-crystal former. The synthons are associated together through non-covalent hydrogen bonding. The universe of pharmaceutical compositions comprising an API and co-crystal former includes any co-crystal comprising an API and co-crystal bound together by noncovalent H-bonding.

(1) Level of skill and knowledge in the art:

HSU (*Acta Crystallographica*, **1974**, *B30*, 843-846, cited in IDS) describes a 1:1 cocrystal of salicylamide and 5-ethylisoamylbarbituric acid (title and abstract). Hydrogen bonding is used to bind the compounds together (abstract; page 845, column 2 to page 846, column 1, paragraph 1).

MIROSHNYK (*Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341, cited previously) describes how cocrystals are bound together and examples of the same (table 1, page 336; table 2, page 339).

(2) Partial structure:

A partial structure encompasses a pharmaceutical composition comprising a cocrystal of an API and a co-crystal former bound together by non-covalent H-bonding.

(3) Physical and/or chemical properties and (4) Functional characteristics:

Examples 1-19 (page 16, paragraph [0056]) to page 33, paragraph [00177]) describe different properties of the compositions selected from crystal data, IR spectroscopy, DSC, TGA, and XRPD. The examples provide a wide range of solid phases having properties such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability.

(5) Method of making the claimed invention:

Example 1 shows a representative method of making a pharmaceutical composition where 50 mg of acetaminophen and 52 mg of 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation lead to colorless needles of 1:1:1 acetaminophen:4,4'-bipyridine:water co-crystal (figure 4B).

The MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 37-50 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any a pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of examples 1-18 and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

***Response to Arguments***

Applicants argue that the claims fulfill the requirements of written description. The table below shows the components, the ratio of components to one another, and the type of interaction between the components.

| Example # | Active Pharmaceutical ingredient (API) | Co-crystal former #1 (CCF1) | Co-crystal former #2 (CCF2) | Stoichiometry of components (API: CCF1: CCF2) | Hydrogen bond type(s) |
|---|---|---|---|---|---|
| 1 | acetaminophen | 4,4'-bipyridine | water | 1:1:1 | H (amide)---N (pyridine N or imine) and H (hydroxy)---O (water) |
| 2 | Phenytoin | Pyridine | | 1:1 | N (pyridine N or imine) ---H (amide) |
| 3 | Aspirin | 4,4'-bipyridine | | 2:1 | N pyridine N or imine)---H (carboxylic acid) |
| 4 | Ibuprofen | 4,4'-bipyridine | | 2:1 | N pyridine N or imine)---H (carboxylic acid) |

| | | | | |
|---|---|---|---|---|
| 5 | Flurbiprofen | 4,4'-bipyridine | 2:1 | N pyridine N or imine---H (carboxylic acid) |
| 6 | Flurbiprofen | Trans-1,2-bis-(4-pyridyl)ethylene | 2:1 | N pyridine N or imine---H (carboxylic acid) |
| 7 | Carbazepine | *p*-phthaldehyde | 1:1 | O (amide)---H (aldehyde) and O (aldehyde)---H (amide) |
| 8 | Carbazepine | Nicotinamide | 1:1 | N (amide)---H (amide) and O (amide)---H (amide) |
| 9 | Carbazepine | Saccharin | 1:1 | O (amide)---H (amide) and O (sulfonyl)---H (amide) |
| 10 | Carbazepine | 2,6-pyridinecarboxylic acid | 2:3 | O (amide)---H (carboxylic acid) |
| 11 | Carbazepine | 5-nitroisophthalic acid | 1:1 | O (amide)---H (carboxylic acid) |

| | | | | |
|---|---|---|---|---|
| 12 | Carbazepine | Acetic acid | 1:1 | O (amide)---H (carboxylic acid) |
| 13 | Carbazepine | 1,3,5,7-adamantanecarboxylic acid | 1:1 | O (amide)---H (carboxylic acid) |
| 14 | Carbazepine | Benzoqunone | 1:1 | O (ketone)---H (amide) |
| 15 | Carbazepine | Butyric acid | 1:1 | O (amide)---H (carboxylic acid) and O (carboxylic acid)---H (amide) |
| 16 | Carbazepine | DMSO | 1:1 | O (sulfone)---H (amide) |
| 17 | Carbazepine | Formamide | 1:1 | O (amide)---H (amide) and O (amide)---H (amide) |
| 18 | Carbazepine | Formic acid | 1:1 | O (amide)---H (carboxylic acid) and O (carboxylic acid)---H (amide) |
| 19 | Carbazepine | Trimesic acid | 1:1 | O (amide)---H (carboxylic acid) and O |

(carboxylic acid)---H (amide)

The rejection is maintained because the instant claims do not show possession of the complete scope of non-covalent interactions through hydrogen bonding. Applicants argue that examples 1-19 of the specification show a structure function relationship of groups that can participate in H-bonding. Although these examples show the relationship of different groups for H-bonding (as seen in the table above), they do not limit the scope of the claims. The broad and reasonable interpretation of claim 37 encompasses more than groups participating in H-bonding in examples 1-19. Additionally, the types of H-bonding described in the examples are not incorporated in the instant rejected claims. Therefore, under BRI, it would be improper to import only the types of H-bonding in the examples into the claims.

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claims 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the required structural components of an API and a co-crystal former and the functional groups that are used for non-covalent hydrogen bonding. None of claims 37-50 fully define the required structural elements of the API or the cocrystal former. Rather, an API and cocrystal former are defined by their properties. Hsu (same reference as above) prepares a complex of salicylamide and 5-ethyl-5-isoamylbarbituric acid. Miroshnyk (same reference as above) describes three broad methods of non-covalent H-bonding interactions and various combinations of seven different API's with various cocrystal formers.

***Response to Arguments***

This rejection is maintained because the applicants have not fully defined the complexes formed. Claims 37-50 do not fully characterize or describe the active pharmaceutical ingredient (API) and the co-crystal former. Claim 37 only recites that the API is pharmaceutically active. What or how is the ingredient active? What are the required

structural features of the API? The co-crystal former is unclear because it only defined as having a complimentary chemical functionality to the API. Claim 38 recites four different generic co-crystal formers defined by property not by the required structural elements. One looking at the claim cannot determine the complex that the pharmaceutical composition contains. Applicants point to a laundry list of different functional groups that can participate in H-bonding. It is improper to limit the claims with the specification. Paragraph [0009] is open-ended ("non-limiting") with regard to a functional group that can be used.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 45 of U.S. Patent No. 10633344 (hereinafter '344). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of '344. Claim 37 of '344 overlaps with instant claims 37 and 39. Claim 45 of '344 is embraced by instant claims 37 and 40.

Claims 37, 38 and 42 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37, 38, and 42 of copending Application No. 16/270981 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 16/270981. Claims 37, 38, and 42 of '981 overlap with instant claims 37, 38, and 42. Example 1 (page 16, paragraph [0056] to page 17, paragraph [0059]) shows a co-crystal of acetaminophen, bipyridine, and water.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Response to Arguments***

The terminal disclaimers filed 9 October 2020 are not approved because the person who signed the terminal disclaimer is not the applicant, patentee, or an attorney or agent of record (see 37 CFR 1.321 (a) and (b) and FP 14.26.08). Additionally, applicant has requested the rejections be held in abeyance. Consequently the double patenting rejections are maintained

***Conclusion***

Claims 37-50 are not presently allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on 9:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1699

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1699 |

| CPC - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| c07d223/26.cpc. and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | 02/19/2019 | NJ |

| CPC Combination Sets - Searched* | | |
|---|---|---|
| **Symbol** | **Date** | **Examiner** |
| | | |

| US Classification - Searched* | | | |
|---|---|---|---|
| **Class** | **Subclass** | **Date** | **Examiner** |
| | | | |

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
| c07d223/26.cpc. and (cocrystal co NEAR crystalcocrystals co near crystals).clm. | 02/19/2019 | NJ |
| stn registry and hcaplus | 02/19/2019 | NJ |
| inventor search in PALM and EAST | 02/19/2019 | NJ |
| stn registry and hcaplus | 10/30/2019 | NJ |

| Interference Search | | | |
|---|---|---|---|
| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| C07D | 223/26 | 02/19/2019 | NJ |

| | |
|---|---|
| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 363 of 415

| FORM PTO-1449/A and B (modified PTO/SB/08) **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** | | | | APPLICATION NO.: 15/639,223 | ATTY. DOCKET NO.: U0157.70023US03 |
|---|---|---|---|---|---|
| | | | | FILING DATE: June 30, 2017 | CONFIRMATION NO.: 8089 |
| | | | | FIRST NAMED INVENTOR: Michael J. Zaworotko | |
| Sheet | 1 | of | 1 | GROUP ART UNIT: 1699 | EXAMINER: N. E. Jarrell |

**U.S. PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | U.S. Patent Document | | Name of Patentee or Applicant of Cited Document | Date of Publication or Issue of Cited Document MM-DD-YYYY |
|---|---|---|---|---|---|
| | | Number | Kind Code | | |
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**FOREIGN PATENT DOCUMENTS**

| Examiner's Initials # | Cite No. | Foreign Patent Document | | | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY | Translation (Y/N) |
|---|---|---|---|---|---|---|---|
| | | Office/ Country | Number | Kind Code | | | |
| | | WO | 2006/007448 | A2 | Transform Pharmaceuticals, Inc. | 01-19-2006 | |
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**OTHER ART – NON PATENT LITERATURE DOCUMENTS**

| Examiner's Initials # | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | Translation (Y/N) |
|---|---|---|---|
| | | KOBAYASHI et al., Supramolecular architecture consisting of an enantiopure amine and an achiral carboxylic acid: application to the enantioseparation of racemic alcohols. Org Lett. 2004 Aug 19;6(17):2941-4. doi: 10.1021/ol048948b. | |
| | | KODAMA et al., Two-component supramolecular helical architectures: creation of tunable dissymmetric cavities for the inclusion and chiral recognition of the third components. Chemistry. 2007;13(7):2144-52. doi: 10.1002/chem.200601295. | |
| | | | |

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

| EXAMINER: | DATE CONSIDERED: |
|---|---|
| /NOBLE E JARRELL/ | 07/28/2021 |

# EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

**9372490.1**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.J/

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BOSTON, MA 02210-2206

**Courtesy Reminder for**
**Application Serial No: 15/639,223**

Attorney Docket No: U0157.70023US03
Customer Number: 23628
Date of Electronic Notification: 08/11/2021

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

To view your correspondence online or update your email addresses, please visit us anytime at **https://ppair-my.uspto.gov/pair/PrivatePair.**
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (12-20)

# CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

| Practitioner Docket No.: | Application No.: | Filing Date: |
|---|---|---|
| U0157.70023US03 | 15/639,223-Conf. #8089 | June 30, 2017 |

| First Named Inventor: | Title: |
|---|---|
| Michael J. Zaworotko | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL |

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).

2. The above-identified application contains an outstanding final rejection.

3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.

4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.

5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.

6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).

7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]

8. By filing this certification and request, applicant acknowledges the following:

- Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
- The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
  - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
  - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
    - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
    - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

| Signature | Date | Practitioner Registration No. |
|---|---|---|
| /David F. Cauble/ | November 12, 2021 | 73,490 |
| **Name (Print/Typed)** | **Telephone Number** | |
| David F. Cauble, PhD, JD | 617.646.8000 | |

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of 1 forms are submitted.

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 12, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

19780515.1

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 12, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

## RESPONSE AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

In response to the Final Office Action dated August 11, 2021, please enter the following in the above-identified U.S. patent application. Thursday, November 11, 2021 was a Federal Holiday. As such, this Response is timely filed on Friday, November 12, 2021.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks** begin on page 5 of this paper.

## AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior listings, and versions, of claims currently in the application.

1 – 36. (Canceled)

37. (Currently amended) 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-crystal former and each supramolecular synthon comprising a heterosynthon formed via non-covalent hydrogen bonding,

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, and wherein the first chemical functionality is selected from carboxylic acid, amide, N-heterocycle, and alcohol;

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

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

wherein the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.

38. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a food additive, a low toxicity organic, and a metal-organic complex.

39. (Previously presented) The pharmaceutical composition of claim 37, wherein the at least one co-crystal former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 368 of 415

40. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and one co-crystal former.

41. (Previously presented) The pharmaceutical composition of claim 37, wherein each supramolecular synthon is formed from stoichiometric amounts of one active pharmaceutical ingredient (API) and one co-crystal former.

42. (Cancelled)

43. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an acid.

44. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amine.

45. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an amide.

46. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise an alcohol.

47. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon.

48. (Cancelled)



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 369 of 415

49. (Previously presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthons comprise a homosynthon and a heterosynthon.

50. (Currently amended) The pharmaceutical composition of claim ~~48~~ 1, wherein the heterosynthon comprises an alcohol/amine interaction.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 370 of 415

## REMARKS

Claims 37-50 were previously pending in this application. By way of amendment, claims 37 and 50 have been amended, and claims 42 and 48 have been cancelled. Claim 37 has been amended to recite the elements of claims 39 and 48, and to specify that the first chemical functionality is selected from carboxylic acid, amide, N-heterocycle, and alcohol. Support for this amendment can be found in paragraph [0048] of the Application as originally filed. Claim 37 has been further amended to specify that the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol. Support for this amendment can be found, for example, in original claim 13. No new matter is added.

***Claim Rejections – 35 USC § 112***

Claims 37-50 are rejected under 35 U.S.C. 112 (pre-AIA), first paragraph on the ground that the claims allegedly lack written description. Applicant disagrees. However, solely to expedite prosecution, claim 37 has been amended to specify that each supramolecular synthon comprises a heterosynthon formed via non-covalent hydrogen bonding, and that the first chemical functionality is selected from carboxylic acid, amide, N-heterocycle, and alcohol.

Page 7 of the Office Action, the Office maintains that Applicant has not shown possession of the complete scope of non-covalent interactions through hydrogen bonding. The Office concedes that examples 1-19 show the relationship of different groups for H-bonding, but argues that "claim 37 encompasses more than the groups…of examples 1-19," noting that "the types of H-bonding described in the examples are not incorporated in the instant rejected claims." Solely to expedite prosecution, claim 37 has been amended to specify that the first chemical functionality is selected from the functional groups exemplified in examples 1-19.

For example, the API of Example 1 (acetaminophen), comprises both an alcohol and an amide. The API of Example 2 (phenytoin) comprises an N-heterocycle. The API of Example 3 (acetylsalicylic acid) comprises a carboxylic acid. The API of Example 4 (ibuprofen) comprises a carboxylic acid. The API of Examples 5 and 6 (flurbiprofen) comprises a carboxylic acid. The API of Examples 7-19 (carbamazepine) comprises an H-heterocycle in combination with 13 different co-



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 371 of 415

formers. These examples correspond to Figures 3, 5B, 6C, 7C-D, 8C-D, 9A-B, 10B, 11, 12, and 14A-B through 23A-B.

As amended, claim 37 recites the chemical functional groups of the API that form hydrogen bonds with the co-former. The recited groups are exemplified in the Examples and Figures discussed above. Amended claim 37 also recites specific functional groups that are present in the supramolecular synthons. These functional groups are also exemplified in the Examples and Figures discussed above. As such, claim 37 is adequately supported by the description of the Application as filed, and Applicant requests withdrawal of this rejection.

Claims 37-50 are rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Applicant notes that the Office has not elaborated on the grounds for this rejection in the present office action. In contrast, in the non-final rejection dated February 5, 2021, the Office made the same rejection, explaining that it considered the term "GRAS compound" to be unclear. In its response of May 27, 2021, Applicant deleted the term "GRAS compound." As such, Applicant believes that the rejection under 35 U.S.C. 112 (pre-AIA) is overcome.

Claims 37-50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements, such as omission amounting to a gap between the elements. Specifically, the Office alleges that the claims omit "the required structural components of an API and co-crystal former and the functional groups that are used for non-covalent hydrogen bonding. Applicant respectfully disagrees. However, solely to expedite prosecution, claim 37 has been amended to specify that the supramolecular synthon comprises a heterosynthon, that the first chemical functionality of the API is selected from carboxylic acid, amide, N-heterocycle, and alcohol, and that the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol.

Claims 37-50 do not omit essential elements and Applicant requests withdrawal of this rejection.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 372 of 415

***Double Patenting***

Claims 37-50 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 45 of U.S. Patent No. 10,633,344. The Office states that claim 37 of '344 overlaps with instant claims 37 and 39, and that claim 45 of '344 is embraced by instant claims 37 and 40.

As a preliminary matter, Applicant notes that U.S. Patent No. 10,633,344 only has 21 claims, and as such does not have a claim 37 or 45. For the purpose of this Response, however, Applicant assumes that "claim 37 of '344" corresponds to claim 1 as issued in U.S. Patent No. 10,633,344 and that "claim 45 of '344" corresponds to claim 15 as issued in U.S. Patent No. 10,633,344. As described above, instant claim 37 has been amended to specify that the supramolecular synthon comprises a heterosynthon, that the first chemical functionality of the API is selected from carboxylic acid, amide, N-heterocycle, and alcohol, and that the supramolecular synthons comprise an acid, an amide, an amine, or an alcohol. The claims of 10,633,344, alone or in combination, do not recite all of the elements of amended claim 37. As such, amended claim 37 is not anticipated by any claim of 10,633,344, and the Office has not provided a rationale for the obviousness of amended claim 37 over any claim of 10,633,344. As such, Applicant requests withdrawal of this rejection.

Claims 37, 38, and 42 are previously rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37, 38, and 42 of copending Application No. 16/270,981. Claim 37 has been amended to recite the elements of claim 48. Claim 48 is not rejected. Accordingly, Applicant requests withdrawal of this rejection.



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 373 of 415

## CONCLUSION

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number indicated below to discuss any outstanding issues.

Applicant believes no fee is due with this Amendment. However, if a fee is due with this Amendment, please charge our Deposit Account No. 23/2825, under Docket No. U0157.70023US03 from which the undersigned is authorized to draw.

Dated: November 12, 2021

Respectfully submitted,

By /David F. Cauble/
David F. Cauble, PhD, JD
Registration No.: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 374 of 415

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 44270801 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 12-NOV-2021 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 15:01:07 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26561<br>4a406530e3e6b3a76de7475aea6550dc2bd e0f82 | no | 1 |
| **Warnings:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Information:** | | | | | |
| 2 | After Final Consideration Program Request | U015770023US03-RAFPP-DFC.pdf | 31175<br>b3bf5a3a61a051d5c5a71e13c9289308ce39ca00 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | | U015770023US03-116AMN-DFC.pdf | 48515<br>d6c909e281a92cd59dac0a5df4bc6eb0535b7150 | yes | 8 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Response After Final Action | 1 | 1 |
| Claims | 2 | 4 |
| Applicant Arguments/Remarks Made in an Amendment | 5 | 8 |

| | |
|---|---|
| **Warnings:** | |
| **Information:** | |
| **Total Files Size (in bytes):** | 106251 |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1699 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [x] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Certification and Request for Consideration Under The After Final Consideration Pilot Program

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | November 12, 2021 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 12, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9780513.1**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 11/30/2021

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/30/2021 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| ***Advisory Action Before the Filing of an Appeal Brief*** | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (FITF) Status** No |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 12 November 2021 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☑ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☑ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection.The current period for reply expires ____ months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   *Examiner Note*: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☑ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☑ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See Continuation Sheet (See 37CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicants reply has overcome the following rejection(s): _____
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☑ For purposes of appeal, the proposed amendment(s):(a) ☑ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed:_____.
    Claim(s) objected to:_____.
    Claim(s) rejected:37-50.
    Claim(s) withdrawn from consideration:_____.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1699



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 379 of 415

Continuation of 3. NOTE: A new search is required based on the amendments to parent claim 37. The claim set of the final rejection did not require the limitations added on 12 November 2021. After looking at the double patenting rejection, it would be maintained because an alcohol can be present in the supramolecular synthon. Additionally, the written description would be maintained because the prepared complexes do not completely support the amended claims. Example 2 provided support for pyridine in the active pharmaceutical ingredient.

Docket No.: U0157.70023US03
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| First Named Inventor: | Michael J. Zaworotko |
| Application No.: | 15/639,223 |
| Confirmation No.: | 8089 |
| Filed: | June 30, 2017 |
| For: | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| Examiner: | N. E. Jarrell |
| Art Unit: | 1699 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: November 12, 2021 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

## RESPONSE AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

## INTRODUCTORY COMMENTS

In response to the Final Office Action dated August 11, 2021, please enter the following in the above-identified U.S. patent application. Thursday, November 11, 2021 was a Federal Holiday. As such, this Response is timely filed on Friday, November 12, 2021.

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks** begin on page 5 of this paper.

DO NOT ENTER: /N.J/

11/24/2021

9752659.1

| Request for Continued Examination (RCE) Transmittal | | |
|---|---|---|
| Address to:<br>Mail Stop RCE<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Application Number | 15/639,223-Conf. #8089 |
| | Filing Date | June 30, 2017 |
| | First Named Inventor | Michael J. Zaworotko |
| | Art Unit | 1699 |
| | Examiner Name | N. E. Jarrell |
| | Attorney Docket Number | U0157.70023US03 |

**This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.**

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C 371, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO on page 2.)

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [x] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [ ] Enclosed
     - i. [ ] Amendment/Reply
     - ii. [ ] Affidavit(s)/ Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [ ] Other _____
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. [ ] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 23/2825 .
     - i. [x] RCE fee required under 37 CFR 1.17(e)
     - ii. [x] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [x] Payment by credit card (~~Form PTO-2038 enclosed~~)

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

***SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED***

| | | | |
|---|---|---|---|
| Signature | /David F. Cauble/ | Date | January 7, 2022 |
| Name (Print/Type) | David F. Cauble, PhD, JD | Registration No. | 73,490 |

***CERTIFICATE OF MAILING OR TRANSMISSION***

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

| | | | |
|---|---|---|---|
| Signature | | | |
| Name (Print/Type) | | Date | |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 7, 2022 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9937520.1**

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 15639223 |
| **Filing Date:** | 30-Jun-2017 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Attorney Docket Number:** | U0157.70023US03 |

Filed as Small Entity

**Filing Fees for Utility under 35 USC 111(a)**

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| Extension - 2 months with $0 paid | 2252 | 1 | 320 | 320 |
| **Miscellaneous:** | | | | |
| RCE- 1ST REQUEST | 2801 | 1 | 680 | 680 |
| | | **Total in USD ($)** | | **1000** |

| Electronic Acknowledgement Receipt | |
|---|---|
| **EFS ID:** | 44693648 |
| **Application Number:** | 15639223 |
| **International Application Number:** | |
| **Confirmation Number:** | 8089 |
| **Title of Invention:** | MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT |
| **First Named Inventor/Applicant Name:** | Michael J. Zaworotko |
| **Customer Number:** | 23628 |
| **Filer:** | David F. Cauble/Cathy Nicholson |
| **Filer Authorized By:** | David F. Cauble |
| **Attorney Docket Number:** | U0157.70023US03 |
| **Receipt Date:** | 07-JAN-2022 |
| **Filing Date:** | 30-JUN-2017 |
| **Time Stamp:** | 13:12:02 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | CARD |
| Payment was successfully received in RAM | $1000 |
| RAM confirmation Number | E202217D12232766 |
| Deposit Account | |
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| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | Transmittal Letter | U015770023US03-TRN-DFC.pdf | 26293<br>9a79f6d4859566bc6932433f6218c6ee029ec6d | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | U015770023US03-FEE-DFC.pdf | 37607<br>fefdf2c9e819eda0270a371f84a3d1e535dff21f | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Extension of Time | U015770023US03-EXT-DFC.pdf | 25185<br>b924777a38b57bf8487bed1be9d7d9c15ba42846 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Request for Continued Examination (RCE) | U015770023US03-RCE-DFC.pdf | 29129<br>1a37847620ec52b0e7c839d80158d3e84ad3f56c | no | 1 |
| **Warnings:** | | | | | |
| This is not a USPTO supplied RCE SB30 form. | | | | | |
| **Information:** | | | | | |
| 5 | Fee Worksheet (SB06) | fee-info.pdf | 40680<br>9de7781000f8af7e44b4a2fdd012f79d5e496739 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 158894 | | |

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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Total Number of Pages in This Submission | |

| | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Art Unit | 1699 |
| Examiner Name | N. E. Jarrell |
| Attorney Docket Number | U0157.70023US03 |

## ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Request for Continued Examination (RCE)

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | WOLF, GREENFIELD & SACKS, P.C. | | |
| Signature | /David F. Cauble/ | | |
| Printed name | David F. Cauble, PhD, JD | | |
| Date | January 7, 2022 | Reg. No. | 73,490 |

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 7, 2022 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9937517.1**

# FEE TRANSMITTAL

| Complete if known | |
|---|---|
| Application Number | 15/639,223-Conf. #8089 |
| Filing Date | June 30, 2017 |
| First Named Inventor | Michael J. Zaworotko |
| Examiner Name | N. E. Jarrell |
| Art Unit | 1699 |
| Practitioner Docket No. | U0157.70023US03 |

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($)1,000.00

**METHOD OF PAYMENT** (check all that apply)

[ ] Check [X] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

[ ] Charge fee(s) indicated below

[ ] Charge fee(s) indicated below, **except for the filing fee**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17, **except for any excess claims fees or multiple dependent claim fee**

[ ] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17

[X] Credit any overpayment of fee(s)

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**FEE CALCULATION**

**1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)**

| | FILING FEES | | | SEARCH FEES | | | EXAMINATION FEES | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Application Type** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **U ($)** | **S ($)** | **M ($)** | **Fees Paid ($)** |
| Utility | 320 | 160* | 80 | 700 | 350 | 175 | 800 | 400 | 200 | |
| Design | 220 | 110 | 55 | 160 | 80 | 40 | 640 | 320 | 160 | |
| Plant | 220 | 110 | 55 | 440 | 220 | 110 | 660 | 330 | 165 | |
| Reissue | 320 | 160 | 80 | 700 | 350 | 175 | 2,320 | 1,160 | 580 | |
| Provisional | 300 | 150 | 75 | 0 | 0 | 0 | 0 | 0 | 0 | |

* The $160 small entity status filing fee for a utility application is further reduced to $80 for a small entity status applicant who files the application via EFS-Web.

**2. EXCESS CLAIM FEES**

| **Fee Description** | **Undiscounted Fee ($)** | **Small Entity Fee ($)** | **Micro Entity Fee ($)** |
|---|---|---|---|
| Each claim over 20 (including Reissues) | 100 | 50 | 25 |
| Each independent claim over 3 (including Reissues) | 480 | 240 | 120 |
| Multiple dependent claims | 860 | 430 | 215 |

| **Total Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** | **Multiple Dependent Claims** | |
|---|---|---|---|---|---|
| | | | | **Fee ($)** | **Fee Paid ($)** |
| _____ - 20 or HP = | _____ | x _____ | = _____ | _____ | _____ |

HP = highest number of total claims paid for, if greater than 20.

| **Indep. Claims** | **Extra Claims** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|
| _____ - 4 or HP = | _____ | x _____ | = _____ |

HP = highest number of independent claims paid for, if greater than 3.

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

| **Total Sheets** | **Extra Sheets** | **Number of each additional 50 or fraction thereof** | **Fee ($)** | **Fee Paid ($)** |
|---|---|---|---|---|
| _____ - 100 = | _____ /50 = | _____ (round **up** to a whole number) x | _____ | = _____ |

**4. OTHER FEE(S)**

| | **Fees Paid ($)** |
|---|---|
| Non-English specification, $130 fee (no small or micro entity discount) | |
| **Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)** | |
| Other (e.g., late filing surcharge): 2252 Extension for response within second month | 320.00 |
| 2801 Request for continued examination (RCE) - 1st ... | 680.00 |

**SUBMITTED BY**

| | | | | | |
|---|---|---|---|---|---|
| Signature | /David F. Cauble/ | Registration No. (Attorney/Agent) | 73,490 | Telephone | 617.646.8000 |
| Name (Print/Type) | David F. Cauble, PhD, JD | | | Date | January 7, 2022 |

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Dated: January 7, 2022 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

9937515.1

PTO/AIA/22 (10-20)
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| **PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)** | Docket Number (Optional) U0157.70023US03 |
|---|---|
| Application Number 15/639,223-Conf. #8089 | Filed June 30, 2017 |
| For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT | |
| Art Unit 1699 | Examiner N. E. Jarrell |

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

| | Fee | Small Entity Fee | Micro Entity Fee | |
|---|---|---|---|---|
| ☐ One month (37 CFR 1.17(a)(1)) | $220 | $110 | $55 | $ |
| ☒ Two months (37 CFR 1.17(a)(2)) | $640 | $320 | $160 | $ 320.00 |
| ☐ Three months (37 CFR 1.17(a)(3)) | $1,480 | $740 | $370 | $ |
| ☐ Four months (37 CFR 1.17(a)(4)) | $2,320 | $1,160 | $580 | $ |
| ☐ Five months (37 CFR 1.17(a)(5)) | $3,160 | $1,580 | $790 | $ |

☒ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. ~~Form PTO-2038 is attached~~.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

☒ Payment made via EFS-Web.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

I am the

☐ applicant.

☐ attorney or agent of record. Registration number _____.

☒ attorney or agent acting under 37 CFR 1.34. Registration number 73,490.

| /David F. Cauble/ | January 7, 2022 |
|---|---|
| Signature | Date |
| David F. Cauble, PhD, JD | 617.646.8000 |
| Typed or printed name | Telephone Number |

**NOTE:** This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

**Certificate of Electronic Filing under 37 C.F.R. § 1.8**

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Dated: January 7, 2022 Signature: /Cathy Nicholson/ (Cathy T. Nicholson)

**9937521.1**

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 03/22/2022
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 03/22/2022 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Office Action Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | |
|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (FITF) Status** No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 07 January 2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5) ☑ Claim(s) 37-41,43-47 and 49-50 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 37-41,43-47 and 49-50 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

**DETAILED ACTION**

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7 January 2022 has been entered. Newly amended claims 37-41, 43-47, 49, and 50 are pending and are examined.

***Claim Objections***

Claims 40 and 41 are duplicate objected to because of the following informalities: each claim has the same language. Consequently, the claims are duplicative. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him.

Claim(s) 37-41, 43-47, 49, and 50 is/are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph due to lack of written description.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons. Each synthon is formed from a stoichiometric amount of at least one active pharmaceutical ingredient (API) and at least one co-crystal former. The synthons are associated together through non-covalent hydrogen bonding. The universe of pharmaceutical compositions comprising an API and co-crystal former includes any co-crystal comprising an API and co-crystal bound together by noncovalent H-bonding.

(1) Level of skill and knowledge in the art:

HSU (*Acta Crystallographica*, **1974**, *B30*, 843-846, cited in IDS) describes a 1:1 cocrystal of salicylamide and 5-ethylisoamylbarbituric acid (title and abstract). Hydrogen bonding is used to bind the compounds together (abstract; page 845, column 2 to page 846, column 1, paragraph 1).

MIROSHNYK (*Expert Opinion in Drug Delivery*, **2009**, *6(4)*, 333-341, cited previously) describes how cocrystals are bound together and examples of the same (table 1, page 336; table 2, page 339).

(2) Partial structure:

A partial structure encompasses a pharmaceutical composition comprising a cocrystal of an API and a co-crystal former bound together by non-covalent H-bonding. The API has a functional group selected from a carboxylic acid, carboxylic amide, an N-heterocycle, and an alcohol.

(3) Physical and/or chemical properties and (4) Functional characteristics:

Examples 1-19 (page 16, paragraph [0056]) to page 33, paragraph [00177]) describe different properties of the compositions selected from crystal data, IR spectroscopy, DSC, TGA, and XRPD. The examples provide a wide range of solid phases having properties such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability.

(5) Method of making the claimed invention:

Example 1 shows a representative method of making a pharmaceutical composition where 50 mg of acetaminophen and 52 mg of 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation lead to colorless needles of 1:1:1 acetaminophen: 4,4'-bipyridine: water co-crystal (figure 4B).

The MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 37-41, 43-47, 49, and 50 is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any a pharmaceutical composition comprising an API and a co-crystal former that are associated through non-covalent hydrogen binding. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of examples 1-18 and

compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

***Response to Arguments***

Applicants argue that the claims fulfill the requirements of written description. The table below shows the components, the ratio of components to one another, and the type of interaction between the components.

| Example # | Active Pharmaceutical ingredient (API) | Co-crystal former #1 (CCF1) | Co-crystal former #2 (CCF2) | Stoichiometry of components (API: CCF1: CCF2) | Hydrogen bond type(s) |
|---|---|---|---|---|---|
| 1 | acetaminophen | 4,4'-bipyridine | water | 1:1:1 | H (amide)---N (pyridine N or imine) and H (hydroxy)---O (water) |
| 2 | Phenytoin | Pyridine | | 1:1 | N (pyridine N or imine) ---H (amide) |
| 3 | Aspirin | 4,4'-bipyridine | | 2:1 | N pyridine N or imine)---H (carboxylic acid) |
| 4 | Ibuprofen | 4,4'-bipyridine | | 2:1 | N pyridine N or imine)---H |

| | | | | |
|---|---|---|---|---|
| | | | | (carboxylic acid) |
| 5 | Flurbiprofen | 4,4'-bipyridine | 2:1 | N pyridine N or imine---H (carboxylic acid) |
| 6 | Flurbiprofen | Trans-1,2-bis-(4-pyridyl)ethylene | 2:1 | N pyridine N or imine---H (carboxylic acid) |
| 7 | Carbazepine | *p*-phthaldehyde | 1:1 | O (amide)---H (aldehyde) and O (aldehyde)---H (amide) |
| 8 | Carbazepine | Nicotinamide | 1:1 | N (amide)---H (amide) and O (amide)---H (amide) |
| 9 | Carbazepine | Saccharin | 1:1 | O (amide)---H (amide) and O (sulfonyl)---H (amide) |
| 10 | Carbazepine | 2,6-pyridinecarboxylic acid | 2:3 | O (amide)---H (carboxylic acid) |

| | | | | |
|---|---|---|---|---|
| 11 | Carbazepine | 5-nitroisophthalic acid | 1:1 | O (amide)---H (carboxylic acid) |
| 12 | Carbazepine | Acetic acid | 1:1 | O (amide)---H (carboxylic acid) |
| 13 | Carbazepine | 1,3,5,7-adamantanecarboxylic acid | 1:1 | O (amide)---H (carboxylic acid) |
| 14 | Carbazepine | Benzoquinone | 1:1 | H (amide)---O (ketone) |
| 15 | Carbazepine | Butyric acid | 1:1 | O (amide)---H (carboxylic acid) and O (carboxylic acid)---H (amide) |
| 16 | Carbazepine | DMSO | 1:1 | H (amide)---O (sulfone) |
| 17 | Carbazepine | Formamide | 1:1 | O (amide)---H (amide) and O (amide)---H (amide) |
| 18 | Carbazepine | Formic acid | 1:1 | O (amide)---H (carboxylic acid) and O (carboxylic acid)---H (amide) |

| | | | | |
|---|---|---|---|---|
| 19 | Carbazepine | Trimesic acid | 1:1 | O (amide)---H (carboxylic acid) and O (carboxylic acid)---H (amide) |

***Response to Arguments***

The rejection is maintained because the instant claims do not show possession of the complete scope of non-covalent interactions through hydrogen bonding. Applicants argue that examples 1-19 of the specification show a structure function relationship of groups that can participate in H-bonding. Although these examples show the relationship of different groups for H-bonding (as seen in the table above), they do not limit the scope of the claims. The broad reasonable interpretation (BRI) of claim 37 encompasses more than the functional groups participating in H-bonding in examples 1-19. The whole structure of each component of the co-crystal has to be taken into consideration. The functional groups only represent a one part of the API and one or more co-crystal former(s).

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-41, 43-47, 49, and 50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention. Claim 50 is unclear because it depends on claim 1, which has been cancelled.

Claims 37-41, 43-47, 49, and 50 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the required structural components of an API and a co-crystal former. None of claims 37-41, 43-47, 49, and 50 fully define the required structural elements of the API or the cocrystal former. In the examined claims, the API and cocrystal former are defined by the present functional groups that participate in hydrogen bonding and ratio between the API and co-crystal former.

The term "low toxicity organic" in claim 38 is a relative term which renders the claim indefinite. The term "low toxicity organic" is not defined by the claim, the specification does not provide a standard for ascertaining the

requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without guidance, the metes and bounds of the toxicity type and what is considered low renders the claim unclear. OSHA describes different types of hazards and ways to measure them (OSHA Hazard Communication guidance, **2016**, pages 1-424).

Claim 47 recites the limitation that the supramolecular synthons comprise a homosynthon. There is insufficient antecedent basis for this limitation in the claim because parent claim 37 states that the supramolecular synthon comprises a heterosynthon. For proper antecedent basis, the claim could say "wherein the supramolecular synthons further comprise a homosynthon".

***Response to Arguments***

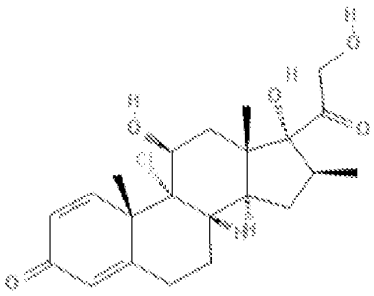
This rejection is maintained because the applicants have not fully defined the complexes formed. Claims 37-41, 43-47, 49, and 50 do not fully characterize or describe the active pharmaceutical ingredient (API) and the co-crystal former. Claim 37 only recites that the API is pharmaceutically active. In what way is the API active? What are the required structural features of the API? The co-crystal former is unclear because it only defined as having a complimentary chemical functionality to the API. Claim 38 recites four different generic co-crystal formers defined by a class with no recited required structural elements. One looking at the claims cannot immediately envisage a supramolecular synthon comprising an API and co-crystal carrier. It is improper to limit the claims with the specification.

***Claim Rejections - 35 USC § 102***

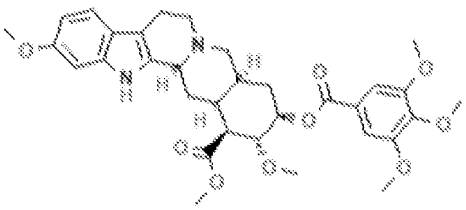
The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

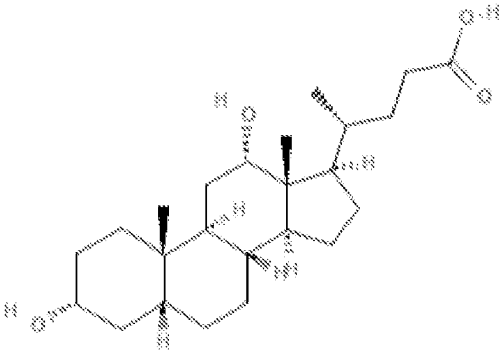
Claim(s) 37, 40, 41, 46, and 49 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by LEI (*Journal of Chinese Pharmaceutical Sciences*, **1999**, *8(3)*, 142-147). Lei describes two solvates of beclomethasone dipropionate (BDP), ethyl acetate (BDP-EtOAc) and trichlorofluoromethane (BDP-P11) (abstract; page 142, column 1, paragraph 5 to page 143, column 2, paragraph 1). These compounds are used in inhalers (page 143, column 2, paragraph 4). The ratio of BDP to EtOAc or P11 is 1:1 in both solvates. Oleic acid Is the carrier in the inhaler. In BDP a hydroxyl H interacts with an ester O or a halogen.



Claim(s) 37, 40, 41, 43, 44, and 50 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by MALONE (*Journal of Pharmaceutical Sciences*, **1966**, *55(9)*, 972-974). Malone describes stoichiometric solvates of reserpine with desoxycholic acid (page 973, table 1). These compounds are used in oral compositions (page 972, column 2, paragraph 4; page 973, table II). Reserpine comprises an *N*-heterocycle and desoxycholic acid has an acid and an alcohol.



reserpine



***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

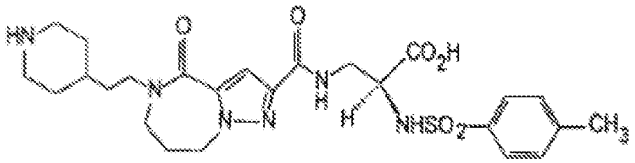
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 37, 40, 41, 43-45, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over BRAY (*Pharmaceutical Development and Technology*, **1999**, *4:1*, 81-87).

***Determining the scope and contents of the prior art***

Bray describes a pentahydrate of L-738167 (page 82, column 1; page 84, table 2). Since form B is the most stable at 90% relative humidty, it is suitable for development into an oral dosage form (page 87, column 1, paragraphs 2-4). L-738167 has an *N*-heterocycle, an amide, and an acid. One of these groups interacts with a hydroxy OH of water.




1

Structure 1. L-738,167.

***Ascertaining the differences between the prior art and the claims at issue***

In the claims at issue, a pharmaceutical composition with a supramolecular complex in which one of the synthons has a carboxylic acid, amide, N-heterocycle, and alcohol. In the prior art, Bray implies an oral dosage form can be prepared with a pentahydrate of L-738167.

***Resolving the level of ordinary skill in the pertinent art***

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position (MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group).

***Considering objective evidence present in the application indicating obviousness or nonobviousness***

A reasonable expectation of success to make an oral dosage form with the pentahydrate of L-738167 because it absorbs the least amount of water at 90% relative humidity (page 86, column 1, paragraph 3).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the foregoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success

in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known technique to improve similar devices (methods, or products) in the same way;
(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or

patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37, 40, 41, 45, 46, 47, and 49 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 10-13 of U.S. Patent No. 10633344 (hereinafter '344). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of '344. Claim 37 of '344 overlaps with instant claims 37 and 39. Claims 10-13 of '344 are embraced by instant claims 37 and 40. Example 1 is an example of both a homosynthon and heterosynthon because the hydroxyl group acetaminophen can interact with a H of water and the amide H interacts with an N of 4,4-bipyridine (column 11, line 60 to column 12, line 23).

Claims 37, 38 and 46 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 37 and 42 of copending Application No. 16/270981 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims are embraced by the specified claims of 16/270981. Claims 37, 38, and 42 of '981 overlap with instant claims 37, 38, and 42. Example 1 (page 16, paragraph [0056] to page 17, paragraph [0059]) shows a co-crystal of acetaminophen, bipyridine, and water. Acetaminophen has both amide and hydroxyl groups.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Response to Amendment***

Newly amended claims 37-41, 43-47, 49, and 50 have been examined with respect to double patenting.

***Conclusion***

Claims 37-41, 43-47, 49, and 50 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE E JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached 9:00 AM to 5:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NOBLE E JARRELL/
Primary Examiner, Art Unit 1699

| Notice of References Cited | Application/Control No. 15/639,223 | Applicant(s)/Patent Under Reexamination Zaworotko et al. | |
|---|---|---|---|
| | Examiner NOBLE E JARRELL | Art Unit 1699 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | CPC Classification | US Classification |
|---|---|---|---|---|---|---|
| | A | | | | | |
| | B | | | | | |
| | C | | | | | |
| | D | | | | | |
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**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | CPC Classification |
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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | OSHA Hazard Communication guidance, 2016, pages 1-424 (Year: 2016) |
| | V | LEI. Journal of Chinese Pharmaceutical Sciences, 1999, 8(3), 142-147 (Year: 1999) |
| | W | MALONE. Journal of Pharmaceutical Sciences, 1966, 55(9), 972-974 (Year: 1966) |
| | X | BRAY. Pharmaceutical Development and Technology, 1999, 4:1, 81-87 (Year: 1999) |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1699 |

| CPC - Searched* | | |
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| **Symbol** | **Date** | **Examiner** |
| c07d223/26.cpc. and (cocrystal co NEAR crystal cocrystals co near crystals).clm. | 02/19/2019 | NJ |

| CPC Combination Sets - Searched* | | |
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| US Classification - Searched* | | | |
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| **Class** | **Subclass** | **Date** | **Examiner** |
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* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

| Search Notes | | |
|---|---|---|
| **Search Notes** | **Date** | **Examiner** |
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| stn registry and hcaplus | 02/19/2019 | NJ |
| inventor search in PALM and EAST | 02/19/2019 | NJ |
| stn registry and hcaplus | 10/30/2019 | NJ |
| stn registry and hcaplus | 03/11/2022 | NJ |

| Interference Search | | | |
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| **US Class/CPC Symbol** | **US Subclass/CPC Group** | **Date** | **Examiner** |
| C07D | 223/26 | 02/19/2019 | NJ |

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| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |



NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 406 of 415

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
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| | 15/639,223 | Zaworotko et al. |
| | Examiner | Art Unit |
| | NOBLE E JARRELL | 1699 |

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| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1625 | |



NOVARTIS EXHIBIT 1522
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Page 407 of 415

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L10          1572 SEA SPE=ON   ABB=ON   PLU=ON   L6 AND L5
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     FILE 'HCAPLUS' ENTERED AT 12:29:40 ON 11 MAR 2022
                  E SOLVATES/CT
                  E E3+ALL
L1                QUE SPE=ON   ABB=ON   PLU=ON   SOLVATES+NT/CT
                  E CRYSTALS/CT
                  E E3+ALL
L2                QUE SPE=ON   ABB=ON   PLU=ON   CRYSTALS+NT/CT
                  E E86+ALL
                  E CRYSTALLINITY/CT
                  E E3+ALL
L3                QUE SPE=ON   ABB=ON   PLU=ON   CRYSTALLINITY+OLD/CT
                  E E15+ALL
L4                QUE SPE=ON   ABB=ON   PLU=ON   CRYSTALLIZATION+NT/CT
                  E HYDRATES/CT
                  E E3+ALL
                  E E10+ALL
L5          21637 SEA SPE=ON   ABB=ON   PLU=ON   L1 AND (L2 OR L3 OR L4)
                  E DRUG DELIVERY SYSTEMS/CT
                  E E3+ALL
L6                QUE SPE=ON   ABB=ON   PLU=ON   "DRUG DELIVERY SYSTEMS"+OLD,NT/CT
L7              890 SEA SPE=ON   ABB=ON   PLU=ON   L5 AND L6
L8             1042 SEA SPE=ON   ABB=ON   PLU=ON   L6 (L) (SOLVATE? OR HYDRATE?)
L9              257 SEA SPE=ON   ABB=ON   PLU=ON   L8 AND (L2 OR L3 OR L4)
L10             172 SEA SPE=ON   ABB=ON   PLU=ON   L8 AND L6 (L) ?CRYSTAL?
L11               QUE SPE=ON   ABB=ON   PLU=ON   PRD<=20030303 OR AD<=20030303 OR
                  PD<=20030303
L12              16 SEA SPE=ON   ABB=ON   PLU=ON   L11 AND L9
L13              19 SEA SPE=ON   ABB=ON   PLU=ON   L10 AND L11
L14              27 SEA SPE=ON   ABB=ON   PLU=ON   (L12 OR L13)

     FILE HOME

     FILE HCAPLUS

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     FILE COVERS 1907 - 11 Mar 2022 VOL 178 ISS 1
     FILE LAST UPDATED: 10 Mar 2022 (20220310/ED)

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NOVARTIS EXHIBIT 1522
Novartis v. Regents, IPR2023-01347
Page 411 of 415

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/639,223 | 06/30/2017 | Michael J. Zaworotko | U0157.70023US03 | 8089 |

23628 7590 05/02/2022

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/02/2022 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

| *Applicant-Initiated Interview Summary* | **Application No.** 15/639,223 | **Applicant(s)** Zaworotko et al. | | |
|---|---|---|---|---|
| | **Examiner** NOBLE E JARRELL | **Art Unit** 1699 | **AIA (First Inventor to File) Status** No | **Page** 1 of 1 |

| **All Participants** (applicant, applicants representative, PTO personnel) | **Title** | **Type** |
|---|---|---|
| NOBLE E JARRELL | Primary Examiner | Telephonic |
| David Cauble | Attorney of Record | |

**Date of Interview:** 27 April 2022

**Issues Discussed:**

**Other**

Mr. Cauble asked for a copy of the reference in the firs t 102 rejection. It was inadvertently not attached. It is attached to this communication.

| /NOBLE E JARRELL/<br>Primary Examiner, Art Unit 1699 | |
|---|---|

**Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04**
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

**Applicant recordation instructions:** The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

**Examiner recordation instructions:** Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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23628 7590 12/06/2022

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600 ATLANTIC AVENUE
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| EXAMINER | |
|---|---|
| JARRELL, NOBLE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1699 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
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WGS_eOfficeAction@WolfGreenfield.com

| Notice of Abandonment | Application No. 15/639,223 | Applicant(s) Zaworotko et al. |
|---|---|---|

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--*

This application is abandoned in view of:

1. ☑ Applicant's failure to timely file a proper reply to the Office letter mailed on 22 March 2022.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. ( A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a *bona fide* attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 8 below).
   (d) ☑ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37 CFR 1.18 is $ _____. The publication fee, if required by 37 CFR 1.18(d), is $ _____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33(b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Patent Trial and Appeal Board rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The dismissal of the appeal in an application having no allowed claims. (When an appeal is dismissed in an application having no allowed claims the application stands abandoned. See MPEP 1215.04 subsections I-V for an explanation of the reasons why an appeal is dismissed.)

8. ☐ The reason(s) below:

_____

/KIMBERLY D JONES/

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.