Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
Title of Invention:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Filer:	Jessica Russell Colantonio/Allison Parker
Attorney Docket Number:	U0157.70023US02

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 - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**700**

Electronic Acknowledgement Receipt	
EFS ID:	25372581
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	Jessica Russell Colantonio/Allison Parker
Filer Authorized By:	Jessica Russell Colantonio
Attorney Docket Number:	U0157.70023US02
Receipt Date:	01-APR-2016
Filing Date:	13-FEB-2014
Time Stamp:	15:09:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$700
RAM confirmation Number	1516
Deposit Account	232825
Authorized User	COLANTONIO, JESSICA R.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 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	U015770023US02-TRN-JQC.pdf	24633 3d523e2c28b9f3b2ca419dfa87a58293d6fca04e	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US02-FEE-JQC.pdf	31453 731249d236e36a118331435bada1953455110e6f	no	1
Warnings:					
Information:					
3	Extension of Time	U015770023US02-EXT-JQC.pdf	23274 53d3165e42ba878a5b5508645809363ea806a3a2	no	1
Warnings:					
Information:					
4		U015770023US02-AMN-JQC.pdf	163394 e9ae15c72eefd98f356aafdbb4ff4c392501231d	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	7
Applicant Arguments/Remarks Made in an Amendment	8	15

Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30945 21a7e4599f5ee22f484f0d1e5b0217b304311c82	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	273699		

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	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

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	/Jessica R. Colantonio/		
Printed name	Jessica R. Colantonio, Ph.D.		
Date	April 1, 2016	Reg. No.	66,132

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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 Electronic Signature for Allison E. Parker: /Allison E. Parker/

4680578.1

PTO/SB/17 (03-13)
Approved for use through 01/31/2014. 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

FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[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 ($) 700.00

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	
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 ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
41 - or HP =	x	=			

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

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
2 - 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): 2253 Extension for response within third month	700.00

SUBMITTED BY

Signature	/Jessica R. Colantonio/	Registration No. (Attorney/Agent)	66,132	Telephone	617.646.8000
Name (Print/Type)	Jessica R. Colantonio, Ph.D.			Date	April 1, 2016

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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 Electronic Signature for Allison E. Parker: /Allison E. Parker/

4680577.1

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. 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) U0157.70023US02
Application Number 14/179,862-Conf. #7725	Filed February 13, 2014
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT	
Art Unit 1627	Examiner S. Javanmard

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	$
[X] Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 700.00
[ ] 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	$

[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.

[X] attorney or agent of record. Registration number 66,132 .

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

/Jessica R. Colantonio/ — Signature
April 1, 2016 — Date

Jessica R. Colantonio, Ph.D. — Typed or printed name
617.646.8000 — 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 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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 — Electronic Signature for Allison E. Parker: /Allison E. Parker/

4680579.1

PTO/SB/17 (03-13)
Approved for use through 01/31/2014. 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

FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

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[ ] 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 ($) 700.00

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	
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Plant	180	90	45	380	190	95	580	290	145	
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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 ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
41 - or HP =	_____ x	_____ =	_____	_____	_____

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

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
2 - 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): 2253 Extension for response within third month	700.00

SUBMITTED BY

Signature	/Jessica R. Colantonio/	Registration No. (Attorney/Agent)	66,132	Telephone	617.646.8000
Name (Print/Type)	Jessica R. Colantonio, Ph.D.			Date	April 1, 2016

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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 Electronic Signature for Allison E. Parker: /Allison E. Parker/

4680577.1

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	1	of	2	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

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		

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			

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], Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. ICH Harmonised Tripartite Guideline. 1999 Oct 6; 4:46.	
	*	[NO AUTHOR LISTED], X-ray Diffraction. In: The United States Pharmacopeia – The National Formulary (USP #24 NF19). 2000 Jan. Chapter 941: 2005-7	
	*	ABOURAHMA et al., Network Hydrogen Bonding in Two New Cocrystals Sustained by [Mn(CO)3(OH)]4, a tetrahedral hydrogen bond donor. J Chem Crystallogr. 1995 Nov; 25:731-736.	
	*	ALMARSSON et al., The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. Pharm Pat Anal. 2012 Jul;1(3):313-27. doi: 10.4155/ppa.12.29.	
	*	BEDU-ADDO, Understanding Lyophilization Formulation Development. Pharmaceutical Technology. 2004 Mar: 10-18.	
	*	BERGE et al., Pharmaceutical salts. J Pharm Sci. 1977 Jan;66(1):1-19.	
	*	BYRN et al., Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm Res. 1995 Jul;12(7):945-54.	
	*	DUKE, Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001, CRC Press LLC, page 419.	
	*	EVGEN'EV et al., Selective determination of 4-aminobenzoic and 4-aminosalicylic acid derivatives in mixtures by flow-injection analysis. J Anal Chem. 2000 July;55(7):696-702.	

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) **INFORMATION DISCLOSURE STATEMENT BY APPLICANT**				APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
				FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	2	of	2	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

	*	SMITH et al., The utility of 4-aminobenzoic acid in promotion of hydrogen bonding in crystallization processes: the structures of the cocrystals with halo and nitro subsituted aromatic compounds, and the crystal structures of the adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1). J Chem Crystallogr. 1997 May; 27(5):307-317.	

[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.

*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 Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
Title of Invention:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Filer:	Jessica Russell Colantonio/Eileen Moore
Attorney Docket Number:	U0157.70023US02

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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt	
EFS ID:	25378221
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	Jessica Russell Colantonio/Eileen Moore
Filer Authorized By:	Jessica Russell Colantonio
Attorney Docket Number:	U0157.70023US02
Receipt Date:	01-APR-2016
Filing Date:	13-FEB-2014
Time Stamp:	17:24:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$90
RAM confirmation Number	4047
Deposit Account	232825
Authorized User	COLANTONIO, JESSICA R.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 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	U015770023US02-TRN-JQC.pdf	24562 ad86cbb94e6043ee54e76f836043be2093e76276	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US02-FEE-JQC.pdf	31873 46327a49211fd3ba329dd64ead9c9526d1967ad0	no	1
Warnings:					
Information:					
3		U015770023US02-IDS-JQC.pdf	43386 b26e2fd9be65c9983ed78ecaa71fe119c8565e90	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	5

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30732 e5110ab7d1ae8a1e154e94721fc4da341d06f8a5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	130553		

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	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

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

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica R. Colantonio/		
Printed name	Jessica R. Colantonio, Ph.D.		
Date	April 1, 2016	Reg. No.	66,132

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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 Electronic Signature for Eileen M. Moore: ___/Eileen M. Moore/_____

PTO/SB/17 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[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 ($) 90.00

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	
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 ($)	Fee Paid ($)
41 - 41 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 ($)	Fee Paid ($)
2 - 3 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	90.00

SUBMITTED BY

Signature	/Jessica R. Colantonio/	Registration No. (Attorney/Agent)	66,132	Telephone	617.646.8000
Name (Print/Type)	Jessica R. Colantonio, Ph.D.			Date	April 1, 2016

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 electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: April 1, 2016 Electronic Signature for Eileen M. Moore: /Eileen M. Moore/

DOCKET NO.: U0157.70023US02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Sahar Javanmard
Art Unit:	1627

CERTIFICATE OF ELECTRONIC FILING UNDER 37 C.F.R. § 1.8

The undersigned hereby certifies that this paper, along with any paper referred to as being attached or enclosed, is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4), on the 1st day of April, 2016.

__/Eileen M. Moore/_____
Eileen M. Moore

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 $90.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

UM00000426
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 379 of 725

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.

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

UM00000427
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 380 of 725

Account No. 23/2825 under Docket No. U0157.70023US02 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /Jessica R. Colantonio/
Jessica R. Colantonio, Ph.D.
Reg. No. 66,132
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US02
Date: April 1, 2016
xx

UM00000428
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 381 of 725

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 Substitute for Form PTO-875	Application or Docket Number 14/179,862	Filing Date 02/13/2014	☐ 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	04/01/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $210 =	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	(Column 3) 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.

LIE
/BRENDA TURNER/

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.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 07/12/2016

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/12/2016	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

UM00000430
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 383 of 725

Office Action Summary	Application No. 14/179,862	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 *4/1/16*.

☐ 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 and 52-58* 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 and 52-58* 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

Status of the Application

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

This Office Action is in response to applicant's arguments filed on April 1, 2016. Claim(s) 37-50 and 52-58 are pending and examined herein.

Response to Arguments

The outstanding nonstatutory double patenting rejection is hereby maintained as a result of Applicant's decision to hold said rejection in abeyance.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being anticipated by McCoy (CA 1148020A1) have been fully considered. Applicant argues:

> "McCoy discloses improved amino acid food additives which comprises a uniform dehydrated cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material. (McCoy, Abstract). McCoy discloses physical mixtures of multiple components in non-stoichiometric ratios. Indeed, McCoy discloses that "[g]enerally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of cocrystallizer are used." (McCoy, page 7, lines 10-15, emphasis added). The equal amounts of cocrystallizer disclosed by McCoy are equal amount by weight, not equal amount by moles."

Further, Applicant argues:

> "There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, e.g., a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase (e.g., Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004; a copy of which is provided herewith in connection with an Information Disclosure Statement). One skilled in the art would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed.

Examiner respectfully notes that as set forth on record previously and as discussed below, McCoy teaches "an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1". As pointed out by Applicant, McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed. Nonetheless, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, it is the opinion of the Examiner that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces such proportions to be possible.

Furthermore, with respect to freeze-drying, Applicant states that such a technique yields a mixture of crystalline and amorphous phase. Although a mixture is afforded, a portion of the mixture is crystalline, thereby still rendering the instant invention obvious.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered and are not fully persuasive.

Applicant argues:

> "Huffman is not analogous art as required by MPEP §2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors. With respect to the field of endeavor, the present claims are directed to methods relating to co-crystal formation with an active pharmaceutical ingredient (API) and therefore relate to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts."

With respect to this argument, Examiner respectfully notes that the instant claims are drawn to a method for designing and preparing a cocrystal, wherein the first chemical functionality is an API, with certain requirements as set forth in claim 37 and a cocrystal former. Although the claim 37 requires an API, it does not mandate that the endeavor relate to the pharmaceutical arts. The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144. Moreover, it is respectfully noted that many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic (references can be provided if requested).

Therefore, based on the foregoing reasons, said rejection is hereby maintained/modified for claim 37 and dependent claims thereon.

The rejections are maintained and made of record in the Final office action below for Applicant's convenience as necessitated by amendment.

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 claims at issue 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); and *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 a nonstatutory double patenting ground provided the reference application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form 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 http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 and 52-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 28, 37, 39-51, 53-60, and 62-66 of copending Application No. 10/378,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the copending claims are drawn to the method of designing said co-crystals. The two inventions overlap greatly in scope and the utilities are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality

as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and

nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at last one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred (page 6-7).

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and heterosynthons as required by the instant claims are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also

envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different fuctionalities, giving rise to heterosynthons. Therefore, preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds.

Examples of organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48, o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenox yacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17, malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethyisulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic,

naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3 pyridinecarboxylic, pentanetricarboxylic, cyanoacetic (column 1-2, bridging paragraph).

Huffman teaches substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Huffman teaches piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention. Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenyl hydrazine, hexanediamine, methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine , diethylamine, diethanolamine, hydroxyethyl diethylenetriamine, isooctylamine, n-decylamine, methylethanolamine, tetramethylguanidine, methyl diethanolamine, 2-amino--propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide (column 2, lines 44-68).

In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to

dryness, and the cocrystal adduct is washed with hexane and dried (column 2, lines 30-35).

Huffman does not teach the co-crystal complexes in pharmaceutical compositions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct. See *In re Dillon* 16 U.S.Q.P.2d 1897, 1900 (CAFC 1990) (en banc) ("it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that Wright suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law. ").

Therefore, it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 37-50 and 52-58 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). 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.

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/SAHAR JAVANMARD/

Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400	4/4/2014	SJ
	updated 10/2014		SJ

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched inventor names)	4/4/2014	SJ
EAST (keyword search)	4/4/2014	SJ
updated 10/2014		SJ
Google Patents (searched:organic acids amines adducts crystals)	12/12/2014	SJ
updated 7/7/16		SJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/SAHAR JAVANMARD/ Examiner.Art Unit 1627	

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	1	of	2	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

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		

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			

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], Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. ICH Harmonised Tripartite Guideline. 1999 Oct 6; 4:46.	
	*	[NO AUTHOR LISTED], X-ray Diffraction. In: The United States Pharmacopeia – The National Formulary (USP #24 NF19). 2000 Jan. Chapter 941: 2005-7	
	*	ABOURAHMA et al., Network Hydrogen Bonding in Two New Cocrystals Sustained by [Mn(CO)3(OH)]4, a tetrahedral hydrogen bond donor. J Chem Crystallogr. 1995 Nov; 25:731-736.	
	*	ALMARSSON et al., The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. Pharm Pat Anal. 2012 Jul;1(3):313-27. doi: 10.4155/ppa.12.29.	
	*	BEDU-ADDO, Understanding Lyophilization Formulation Development. Pharmaceutical Technology. 2004 Mar: 10-18.	
	*	BERGE et al., Pharmaceutical salts. J Pharm Sci. 1977 Jan;66(1):1-19.	
	*	BYRN et al., Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm Res. 1995 Jul;12(7):945-54.	
	*	DUKE, Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants, 2001, CRC Press LLC, page 419.	
	*	EVGEN'EV et al., Selective determination of 4-aminobenzoic and 4-aminosalicylic acid derivatives in mixtures by flow-injection analysis. J Anal Chem. 2000 July;55(7):696-702.	

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).

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

FORM PTO-1449/A and B (modified PTO/SB/08) **INFORMATION DISCLOSURE STATEMENT BY APPLICANT**				APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
				FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	2	of	2	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

	*	SMITH et al., The utility of 4-aminobenzoic acid in promotion of hydrogen bonding in crystallization processes: the structures of the cocrystals with halo and nitro subsituted aromatic compounds, and the crystal structures of the adducts with 4-nitroaniline (1:1), 4-(4-nitrobenzyl)pyridine (1:2), and (4-nitrophenyl)acetic acid (1:1). J Chem Crystallogr. 1997 May; 27(5):307-317.	

[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:
/Sahar Javanmard/	07/08/2016

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. /S.J./

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/21/2014	10/20/2014	09/29/2015	07/08/2016					
	1	-	-	-	-					
	2	-	-	-	-					
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	33	-	-	-	-					
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	35	-	-	-	-					
	36	-	-	-	-					

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/21/2014	10/20/2014	09/29/2015	07/08/2016					
	37	✓	✓	✓	✓					
	38	✓	✓	✓	✓					
	39	✓	✓	✓	✓					
	40	✓	✓	✓	✓					
	41	✓	✓	✓	✓					
	42	✓	✓	✓	✓					
	43	✓	✓	✓	✓					
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	55	✓	✓	✓	✓					
	56		✓	✓	✓					
	57		✓	✓	✓					
	58		✓	✓	✓					

UM00000450
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
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From: PAIR_eOfficeAction@uspto.gov
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Application	Document	Mailroom Date	Attorney Docket No.
14179862	CTNF	07/12/2016	U0157.70023US02
	1449	07/12/2016	U0157.70023US02

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 07/21/2016
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/21/2016	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):

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NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
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Office Action Summary	Application No. 14/179,862	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 *4/1/16*.

☐ 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 and 52-58* 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 and 52-58* 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: _____.

UM00000453
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 406 of 725

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
14/179,862	13 February, 2014	ZAWOROTKO ET AL.	U0157.70023US02

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

EXAMINER	
SAHAR JAVANMARD	
ART UNIT	PAPER
1627	20160713

DATE MAILED:

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

Commissioner for Patents

The Office action mailed 7/12/16 was inadvertently labeled as a "Non-Final Office". As is evident from the contents of the Office action, it is Final. Attached is a corrected PTOL-326, indicating the correct status of the Final Office action.

/SAHAR JAVANMARD/
Examiner, Art Unit 1627

PTO-90C (Rev.04-03)

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jul 21, 2016 05:30:51 AM

Dear PAIR Customer:

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

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	M327	07/21/2016	U0157.70023US02

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

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
- [x] 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	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	January 12, 2017	Reg. No.	31,616

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: January 12, 2017 Electronic Signature: /Trish McDonald/

5197443.1

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
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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): U0157.70023US02

Application Number	14/179,862-Conf. #7725	Filed	February 13, 2014

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

Art Unit	1627	Examiner	S. Javanmard

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	$ 700.00
☐	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 31,616 .

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

/Edward R. Gates/ — Signature
January 12, 2017 — Date

Edward R. Gates — Typed or printed name
617.646.8000 — 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 CFR § 1.8

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Dated: January 12, 2017 Electronic Signature: /Trish McDonald/

5197445.1

PTO/SB/17 (03-13)
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FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[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): _____

[ ] 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)

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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	280	140*	70	600	300	150	720	360	180	
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 ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
41 - 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 $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): 2253 Extension for response within third month	700.00
2401 Notice of appeal	400.00

SUBMITTED BY

Signature	/Edward R. Gates/	Registration No. (Attorney/Agent)	31,616	Telephone	617.646.8000
Name (Print/Type)	Edward R. Gates			Date	January 12, 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: January 12, 2017 Electronic Signature: /Trish McDonald/

5197442.1

NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD	Docket Number (Optional) U0157.70023US02

In re Application of
Michael J. Zaworotko et al.

Application Number	Filed
14/179,862-Conf. #7725	February 13, 2014

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

Art Unit	Examiner
1627	S. Javanmard

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)) $ 800.00

[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: $ 400.00

[ ] 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.

[X] 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 31,616 [ ] attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Edward R. Gates/

Typed or printed name Edward R. Gates

Telephone Number 617.646.8000

Date January 12, 2017

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 CFR § 1.8

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Dated: January 12, 2017 Electronic Signature: /Trish McDonald/

Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
Title of Invention:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Filer:	Edward R. Gates/Trish McDonald
Attorney Docket Number:	U0157.70023US02

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	400	400
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**1100**

Electronic Acknowledgement Receipt	
EFS ID:	28052298
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	Edward R. Gates/Trish McDonald
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US02
Receipt Date:	12-JAN-2017
Filing Date:	13-FEB-2014
Time Stamp:	18:35:30
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	011317INTEFSW18391300
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: 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	U015770023US02-TRN-ERG.pdf	24914 839f9aad5edd7820f07b0acd299050836abf1bf0	no	1
Warnings:					
Information:					
2	Extension of Time	U015770023US02-EXT-ERG.pdf	23588 9cdf98a478b2f6d8a3a939ac6c7d625e02e069a3	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	U015770023US02-FEE-ERG.pdf	31943 958e8d67dcf07e5707a7a6e26aaf4386426ff3b1	no	1
Warnings:					
Information:					
4	Notice of Appeal Filed	U015770023US02-NAPL-ERG.pdf	20772 ec6f0eeffdd5588577683e6054badda22e3ad2a4	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32365 cdae53dec7ad00eeeb161e1911db22b2c3fcfb26	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	133582		

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 07/19/2017

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/19/2017	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

UM00000465
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 418 of 725

Notice of Abandonment	Application No.	Applicant(s)
	14/179,862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

-- 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 *12 July 2016*.
   (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 7 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 Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☒ The reason(s) below:

CALLED TO CONFIRM ABANDONMENT OF THE APPLICATION WITH ATTORNEY EDWARD GATES. CALL WAS NOT RETURNED.

	/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627

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.

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jul 19, 2017 03:57:31 AM

Dear PAIR Customer:

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

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
14179862	ABN	07/19/2017	U0157.70023US02

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Sahar Javanmard
Art Unit:	1627

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Dated: August 10, 2017 Electronic Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

PETITION UNDER 37 C.F.R. § 1.181

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

Dear Commissioner:

Applicant respectfully submits this Petition under 37 C.F.R. § 1.181 to the Director of the United States Patent and Trademark Office (USPTO) in response to the Notice of Abandonment mailed July 19, 2017. The Notice of Abandonment indicates that the above-referenced application became abandoned for failure to timely file a proper reply to the Office letter mailed July 12, 2016.

Applicant respectfully submits that abandonment of the application was improper for the reasons detailed below, and requests that the holding of abandonment be withdrawn.

Applicant timely filed a Notice of Appeal on January 12, 2017 in response to the Office Action mailed July 12, 2016. After filing the Notice of Appeal, Applicant did not receive any communication from the Office indicating that a shortened period for reply was applicable. Therefore, in accordance with 37 C.F.R. § 41.37(a) ("Appellant must file a brief under this section

within two months from the date of filing the notice of appeal under § 41.31"), 37 C.F.R. § 41.31(d) ("The time periods set forth in paragraphs (a)(1) through (a)(3) of this section are extendable under the provisions of § 1.136 of this title for patent applications") and 37 C.F.R. § 1.136 ("[A]pplicant may extend the time period for reply up to the earlier of the expiration of any maximum period set by statute or five months after the time period set for reply"), Applicant understood the final deadline to be August 12, 2017.

Applicant's representative, David F. Cauble, Ph.D. (Reg. No. 73,490) contacted Examiner Javanmard to clarify why Applicant received a Notice of Abandonment. By way of reply, Examiner Javanmard left a voicemail for Applicant's representative on July 18, 2017, acknowledging that the Notice of Abandonment was issued in error, and advising Applicant to file a Petition to Revive Application Unintentionally Abandoned under 37 C.F.R. § 1.137(a), which is being filed concurrently with this Petition. Insofar as the abandonment of the application was due to the Office's error, Applicant hereby requests a refund of the petition fee of $850 due under § 1.17(m).

Applicant believes that no fee is due in connection with this Petition under 37 C.F.R. § 1.181. However, the undersigned authorizes the Director to charge any fees due to our Deposit Account No. 23/2825, under Docket No. U0157.70023US02, from which the undersigned is authorized to draw.

Dated: August 10, 2017

Respectfully submitted,

By___/David F. Cauble/_____
David F. Cauble, Ph.D.
Registration Number: 73,490
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
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5641290.1

Doc Code: PET.OP
Document Description: Petition for Review by the Office of Petitions

USED IN LIEU OF PTO/SB/64 (12-13)

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(a) Page 1 of 2	Docket Number (Optional) U0157.70023US02

First named inventor: Michael J. Zaworotko

Application No.: 14/179,862-Conf. #7725 Art Unit: 1627

Filed: February 13, 2014 Examiner: Sahar Javanmard

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

Attention: Office of Petitions
Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
FAX (571) 273-8300

NOTE: If information or assistance is needed in completing this form, please contact the Office of Petitions at (571) 272-3282.

The above-identified application became abandoned for failure to file a timely and proper reply to a notice or action by the United States Patent and Trademark Office. The date of abandonment is the day after the expiration date of the period set for reply in the Office notice or action plus any extensions of time actually obtained.

APPLICANT HEREBY PETITIONS FOR REVIVAL OF THIS APPLICATION.

NOTE: A grantable petition requires the following items:

(1) Petition fee;
(2) Reply and/or issue fee;
(3) Terminal disclaimer with disclaimer fee – required for all utility and plant applications filed before June 8, 1995, and for all design applications; and
(4) Statement that the entire delay was unintentional.

1. **Petition fee**

[x] Small entity fee $ 850.00 (37 CFR 1.17(m)). Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Undiscounted fee $ _____ (37.CFR.1.17(m)).

2. **Reply and/or fee**

A The reply and/or fee to the above-noted Office notice or action in the form of Appeal Brief (identify the type of reply):

[ ] has been filed previously on _____.

[x] is enclosed herewith.

B The issue fee and publication fee (if applicable) of $ _____

[ ] has been paid previously on _____.

[ ] is enclosed herewith.

5641291.1

Doc Code: PET.OP
Document Description: Petition for Review by the Office of Petitions

USED IN LIEU OF PTO/SB/64 (12-13)

PETITION FOR REVIVAL OF AN APPLICATION FOR PATENT ABANDONED UNINTENTIONALLY UNDER 37 CFR 1.137(a)

3. **Terminal disclaimer with disclaimer fee**

[X] Since this utility/plant application was filed on or after June 8, 1995, no terminal disclaimer is required.

[ ] A terminal disclaimer (and disclaimer fee (37 CFR 1.20(d)) of $ _____) disclaiming the required period of time is enclosed herewith (see PTO/SB/63).

4. **STATEMENT:** The entire delay in filing the required reply from the due date for the required reply until the filing of a grantable petition under 37 CFR 1.137(a) was unintentional. [NOTE: The United States Patent and Trademark Office may require additional information if there is a question as to whether either the abandonment or the delay in filing a petition under 37 CFR 1.137(a) was unintentional (MPEP 711.03(c), subsections (III)(C) and (D)).]

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

/David F. Cauble/	August 10, 2017
Signature	Date
David F. Cauble	73,490
Typed or Printed Name	Registration Number, if applicable
WOLF, GREENFIELD & SACKS, P.C. 600 Atlantic Avenue Boston, Massachusetts 02210-2206	617.646.8000
Address	Telephone Number

Enclosures:

[X] Fee Payment

[X] Reply

[ ] Terminal Disclaimer Form

[ ] Additional sheet(s) containing statements establishing unintentional delay

[X] Other: _____

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Dated: August 10, 2017 Electronic Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	S. Javanmard
Art Unit:	1627

Certificate of Electronic Filing under 37 CFR § 1.8

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Dated: August 10, 2017 Electronic Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

APPEAL BRIEF

Patent Trial and Appeal Board
US Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313–1450

Dear Commissioner:

Pursuant to 37 C.F.R. § 41.37(a), this Appeal Brief is filed within seven (7) months of the filing of the Notice of Appeal, filed January 12, 2017, and is in furtherance of the Appeal. A petition for extension of time (five months) is submitted concurrently herewith.

The fees required under 37 C.F.R. § 41.20(b)(2) are being paid by credit card using the credit card payment option of the USPTO's Electronic Filing System.

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I. REAL PARTY IN INTEREST

The real parties in interest for this Appeal are:

1. The Regents of the University of Michigan, having a place of business at Wolverine Tower, Room 2071, 3003 S. State Street, Ann Arbor, MI 48109-1280; and
2. University of South Florida, having a place of business at 3802 Spectrum Boulevard, Suite 100, Tampa, FL 33612.

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II. RELATED APPEALS, INTERFERENCES, AND TRIALS

To the best of Appellant's knowledge, there are no other appeals, interferences, trials, or other judicial proceedings which will directly affect, be directly affected by, or have a bearing on the Board's decision in this Appeal.

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III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are twenty one (21) claims pending in this Application.

B. Current Status of Claims

(a) Claims 1-36 and 51 are canceled.

(b) No claims are withdrawn from consideration.

(c) Claims 37-50 and 52-58 are currently pending.

(d) No claims are allowed.

(e) Claims 37-50 and 52-58 are rejected.

C. Claims On Appeal

There are twenty one (21) claims pending in the Application, claims 37-50 and 52-58, all of which are appealed. The pending claims involved in the Appeal are attached hereto as the **Claims Appendix**.

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IV. STATUS OF AMENDMENTS

Appellant did not file any amendments after the final Office Action, mailed July 12, 2016.

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V. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary correlates claim elements to specific embodiments described in the application specification, but does not in any matter limit claim interpretation. Rather, the following summary is provided only to facilitate the Board's understanding of the subject matter of this appeal.

The subject matter of independent claims 37, 41, 52 and 53 relate to a pharmaceutical composition comprising:

(1) a pharmaceutically acceptable carrier (see, *e.g.*, paragraph [0050] of the application as originally filed) and

(2) a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former (paragraphs [0010], [0012], [0041]-[0044], and Figure 24),

(3) 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 (paragraphs [0009], [0011], [0013], [0041], and [0048]),

(4) wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding (paragraphs [0009]-[0012], and [0041]-[0043]),

(5) wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form (paragraphs [0008], [0009], [0013], [0014], [0039], [0043], and [0044]), and

(6) wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former (see, *e.g.*, paragraphs [0010], [0011], [0012], [0040]-[0042], and Figure 24).

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In addition to elements (1)-(6), independent claim 37 specifies that:

(8) each supramolecular synthon comprises an API homosynthon formed via hydrogen bonding (see, *e.g.*, paragraphs [0021], [0022], and [0039]).

Claims 45-49 and 54-55, each of which ultimately depend from claim 37, present a common question of patentability.

In addition to elements (1)-(6), independent claim 41 specifies that:

(9) the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former (see, e.g., page 4, paragraphs [0068], [0074], [0081], and [0088]), and that each of the two APIs is bonded by non-covalent bonding to the one co-former (see, *e.g.*, page 4, paragraphs [0070], [0076], [0083], and [0090]).

In addition to elements (1)-(6), independent claim 52 specifies that:

(10) the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine (see, *e.g.*, paragraphs [0019], [0024], [0048], and [0063]).

Claims 38-40, 42-44, 50 and 56-58, each or which depend from claim 52, present a common question of patentability.

In addition to elements (1)-(6), independent claim 53 specifies that:

(11) each supramolecular synthon comprises a hydrogen bond between an API and co-former, said hydrogen bonds being: (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond (see, *e.g.*, paragraphs [0019], [0021], [0022], [0059], [0063], [0076], [0083], [0090], [0097], [00105], [00112], [00119], [00125], [00132], [00144], [00150], [00156], [00162], [00168], and [00174]).

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VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

As set forth in the final Office Action, mailed July 12, 2016, claims 37-50 and 52-58 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over McCoy (CA 1148020A1), enclosed herewith as *Exhibit A*.

Claims 37-50 and 52-58 are further rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huffman (U.S. Patent No. 3,664,858), enclosed herewith as *Exhibit B*.

The final Office Action mailed July 12, 2016 is also enclosed herewith as *Exhibit C*.

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VII. ARGUMENTS

A. Brief introduction to the claimed invention

The application describes the problem of rational design of crystalline pharmaceuticals, which is hampered by the multiple phases, polymorphs, and solvates formed by drugs.[1] The application describes a solution to this problem using novel crystalline phases[2] containing more than one molecular component[3] (*i.e.*, co-crystals, as claimed) in terms of properties such as solubility, dissolution rate, chemical stability, and bioavailability, *inter alia*.

As described throughout the application,[4] such co-crystals comprise stoichiometric, non-covalent interactions between chemical functionalities (*i.e.*, chemical functional groups such as carboxylic acids, amides, and the like), referred to in the aggregate as supramolecular synthons. Supramolecular synthons may comprise interactions between the same chemical functionality (*i.e.*, a homosynthon) or between different chemical functionalities (*i.e.*, a heterosynthon).

Numerous examples of such co-crystals are disclosed throughout the application, particularly in Examples 1-19 and Figures 5-23.

B. Rejection under 35 U.S.C. § 103(A)

In the Office Action mailed July 12, 2016, the Examiner rejected claims 37-50 and 52-58 under 35 U.S.C. § 103(a) as allegedly being unpatentable over McCoy (CA 1148020A1). The Examiner takes the position that McCoy teaches an amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material,[5] wherein the soluble, edible, cocrystallizer material is preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof.[6]

---

[1] U.S. Application No. 14/179,862, paragraph [0004].
[2] *Id.* at paragraph [0006].
[3] *Id.* at paragraph [0007].
[4] *Id.* at paragraphs [0017], [0023], [0044], [0047]-[0049], [0056], [0063]
[5] Office Action dated July 12, 2016, page 13.
[6] *Id.* at pages 8-9

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McCoy allegedly teaches a method comprising dissolving at least one amino acid material in water along with an effective amount of at least one edible cocrystallizer material, such that the ratio by weight of the cocrystallizer to the amino acid material is from about 0.9:1 to about 6:1.[7] The Examiner notes that, "preferably, equal amounts of amino acid and cocrystallizer are used."[8] The Examiner notes that the solution of amino acid and cocrystallizer is preferably freeze-dried.[9] The Examiner further notes that McCoy does not identify a synthon.[10]

The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time of the invention "to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different functionalities, giving rise to heterosynthons" and therefore that "cocrystals…as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy."[11]

Claims 37-50 and 52-58 are further rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huffman (U.S. Patent No. 3,664,858). The Examiner alleges that Huffman teaches co-crystal complexes or adducts of amines with organic acidic materials, wherein substantially stoichiometric proportions of amine and acid are normally preferred.[12] Allegedly, useful organic acidic materials include carboxylic acids, sulfonic acids, phenolic and fluorosulfone compounds.[13] Allegedly, primary, secondary, and tertiary amines, and hydrazines, are useful, with piperidine and morpholine being preferred.[14]

The Examiner does not afford patentable weight to the claim term "API" (*i.e.*, "active pharmaceutical ingredient"), on the ground that the term allegedly represents only an intended use.[15]

The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Huffman to arrive at the claimed pharmaceutical compositions.[16]

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[7] *Id.* at page 9
[8] *Id.*
[9] *Id.*
[10] *Id.*
[11] *Id.* at pages 9-10
[12] *Id.* at pages 11-12
[13] *Id.* at page 11
[14] *Id.* at page 12
[15] *Id.* at pages 10-11

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C. Brief description of the obviousness standard

A patent may not be obtained "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 to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *Graham v. John Deere Co.*, 383 U.S. 1 (1966); *Richardson–Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact must assess the following: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non–obviousness. *Richardson–Vicks* at 1479–1481.

In *KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. The Court in *KSR* acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *Id.* at 418. Such a reason should be supported by a reasonable expectation of success in combining the elements to arrive at the claimed invention. See *Manual of Patent Examining Procedure § 2143.02. Reasonable Expectation of Success is Required.* Impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. See *KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness).

In determining the differences between claimed subject matter and the prior art, the question under § 103 is not whether the differences *themselves* would have been obvious, but whether the claimed invention *as a whole* would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, (Fed. Cir. 1983). See also the *Manual of Patent Examining Procedure (MPEP) § 2142. Legal*

[16] *Id.* at page 13

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Concept of Prima Facie Obviousness. To reach a proper determination under § 103, the trier of fact must thus step backward in time and into the shoes worn by the hypothetical person of ordinary skill in the art when the invention was unknown and just before it was made, and, in view of all factual information, determine whether the claimed invention – *as a whole* – would have been obvious at that time to that person. A *prima facie* case of obviousness is established when, after putting aside the Appellant's disclosure, and evaluating the claimed invention as a whole, the trier of fact would find that the hypothetical skilled artisan would have had no trouble piecing together the combined teachings of the prior art in the way the claimed invention does, and with a reasonable expectation of success.

Once a *prima facie* case of obviousness has been established, the burden shifts to the Appellant to rebut the case. "A *prima facie* case of obviousness can be rebutted if the Appellant...can show 'that the art in any material respect taught away' from the claimed invention" *In re Haruna*, 249 F.3d 1327, 1335 (Fed. Cir. 2001) (citations omitted). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference,...would be led in a direction divergent from the path that was taken by the Appellant." *Id.* A *prima facie* case of obviousness may also be rebutted with a showing of unexpected results, *e.g.*, showing "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward – that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[17] Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. See *MPEP § 716.02(d). Unexpected Results Commensurate in Scope with the Claimed Invention.*

Furthermore, MPEP § 2144.08 (*Obviousness of Species When Prior Art Teaches Genus*) provides specific guidance to the Examiner who takes the position that a single prior art reference discloses a genus that encompasses, but does not specifically contemplate, the claimed subgenus. When considering the obviousness or non-obviousness of a selection, a proper application of

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

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Graham analysis requires the Examiner to determine whether one of ordinary skill in the art would have been motivated to select the claimed species or subgenus. Specifically, the Examiner must consider:

(a) the size of the prior art genus, *e.g.*, whether the genus is so small that one of skill in the art would readily envisage each member of the genus;[18]

(b) the express teachings, *e.g.*, whether the prior art reference expressly teaches a particular reason to select the claimed species or subgenus;

(c) the teachings of structural similarity, *e.g.*, whether the prior art references teaches any "typical," "preferred," or "optimum" species or subgenus. If such a species or subgenus is structurally similar to that claimed, its disclosure may provide a reason for one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties;[19]

(d) the teachings of similar properties or uses, which provide real world motivation for a person of ordinary skill to make species structurally similar to those in the prior art.[20] Conversely, lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus;[21]

(e) the predictability of the technology, without which it is less likely that structurally similar species will render a claimed species obvious because it may not be reasonable to infer that they would share similar properties.[22]

Based on the evidence as a whole, the Examiner should make express fact-findings relating to the *Graham* factors, focusing primarily on the prior art teachings (a)-(e) discussed above. The fact-findings should specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus.

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[18] See, *e.g.*, In re Petering, 301 F.2d 676, 681 (CCPA 1962).
[19] See, *e.g.*, Dillon, 919 F.2d at 693, 696.
[20] See, *e.g.*, Dillon, 919 F.2d at 697; In re Stemniski, 444 F.2d 581, 586, (CCPA 1971).
[21] See, *e.g.*, In re Albrecht, 514 F.2d 1389, 1392, 1395-96 (CCPA 1975).
[22] See, *e.g.*, *In re May*, 574 F.2d 1082, 1094 (CCPA 1978).

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D. The Examiner has not established a prima facie case of obviousness

1. *McCoy*

The Examiner acknowledges that McCoy does not disclose the specific examples of homo- and heterosynthons required by the claims, and does not disclose the identification of a synthon from the crystal structure.[23] The Examiner acknowledges that McCoy teaches the use of a cocrystallizer in a weight ratio, and not in stoichiometric proportions.[24] Nonetheless, the Examiner holds that the claimed pharmaceutical compositions are obvious, reasoning that "cocrystals…as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy"[25].

Appellant respectfully disagrees, and submits that the question of whether or not the claimed invention is "within the scope" of McCoy is only part of the analysis required to show obviousness. In terms of the factors (a)-(e) listed in MPEP § 2144.08 and summarized herein in Section C., the Examiner only takes a position on factor (a), finding that the claimed invention is within the scope of the prior art, and that the skilled artisan would have "envisioned" cocrystals according to the claims on the basis of McCoy.

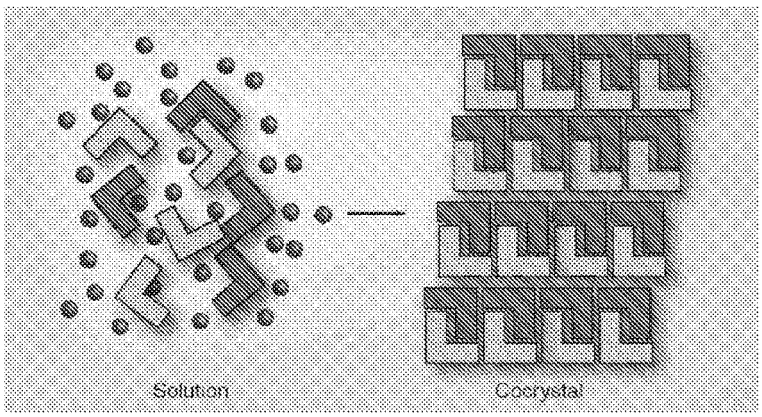
Appellant respectfully disagrees. The claimed invention requires, *inter alia*, a supramolecular synthon comprising stoichiometric amounts (*i.e.*, integer multiples of molar equivalents) of at least one API and at least one co-former. Such stoichiometric amounts are important for intermolecular interactions between two or more independent molecular entities in a co-crystal. Indeed, as provided in the review article by Almarsson, a copy of which was submitted with the Information Disclosure Statement of April 1, 2016, and which is enclosed herewith as *Exhibit D*, "[c]ocrystals are a class of crystalline solids that occur when complementary molecules of different structures are crystallized to form single crystalline phases that contain stoichiometric ratios of the components" (Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012)).

Co-crystal formers encompassed by the presently claimed compositions also contribute to the co-crystal structure in that they are complementary in supramolecular chemistry, *i.e.*, they form

[23] Office Action dated July 12, 2016, page 9.
[24] *Id.* at page 3.
[25] *Id.* at pages 9-10.

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supramolecular synthons with the API molecules."[26] As discussed further below, these multiple-component solids "exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction", which "can afford improved drug solubility, dissolution rate, stability and bioavailability, for example."[27] Figure 1 of Almarsson et al., reproduced below for the Board's convenience, provides a prototypical example of a 1:1 composition co-crystal, and demonstrates that stoichiometric ratios of the complementary components permit formation of the co-crystal structure, *e.g.*, a repeating array of molecules or ions in three dimensions.



Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012) (page 314)

The Examiner considers the claimed invention to be within the scope of McCoy because McCoy teaches cocrystallizer/amino acid compositions having weight ratios of from 0.9:1 to 6:1. There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, *e.g.*, a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. Nor does McCoy suggest that it would be advantageous to select a stoichiometric ratio from the range of weight ratios. In fact, McCoy teaches that the criteria for selecting the optimum amount of cocrystallizer is whether there is "'enough' to

[26] U.S. Application No. 14/179,862, paragraph [0009].
[27] U.S. Application No. 14/179,862, paragraph [0039].

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enable successful dehydration of the amino acid co-crystallizer solution."[28] Based on this teaching, the skilled person would not be motivated to modify McCoy by utilizing a stoichiometric ratio of amino acid to cocrystallizer, and as such could not have envisioned the claimed invention.

Moreover, McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material.[29] One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase (*e.g.*, Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004; a copy of which was submitted with the Information Disclosure Statement of April 1, 2016, and which is enclosed herewith as *Exhibit E*. One skilled in the art would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed.

With regard to factors (b) and (c) of MPEP § 2144.08, the Examiner has not identified an express teaching, or preferred embodiments, of McCoy that would motivate the skilled artisan to select stoichiometric ratios of co-crystals according to the present claims. In fact, as noted above, an express teaching of McCoy relates to the criteria of successful dehydration, wherein "preferably, equal [mass] amounts of amino acid and cocrystallizer are used."[30]

With regard to factor (d), the Examiner has not identified the teaching of a similar property or use that motivate the skilled artisan to prepare co-crystals according to the present claims.

A least for the foregoing reasons, the Examiner has not established a *prima facie* case for the obviousness of the claimed invention, and Appellant respectfully requests reconsideration and reversal of the rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a).

2. *Huffman*

The Examiner has not established a *prima facie* case for rejecting the claims as being unpatentable over Huffman because (a) Huffman is not a proper reference for use in an obviousness rejection, (b) the Examiner has not met their burden of articulating the reasons for rejecting each and every limitation of the pending claims, and (c) one of ordinary skill in the art would not have a

[28] McCoy page 7, lines 7-10.
[29] *Id.* at page 7, lines 17-19.
[30] *Id.* at page 7, lines 14-15.

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reasonable expectation of success in forming a co-crystal of an API having maintained activity and/or improved properties.

Huffman discloses heat-sensitive copy-sheet coatings.[31] Huffman discloses that such coatings and copy-sheets are useful in the preparation of projection transparencies.[32]

As stated in MPEP § 2141.01(a), "In order for a reference to be proper for use in an obviousness rejection under 35 U.S.C. 103, the reference must be analogous art to the claimed invention. *In re Bigio*, 381 F.3d 1320, 1325, 72 USPQ2d 1209, 1212 (Fed. Cir. 2004)." Also as stated in MPEP § 2141.01(a), "a reference is analogous art to the claimed invention if: (1) the reference is from the same field of endeavor as the claimed invention (even if it addresses a different problem); or (2) the reference is reasonably pertinent to the problem faced by the inventor (even if it is not in the same field of endeavor as the claimed invention). See *Bigio*, 381 F.3d at 1325, 72 USPQ2d at 1212." Huffman is not analogous art as required by MPEP § 2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors.

With respect to the field of endeavor, each appealed claim, indeed the entire specification, is directed to a pharmaceutical composition comprising a co-crystal including an active pharmaceutical ingredient (API), and therefore relates to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts.

With respect to the problem faced and whether the reference is reasonably pertinent to that problem, as described in the application, "[u]ndesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs" and crystalline self-assemblies may improve such characteristics, but "many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase" and "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

[31] Huffman, Abstract
[32] *Id.* at column 1, lines 1-11

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a scientific challenge of the highest order."[33] The present application provides, as a solution to this problem, the "design of new pharmaceutical solid phases, such as multiple-component phases, using co-crystal formers that are complementary in the sense of supramolecular chemistry, *i.e.*, they form supramolecular synthons with pharmaceutical molecules or ions."[34] These multiple-component solids "exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction", which "can afford improved drug solubility, dissolution rate, stability and bioavailability, for example."[35]

In contrast, the problem faced in Huffman is that when heating prior art copy-sheets, "the sheet causes dissociation of the adduct with liberation of amine and formation of color-bodies."[36] The solution provided by Huffman is "to produce clear transparent films and coatings containing heat-dissociable amine adducts in non-particulate form" as this coating "does not obscure desired colors or markings on the underlying carrier" and produces "excellent projection transparencies."[37] Producing excellent projection transparencies that do not obscure desired colors or markings is not reasonably pertinent to problem described in the instant application. As described in MPEP §2141.01(a), "[i]n order for a reference to be "reasonably pertinent" to the problem, it must "logically [] have commended itself to an inventor's attention in considering his problem." *In re Icon Health and Fitness, Inc.*, 496 F.3d 1374, 1379-80 (Fed. Cir. 2007) (quoting *In re Clay*, 966 F.2d 656,658, 23 USPQ2 1058, 1061 (Fed. Cir. 1992))." The inventors would not have considered producing excellent projection transparencies that do not obscure desired colors or markings in solving the problem described in the instant application, which relates to the lack of rational design of crystalline pharmaceuticals, which was hampered by the multiple phases formed by most drugs. As a result, Huffman is not analogous art under MPEP § 2141.01(a) and is not a proper reference for use in an obviousness rejection. For this reason alone, this rejection should be withdrawn.

Even if, *arguendo*, Huffman was a proper reference for use in an obviousness rejection, which Appellant asserts is not the case, the Examiner has not met her burden in articulating the

[33] U.S. Application No. 14/179,862, paragraphs [0003] and [0004].
[34] paragraph [0009]
[35] paragraph [0039]
[36] column 1, lines 28-33
[37] Column 1, lines 34-40

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reason for rejecting the claims based on Huffman alone, as Huffman provides no teaching or suggestion to make co-crystals, as recited in the present claims. Huffman makes salts rather than co-crystals. Huffman discloses mixtures of amines and acids, *e.g.*, carboxylic acids. Indeed, one of ordinary skill in the art will readily appreciate that the amines disclosed in Huffman will deprotonate the carboxylic acids disclosed in Huffman to make salts. The present claims recite co-crystals.

Furthermore, Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition. The Examiner's reason for arriving at the claimed subject matter, which relates to pharmaceutical compositions including an active pharmaceutical ingredient (API), is that "it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct."[38] The Examiner provides no evidence or rationale to support this conclusory statement. As outlined in MPEP §2141, subsection III, "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396." Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition comprising a co-crystal of an active pharmaceutical ingredient. As a result, Huffman does not teach or suggest each and every limitation of the claims and therefore does not render the claims obvious.

In addition, the Examiner states that "if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claim are met."[39] The Examiner states that "the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight."[40] Appellant respectfully disagrees, and submits that the recitation of an API comprising a first chemical functionality should be given patentable weight.

[38] Office Action, page 12
[39] Office Action, page 7
[40] *Id.*

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It is well established that a claim term is to be accorded "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention."[41] In the Phillips decision, the Federal Circuit also indicated that evidence for the meaning of a term may be derived from "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art."[42] Appellant respectfully submits that the present specification supports an interpretation of the claim terms "active pharmaceutical ingredient" and "API" as referring to a biologically active pharmaceutical entity having a therapeutic effect on a human or animal, such pharmaceutical entities having prophylactive, palliative, and/or curative effects.[43] In accordance with this interpretation, an API is not defined according to an intended use, but rather according to its properties, and as such should be afforded patentable weight.

Moreover, Appellant respectfully submits that the present specification supports an interpretation where the claim term "wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former" denotes an actual state that fundamentally ties the formation of the supramolecular synthon to the physical characteristics of the API. As a result, the disputed claim language reaches well beyond merely describing an intended use since the claims actively recite an actual configuration, *e.g.*, non-covalent hydrogen bonding between an API and a complementary co-former. The Examiner provides no reasoning why one of ordinary skill in the art would interpret the claim as merely reciting an intended use, as opposed to a state which ties the formation of the supramolecular synthon to the physical characteristics of the API.

In further support of the patentable weight of the term "API," Appellant submits that one of ordinary skill in the art would not have had a reasonable expectation of success in forming a co-crystal with an API. Moreover, one of ordinary skill in the art would not have had a reasonable expectation that a co-crystal of an API would be useful, *e.g.*, maintain activity and/or have improved properties. Indeed, combining an API with a co-crystal co-former could have had a negative impact

[41] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005)
[42] *Id.* at 1314
[43] See, *e.g.*, paragraph [0048]

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on the activity of the API, including decreased solubility, dissolution rate, stability, and/or bioavailability. However, the teachings of the instant application demonstrate the unpredictable finding that APIs could not only be used in co-crystals, but that the co-crystals exhibit improved characteristics as compared to the API alone. For example, the instant application provides, *inter alia*, formation of multiple-component solids which "exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction", and which "can afford improved drug solubility, dissolution rate, stability and bioavailability, for example."[44]

At least for the foregoing reasons, the Examiner has not established a *prima facie* case for the obviousness of the claimed invention, and Appellant respectfully requests reconsideration and reversal of the rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a).

E. The rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a) as being obvious over McCoy should be reversed

Appellant has presented arguments herein challenging the Examiner's *prima facie* case based on McCoy. The Examiner has taken the position that the claimed invention is "within the scope" of McCoy, and that the skilled artisan would have "envisioned" the claimed invention on the basis of McCoy. As such, it is alleged that the claimed invention is an obvious species comprised within a prior art genus. However, the Examiner has not articulated a reasoning as to why one of ordinary skill in the art would have been motivated to select the claimed invention from the alleged prior art genus. In fact, McCoy would not motivate to skilled artisan to prepare the claimed pharmaceutical compositions, and the claimed pharmaceutical compositions could not be readily envisioned without the benefit of the description in the present application. As such, the rejection is the result of impermissible hindsight.

For the foregoing reasons, the rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a) as being obvious over McCoy should be reversed.

[44] See, *e.g.*, paragraph [0039]

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F. The rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a) as being obvious over Huffman should be reversed

The Examiner has not established a *prima facie* case for rejecting the claims as being unpatentable over Huffman because (a) Huffman is not a proper reference for use in an obviousness rejection, (b) the Examiner has not met their burden of articulating the reasons for rejecting each and every limitation of the pending claims, and (c) one of ordinary skill in the art would not have a reasonable expectation of success in forming a co-crystal of an API having maintained activity and/or improved properties.

Huffman is not analogous art as required by MPEP § 2141.01(a) because it is not from the same field of endeavor as the claimed subject matter and is not reasonably pertinent to the problem faced by the inventors. As discussed above, the problem faced in Huffman is that when heating prior art copy-sheets, "the sheet causes dissociation of the adduct with liberation of amine and formation of color-bodies," whereas the problems faced by the inventors of the present application is that "[u]ndesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs." Moreover, Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition comprising a co-crystal of an active pharmaceutical ingredient, as claimed. Finally, Huffman provides no teaching or suggestion that co-crystals of APIs as claimed would demonstrate characteristics as compared to the API alone.

For the foregoing reasons, the rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a) as being obvious over Huffman should be reversed.

G. Non–statutory obviousness–type double patenting rejection

Claims 37-50 and 52-58 are rejected on the ground of non–statutory obviousness–type double patenting as being unpatentable over claims 25, 28, 37, 39-51, 53-60 and 62-66 of U.S. Patent Application No. 10/378,956 (published as US2003/0224006A1).

Appellant notes that the '956 application was allowed to become abandoned, thereby rendering this rejection moot.

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VIII. CONCLUSION

Claims 37-50 and 52-58 are not obvious. Accordingly, the Examiner's rejection under § 103 of claims 37-50 and 52-58 should be reversed.

Appellant believes all fees due with the filing of this Appeal Brief 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. U0157.70023US02, from which the undersigned is authorized to draw.

Dated: August 10, 2017

Respectfully submitted,
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IX. CLAIMS APPENDIX

Claims Involved In The Appeal Of Application, U.S. Serial No. 14/179,862

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-former and each supramolecular synthon comprising an API homosynthon 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,

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

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

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

38. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

39. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon is a chain of supramolecular heterosynthons, each supramolecular

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heterosynthon formed by non-covalent hydrogen bonding of one API to one co-former, and wherein the supramolecular heterosynthons are bonded to one another by non-covalent hydrogen bonding.

40. (Previously Presented) The pharmaceutical composition of claim 52, wherein the co-crystal is a hydrated co-crystal, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon affords a sheet of the API, each of the APIs in the sheet bonded to one another and to a co-former by non-covalent hydrogen bonding to a water molecule.

41. (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-former,

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

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

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

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former, and wherein each of the two APIs is bonded by non-covalent bonding to the one co-former.

42. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, the at least one API in each supramolecular synthon is two APIs, and wherein each of the two APIs is bonded by non-covalent bonding to one of the two co-formers.

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43. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, and wherein one of the two APIs is non-covalently bonded to one of the co-formers and the other of the two APIs is non-covalently bonded to the other of the two co-formers.

44. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

45. (Previously Presented) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs of the at least one API that are bonded to one another through hydrogen bonding to form at least one homosynthon dimer.

46. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two of the co-former and the at least one API is two of the API, wherein the at least one homosynthon dimer is one homosynthon dimer, and wherein the supramolecular synthon forms a tetramer, the tetramer being comprised of the two co-formers and two APIs, and each co-former being attached to the homodimer by hydrogen bonds.

47. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two co-formers, wherein the at least one homosynthon dimer is two homosynthon dimers, and wherein the supramolecular synthon results in a hexamer.

48. (Previously Presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon comprises a chain of homosynthon dimers, each homosynthon dimer

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formed by hydrogen bonding of one of the plurality of the API to another of the plurality of the API, and wherein the homosynthon dimers are bonded to the co-former by hydrogen bonding.

49. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

50. (Previously Presented) The pharmaceutical composition of claim 52, wherein the second chemical functionality complimentary to the first chemical functionality is (i) two identical second chemical functionalities on the co-former, (ii) three identical second chemical functionalities on the co-former, or (iii) four identical second chemical functionalities on the co-former.

51. (Canceled)

52. (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-former,

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

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

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

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

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

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53. (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-former,

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

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

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

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

wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond.

54. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

55. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

56. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carboxamide.

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57. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carbonyl.

58. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is an amine.

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X. EVIDENCE APPENDIX

The following supporting documents are being submitted:

(1) Canadian Patent Application No. (CA 1148020A1) ("McCoy") is submitted herewith as ***Exhibit A***.

(2) U.S. Patent No. 3,664,858 ("Huffman") is submitted herewith as ***Exhibit B***.

(3) The final Office Action mailed July 12, 2016 is also enclosed herewith as ***Exhibit C***.

(4) Almarsson et al., Pharm. Pat. Analyst 1(3):313-327 (2012) is submitted herewith as ***Exhibit D***.

(5) Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004 is submitted herewith as ***Exhibit E***.

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EXHIBIT A

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STABLE DEHYDRATED COCRYSTALLINE AMINO ACID FOOD ADDITIVES

Stephen A. McCoy

and

James L. Bono

Background of the Invention

This invention relates to improved nutritionally useful, amino acid food additives, the method of making them and the fortification of foodstuffs which are deficient in the nutritionally related amino acids. The term "amino acid material" is meant to encompass nutritionally useful amino acid compounds per se, whether they are in the form of amino acid derivatives, their esters, salts or mixtures thereof. The term "proteinaceous foodstuff" is meant to encompass protein per se, whether derived from vegetable or animal sources, and additionally, to manufactured products intended for human or animal consumption containing such proteins as a significant component.

There is considerable impetus to satisfy the protein requirement in the diet of man with protein derived exclusively from vegetable sources. There are essentially two reasons which compel human populations to look to vegetable proteins for a substantial, if not an exclusive, source of dietary protein. The paramount reason is one of efficiency. That is, at least in certain parts of the world, it is no longer feasible, from the standpoint of consumption of energy, to grow a crop, to feed livestock, to obtain required dietary protein. The second reason is best couched in terms of nutrition and health. Manufactured foodstuffs based on vegetable proteins afford the possibility

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of ultimately achieving a perfect balance of nutrients with controlled exclusion of certain identified detrimental agents, such as cholesterol. And, there are subsidiary reasons involving the factor of convenience, and, to some, reasons of personal conviction.

There appears to be no question as to the capacity to obtain vegetable proteins in sufficient quantity. Success in the agriculture of, for example, the legumes (and in particular soy and peanut) have assured the ready procurement of vegetable protein in quantity. And this assurance of quantity is, in part, attributable to the development of associated technologies to exploit and make available this source of native vegetable protein. George Washington Carver, e.g., is famous for his pioneer work in developing numerous ways of preparing and growing the peanut and other vegetable protein for human consumption.

Now the principal concern is one of quality of that vegetable protein. If the vegetable protein is not nutritionally the equivalent of protein derived from animal sources, that is, of comparable quality, the fact that the vegetable protein is obtainable in quantity is of lessened significance. The fact is that proteins derived from a chosen plant species source are not of comparable nutritional quality to animal sources. This is evident, in part, by examination of the amino acid content, or profile, of a chosen plant protein. For example, peanut protein is deficient in the sulfur-containing amino acids, such as methionine; wheat gluten is deficient in lysine. Nutritionists have applied the term "limiting" to such amino acids, and have noticed that a protein characterized by a particular limiting essential amino acid is effectively levelled in nutritive value to the content of the first limiting amino acid. For

example, if a certain vegetable protein was relied upon for the sole source of dietary protein, and if that protein was characterized by an amino acid profile revealing certain limiting amino acids, it would be necessary to consume in the diet an excessive amount of that protein in order to insure the nutritionally required intake of those limiting essential amino acids. Besides the sheer economic waste of such a diet, there is increasing evidence in the scientific literature that excess dietary protein may have detrimental physiological effects.

Fortification of proteinaceous foodstuffs with, e.g., sulfur-containing amino acids, and particularly with respect to methionine, has typically involved direct addition of DL-methionine as the free acid. However, all attempts to fortify methionine deficient foodstuffs with free DL-methionine proved unfeasible because of a severely intractable flavor problem. It was discovered that foodstuffs so fortified with DL-methionine developed off-flavors and became discolored. This effect was particularly noticeable for foodstuffs that were either heated prior to eating, or were stored for an indefinite period in a hydrated condition, but the effect was also noticed after dry storage. The chemical basis for the generation of these off-flavors and unsightly discolorations was, in part, attributable to the well-known Strecker degradation--or more commonly, the Maillard reaction (chemical browning). The Maillard reaction is particularly distressing when sulfur-containing amino acids are involved because of the generation and liberation of noxious mercaptans and sulfides, e.g. methional is freely formed in foodstuffs fortified with methionine. Also, distinct from the Maillard reaction, degradative reactions, such as air oxidation of these

sulfur-containing amino acids, adversely affect flavor. Needless to say, alternate means were sought to alleviate the sulfur amino acid deficiencies in vegetable derived proteins.

Some prior art methods are designed to defeat the Maillard reaction in the face of free addition of selected amino acids. Representative diverse means suggested by the prior art are: (1) encapsulation of the free amino acid; (2) simultaneous incorporation of certain alleged anti-browning agents, e.g. pyrocarbonic acid esters, and O-carboxy anhydrides of α-anhydroxy acids (U.S. Pat. No. 3,337,348 granted Aug. 22, 1967); and (3) utilization of the plastein reaction. This last-mentioned means involves the bonding of the added amino acid by peptide linkage to protein molecules which constitute the bulk of the proteinaceous component of the foodstuff. All of the above-listed means are of limited practical utility. Consequently, the prior art continued the search for means in circumvention of the Maillard reaction. Among these means were suggested the utilization of tasteless derivatives of certain amino acids which were relatively inert to degradation yet nutritionally available on ingestion.

For example, some success has been achieved in derivatization of certain sulfur-containing amino acids, especially methionine. For example, Ralph Anthony Damico and Robert Wayne Boggs in U.S. Patent No. 3,878,305, April 15, 1975, discloses that certain N-acyl L-methionine compounds, exhibit increased stability, attenuated taste characteristics and are nutritionally available. Damico and Boggs in U.S.

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Pat. No. 3,952,115 achieved additional successes on ester derivations of N-acyl L-methionine.

While the above amino acid derivatives solved some of the aforementioned problems, direct addition of some amino acid derivatives still causes undesirable flavors in certain foodstuffs. In some cases, they have proven to be unstable in some food systems. The addition of NALM, e.g. peanut butter, results in unwanted appearance, flavor and textural changes upon storage conditions.

It is an object of the present invention to reduce or eliminate the undesirable off-flavors of free amino acid food additives.

Another object is to provide a method of dehydrating an aqueous solution of amino acids, their salts and derivatives using conventional drying techniques to provide an amino acid containing powder having a lower hygroscopicity.

Still another object of the present invention is to provide an improved-tasting amino acid fortified proteinaceous foodstuff, particularly peanut butter.

These and other objects will become apparent in the light of this disclosure.

Summary of the Invention

It has been discovered that neutralization improves the taste of some key amino acid materials because their salts are more bland in many cases. However, due to a strong hydrophilic and hygroscopic

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nature of those salts, as well as many other amino materials, practical dehydration is difficult, if not impossible. Attempts to dehydrate aqueous solutions of many amino acid materials and particularly neutralized salts of amino acid materials by normal drying techniques result in incomplete drying or decomposition. It has been discovered that an effective amount of a cocrystallizer material mixed with amino acid solutions can be successfully dehydrated using conventional drying techniques.

In brief, provided herein is an improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

The amino acid material is preferably selected from the group consisting of: lysine, tryptophan, cystine, cysteine, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, their derivatives, their salts and mixtures thereof. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates; polyhydric alcohols; crystalline organic acids and their salts, and mixtures thereof.

The more preferred amino acid materials are the essential amino acids and their derivatives, particularly N-acyl L-methionine compounds and their salts.

The method of the present invention comprises dissolving at least one amino acid material in water along with an effective amount of at last one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid co-crystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred.

The present invention further provides a means of fortifying foodstuffs, particularly peanut butter, with more stable, better-tasting and nutritional amino acid materials comprising adding to said foodstuffs the improved amino acid food additive of this invention.

Detailed Description of the Invention

A detailed description of the invention is conveniently presented by discussion of three inter-related topics: (A) identification and preparation of the preferred cocrystalline amino acid food additives; (B) class of proteinaceous foodstuffs affected by this invention; and (C) the significance of a more stable and better-tasting amino acid food additive.

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Identification and Preparation of the
Amino Acid Food Additive Cocrystallate

This invention relates to an improved amino acid food additive comprising a uniform dehydrated cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

The amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof. Sodium chloride, although somewhat hygroscopic itself, is surprisingly a more preferred cocrystallizer material. Monosodium glutamate, tartaric acid, sodium tartrate, sodium valerate and suitable vegetable gums can also be used as cocrystallizer material in the practice of this invention.

Other specific cocrystallizer materials contemplated by this disclosure include sugars, and any like edible material which allows the successful dehydration of the amino acid material to provide a stable dehydrated cocrystallate.

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The more preferred amino acid materials are the essential amino acids and their derivatives, particularly N-acyl L-methionine compounds and their salts.

TABLE I

Preferred Amino Acids

Common Name	Chemical Name
lysine	alpha, epsilon-diaminocaproic acid
tryptophan	alpha amino-3-indolepropionic acid
methionine	alpha-amino-gamma-methylmercaptobutyric acid
threonine	alpha-amino-beta-hydroxybutyric acid
phenylalanine	alpha-amino-beta-phenylpropionic acid
leucine	1-amino-4-methylpentanoic acid
valine	2-amino-3-methylbutanoic acid
isoleucine	2-amino-3-methylpentanoic acid
histidine	alpha-amino-4 (or 5)-imidazolepropionic acid

Additional preferred amino acid materials are the salts of N-acetyl L-methionine, and analogous N-acyl derivatives of L-methionine, as well as the N-acyl derivatives of cystine and cysteine. The N-acetyl derivatives of L-methionine, L-cystine, and L-cysteine (N-acetyl L-methionine, N,N'-diacetyl L-cystine, and N-acetyl L-cysteine salts, respectively) are the most preferred supplements, but the invention fully comprehends the useful derivatives of other amino acids, and particularly their salts and mixtures thereof.

A preferred method of the present invention comprises dissolving at least one amino acid material

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in water along with an effective amount of at least one edible cocrystallizer material. Then the solution is preferably neutralized to form a salt of the amino acid such that the ratio by weight of the amount of cocrystallizer material to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Equal amounts of amino acid and cocrystallizer appear to work best. Of course, the solution is neutralized with an appropriate edible base like NaOH, $Ca(OH)_2$, KOH, and the like.

The final pH range of the solution can be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred. Thin film evaporation drying and forced air drying are also appropriate techniques.

The present invention further provides a means of fortifying foodstuffs, particularly peanut butter, with more stable and better-tasting amino acid materials comprising adding to said foodstuffs the improved amino acid food additive of this invention.

Class of Foodstuffs

The actual method of incorporation of the dehydrated cocrystalline amino acid food additives encompassed by this invention to obtain the fortified proteinaceous foodstuff, is of course controlled by the nature of the particular foodstuff. For materials such as soybean flour, the compositions may be added as dry powders; for manufactured proteinaceous foodstuffs such as nut butters, the cocrystalline amino acid food additives may be incorporated as a minor ingredient, or enter the formulation dispersed in a suitable vehicle, such as oil. However, it is critical that the improved amino acid food additives of this invention remain dry because water will destory its crystalline structure.

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An especially important embodiment of the invention is the fortification of certain proteinaceous source materials, such as the nut butters. Peanut protein is first limiting in lysine, but it is also deficient in threonine and methionine. Consequently, in any scheme of fortification it is necessary to be conscious of the entire amino acid profile of a given proteinaceous material. Such information is readily available from published tables of amino acid content of diverse proteins, for example, Amino Acid Content of Foods and Biological Data on Proteins; Food and Agricultural Organization of the United Nations, No. 24, 1970. In this manner, it is possible to nutritionally balance all amino acids to any desired or optimum level. Therefore, it is understood that this invention encompasses all proteinaceous foodstuffs which are deficient in amino acids, even when that deficiency is not first limiting.

Other proteinaceous foodstuffs contemplated by this invention include, among the oil seeds: peanut, cottonseed, soybean, safflower, sesame, sunflower, rapeseed and flax meal (linseed meal); among the milk protein products: casein, non-fat milk solids, lactalbumin, or whey protein; among the cereal grains: whey (gluten), wheat, corn, barley, oats, rice, rye, wheat bran, and wheat germ; among the marine proteins: fish protein concentrate, and fish muscles soluble; among the plant proteins: leaf (e.g. alfalfa) and coconut; among the single-cell proteins: yeast, and petroleum, methane and carbohydrate feeding microbes; among the animal proteins: collagen (gelatin), keratin, muscle, serum protein, offal, wool, silk waste, meat protein concentrate, and feather meal. Also contemplated by this invention are manufactured proteinaceous foodstuffs formulated in part from selected

proteins from the above representative enumeration. In this respect it is understood that the proteinaceous source material may be fortified directly, and thereby provide a nutritionally balanced proteinaceous foodstuff useful either alone or in combination with other ingredients as a manufactured foodstuff; or fortification may be effected during formulation of the manufactured proteinaceous foodstuff.

Knowing the composition of the proteinaceous foodstuff which it is desired to supplement with the amino acid food additive cocrystallate described herein and the level to which it is desired to supplement the foodstuff, a person of ordinary skill in the art will have no difficulty in determining how much of a particular cocrystallate should be used. In general it will be found about 0.1% to about 5% by weight of the protein level of the food to be supplemented will be satisfactory. A preferred range is from about 0.5% to about 2.5% by weight of the protein in the foodstuff. Amounts outside these ranges can however be used if the desired supplementation can thereby be achieved.

The following examples of additives and peanut butter proteinaceous foodstuffs fortified with amino acid food additives are given to indicate preferred products contemplated in the instant invention. It is, of course, to be understood that those examples are by way of illustration only, and in no way are to be considered as limiting the scope of the invention. Some of the following Examples were subjected to a rapid aging test.

Description of Rapid Aging Test

1. A sample is placed in a headspace flask and the flask sealed.

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2. The sealed flask is placed in an oil bath maintained at 90°C for 16 hours.

3. The flask is cooled to room temperature, 30 ml. of water added and the flask placed in an oil bath maintained at 45°C for 15 minutes.

4. The headspace was analyzed using a modified version of the procedure described by Von Sydow, E., Anderson, J., Anjou, K., Karlsson, G., Land, D., and Griffiths, N., Lebsnsm., Wiss. U. Technol., Vol. 3 (1970) 11-12. The headspace sample was transferred from the headspace flask to the cold trap by passing nitrogen over the sample contained in the flask at a flow rate of 50 ml/min.

Example 1

The following materials were combined:

Solvent	-	400 grams of water
Amino acid materials	-	59 grams of L-lysine hydrochloride 31 grams of N-acetyl L-methionine 20 grams of L-threonine
Cocrysallizer material	-	120 grams sodium chloride

The amino acid materials and cocrystallizer material were dissolved in 400 grams of 150°F water. All solids dissolved. The solution was frozen for 24 hours at 0°F and placed in a vacuum freeze dryer for 24 hours. At the end of this period all of the water had been evaporated and a dry stable, uniform, dehydrated cocrystalline solid matrix remained. This was ground and added to a formula consisting of: peanut paste, sugar, molasses, stabilizer and emulsi-

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fier at a level of 23 grams of the improved cocrystalline amino acid food additive to 1000 grams of peanut butter mix. This level should give a protein efficiency ratio of 2.5. A control peanut butter consisting of the same ingredients and substituting sodium chloride for the cocrystallized material to obtain an equivalent sodium chloride level was prepared. These two materials were paneled by expert panelists and were determined to be equal in flavor.

Example 2

A dehydrated uniform cocrystalline amino acid food additive was produced by mixing:

240 grams of sodium chloride
118 grams of L-lysine hydrochloride
62 grams of N-acetyl L-methionine (NALM)
42 grams of L-threonine
800 grams of water at 150° to solubilize all the materials. This solution was freeze dried for 24 hours.

Example 3

A second dehydrated uniform cocrystalline amino acid additive was prepared by making the same mixture as in Example 2 and then neutralizing with sodium hydroxide to a pH of 6.8. This solution was also freeze dried to provide an additive cocrystallate containing the sodium salts of the amino acid materials.

Peanut butter was produced consisting of peanut - 90%, sugar - 5.8%, stabilizer - 1.4%, emulsifier - .7%, molasses - .5%. No salt (NaCl) was added to this material. This batch was then separated into four equal portions. The first portion of the material was mixed with 1.2% sodium chloride and prepared as peanut butter. The second batch was mixed with 2.2% cocrystallate (Example 3) food additive comprising the sodium salts of the amino acid materials plus 0.1% free sodium chloride. The third batch was mixed with the 2.3% cocrystallized (Example 2) amino acids without neutralization and the fourth batch was mixed with 1.2% sodium chloride, .58% lysine, 0.3% N-acetyl L-methionine, and 0.2% L-threonine. All four of the finished peanut butters contained an equal amount of sodium chloride and equal levels of amino acids, except the control. A direct flavor comparison between the products containing the cocrystalline salts of the amino acids and the cocrystalline amino acids with the products made with the free amino acid addition showed an average of 2 flavor grade improvement in overall flavor between the cocrystalline amino acid food additives and the direct amino acid addition. The cocrystalline amino acid food additive fortified peanut butters were preferred by a panel of expert tasters. A flavor grade of 1 is considered as significant.

A number of embodiments of the present invention are set out in Table II.

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TABLE II

Example	Components Dissolved in 400 gm. 150°F water	Drying Time and Comments
4	50 gm. L-lysine-HCl 150 gm. sucrose	dried in 24 hr. freeze dryer
5	50 gm. L-threonine 150 gm. sucrose	dried in 24 hr. freeze dryer
6	150 gm. NALM 150 gm. sucrose	did not dry after 39 hr.
7	30 gm. L-lysine-HCl 15.5 gm. NALM 10 gm. L-threonine 150 gm. sucrose	required 39 hr. to dry
8	25 gm. NALM 150 gm. sucrose	dried in 24 hr.
9	31 gm. NALM 120 gm. NaCl	dried in 24 hr.
10	50 gm. NALM 100 gm. NaCl	dried in 24 hr.
11	59 gm. L-lysine-HCl 31 gm. NALM 20 gm. L-threonine 120 gm. NaCl	dried in 24 hr.

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The significance of a more stable and better-tasting amino acid food additive with low hygroscopicity

EXAMPLE 12

Sodium NALM, NaCl, Melted Fat, Spread Over the Surface of Extrudate

Two grams of NaCl and 0.5 g of NALM were dissolved in 30 ml of water and the pH of the solution brought to 6.75 by the addition of 0.1N NaOH. The resulting solution was freeze dried. Eight tenths of a gram of the resulting freeze-dried cocrystallate was added to 4 g of melted fat, saturated triglyceride, mix contained in a test tube immersed in a silicone bath maintained at 80°C. A fine stream of nitrogen was bubbled through the melted fat in order to suspend the sodium NALM-NaCl cocrystallate. One and two tenths grams of the suspension were dripped on the surface of 3.75 g of freeze-dried soy meal based meat analog extrudate using a transfer pipet. The resulting sample was used in the rapid aging test.

EXAMPLE 13

NALM, Melted Fat, Spread Over the Surface of Extrudate

Three hundred and thirty-nine mg of finely ground NALM were added to 10 g of melted fat mix in a test tube immersed in a silicone oil bath maintained at 65°C. Suspension of the NALM was achieved by bubbling a fine stream of nitrogen through the melted fat. One and three tenths grams of the suspension were dripped on the surface of 3.75 g of freeze-dried soy meal based meat analog extrudate using a transfer pipet. The resulting sample was subjected to the rapid aging test.

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EXAMPLE 14

Aqueous NALM, Extrudate (freeze-dried)

NALM (0.113 g) was dissolved in 30 ml of water and the solution added to 15 g of soy meal based meat analog extrudate contained in a plastic dish. The extrudate was stirred until nearly all of the solution was absorbed and then freeze-dried. The freeze-dried sample was ground with a mortar and pestle and 3.75 g were subjected to the rapid aging test.

EXAMPLE 15

Aqueous Sodium NALM, Extrudate (freeze-dried)

NALM (0.113 g) was dissolved in 15 ml of water and the pH of the solution brought to 6.75 by the addition of 0.1N sodium hydroxide solution. The solution was diluted to 30 ml and added to 15 g of soy meal based meat analog extrudate. The extrudate was stirred until nearly all of the solution was absorbed. After freeze drying, the sample was ground with a mortar and pestle, and 3.9 g of the ground sample was used in the rapid aging test.

EXAMPLE 16

Aqueous Sodium NALM, NaCl, Extrudate (freeze-dried)

One hundred and thirteen mg of NALM and 0.4 g of NaCl were dissolved in 15 ml of water. The pH of the solution was brought to 6.75 by the addition of 0.1N sodium hydroxide, diluted to 30 ml and added to 15 g of soy meal based meat analog extrudate. The extrudate was stirred until nearly all of the solution was absorbed, then freeze dried. The freeze-dried sample was ground with a mortar and pestle and 3.9 g of the ground sample was used in the rapid aging test.

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EXAMPLE 17

Sodium NALM-NaCl (cocrystallate, Extrudate (dry ingredients ground together)

Three and seventy-five hundredths g of freeze-dried soy meal based meat analog extrudate and 0.193 g of a freeze-dried mixture of sodium NALM and NaCl (1:4-sodium NALM:NaCl) were ground together in a mortar and pestle. The resulting sample was used in the rapid aging test.

EXAMPLE 18

NALM, Extrudate (dry ingredients ground together)

Thirty-eight mg of NALM and 3.75 g of freeze-dried extrudate were ground together with a mortar and pestle. The resulting sample was used in the rapid aging test.

EXAMPLE 19

Peanut Butter + NALM

Fifteen g of peanut butter were heated at 90°C, 38 mg of NALM added, the mixture stirred with a magnetic stirrer and subjected to the rapid aging test.

EXAMPLE 20

Peanut Butter + Sodium NALM-NaCl (cocrystallate)

The experiment described in 19 above was repeated substituting 0.199 g of a sodium NALM-NaCl mixture (1-4 ratio) for the NALM.

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TABLE III

GENERATION OF VOLATILE SULFUR COMPOUNDS IN THE RAPID AGING TEST (90°C, 16 hours)

Samples Subjected to Rapid Aging Test	Volatile Sulfur Compounds Formed in Headspace			
	Hydrogen Sulfide	Methyl Mercaptan	Dimethyl Sulfide	Dimethyl Disulfide
	Peak area measurements (sulfur detector response x 10^3)			
12. Sodium NALM, NaCl cocrystallate, melted fat, spread over the surface of extrudate	0	0	2	0
13. NALM, melted fat, spread over the surface of extrudate	21	1	105	81
14. Aqueous solution of NALM, spread on extrudate (freeze-dried)	0	0	285	1
15. Aqueous solution of sodium NALM, spread on extrudate (freeze-dried)	11	0	584	45
16. Aqueous solution of sodium NALM, NaCl, spread on extrudate (freeze dried)	35	0	850	25
17. Sodium NALM-NaCl (cocrystallate) extrudate (dry ingredients ground together)	14	4	33	33
18. NALM, extrudate (dry ingredients ground together)	0	75	143	824

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19.	Peanut butter + NALM	247	427	410	5
20.	Peanut Butter + sodium NALM-NaCl (cocrystallate)	0	17	150	0

Sodium NALM-NaCl cocrystallate suspended in melted fat, saturated triglyceride, and coated on the surface of dry extrudate is stable in a rapid aging test, whereas NALM is not.

Decomposition is pronounced when aqueous solutions of NALM, sodium NALM, or sodium NALM plus NaCl are intimately mixed with extrudate and subjected to the rapid aging test (Table III, Examples 14, 15 and 16).

Some decomposition occurs when a sodium NALM-NaCl cocrystallate is dry mixed with extrudate and subjected to the rapid aging test, but this composition is much more stable than a dry mix of NALM-extrudate mixture.

Decomposition is pronounced when a peanut butter composition containing NALM is subjected to a rapid aging test. Considerably less decomposition occurs when the same peanut butter composition containing sodium NALM-NaCl cocrystallate is used (Table III, Examples 19 and 20, respectively).

The superior stability of the low hygroscopic Na-NALM-NaCl cocrystallate applied to meat-analog extrudate as compared to comparable amounts of other amino acid materials including NALM itself, or Na-NALM, is dramatically demonstrated by these tests.

WHAT IS CLAIMED IS:

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EXHIBIT B

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United States Patent

Huffman

[15] **3,664,858**

[45] **May 23, 1972**

[54] HEAT-SENSITIVE COPY-SHEET

[72] Inventor: **William A. Huffman**, St. Paul, Minn.

[73] Assignee: **Minnesota Mining and Manufacturing Company**, St. Paul, Minn.

[22] Filed: **Feb. 18, 1970**

[21] Appl. No.: **12,427**

[52] **U.S. Cl.** **117/36.8**, 117/36.2, 117/36.7, 117/155

[51] **Int. Cl.** **B41m 5/18**

[58] **Field of Search** 117/36.8, 36.9, 36.2, 36.7

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[57] **ABSTRACT**

Heat-sensitive copy-sheet coatings comprise highly methanol-soluble amine adducts of organic acidic materials. The sheets may be clear and transparent, becoming light-diffusing on heating. In a preferred form they contain amine-reactive color progenitors and become colored on heating. The presence of a mutual solvent does not cause the color-forming reaction to take place, and the reactants may therefore be coated together in a single application.

14 Claims, No Drawings

HEAT-SENSITIVE COPY-SHEET

This invention relates to heat-sensitive copy-sheets useful in the preparation of copies of graphic originals by thermographic processes involving brief exposure of a differentially radiation-absorptive original to intense heat-producing radiant energy while in heat-conductive contact with the copysheet, and wherein the conversion temperature is between about 90°and about 150° C.

In one aspect the invention relates to clear transparent heat-sensitive copy-sheets useful in the preparation of projection transparencies. In a related aspect the invention relates to copy-sheets with which color projection transparencies may be prepared.

In the preferred practice of the invention the copysheet includes a backing or carrier sheet or film carrying a clear transparent coating comprising a highly methanol-soluble amine adduct of an organic acidic material in conjunction with a polymeric binder.

Heat-dissociable co-crystal complexes or adducts of amines with aromatic hydroxy compounds have previously been suggested as components of heat-sensitive copy-sheets, but only in particulate and light-diffusing form. Thus in U.S. Pat. No. 3,090,697 a dispersion of particles of the heat-dissociable molecular compound or adduct of an amine and a halogenated aromatic hydroxy compound in a suitable binder provides a light-diffusing masking layer which is transparentized on heating. U.S. Pat. Nos. 3,076,707, 3,149,991-2-3, 3,166,433, 3,167,444-5, and 3,185,583-4-5 describe heat-sensitive copysheets containing similar adducts in light-diffusing particulate form, together with amine-reactive color-producing compounds or compositions; heating the sheet causes dissociation of the adduct with liberation of amine and formation of color-bodies.

It has now been found possible to produce clear transparent films and coatings containing heat-dissociable amine adducts in non-particulate form. The coating does not obscure desired colors or markings on the underlying carrier. Where a transparent carrier is employed, the sheet produces excellent projection transparencies.

It has further been found possible to incorporate, in potentially co-reactive association with the amine adduct, various amine-reactive color progenitor compounds and compositions, in many cases without impairing the clarity of the coating, the resulting copy-sheets producing high quality color projection transparencies.

A particular advantage of the compositions and procedures here employed is that the amine adduct and color progenitor are soluble in a common solvent without co-reaction. The materials may therefore be dissolved together and applied as a single stratum, requiring only one coating and drying step. When once applied, the coating is solvent-resistant in that the deliberate or accidental application of solvent does not result in a color-forming reaction. This is in sharp contrast to the behavior of the color-forming components and coatings of the prior art referred to hereinbefore.

The above-described and other advantages are obtained, in accordance with the principles of this invention, by employing heat-dissociable amine adducts of certain organic acidic materials of which benzoic and salicylic acid are presently preferred examples. A preferred class of acidic materials consists of those which exhibit a pKa value not higher than about 6 and preferably are substantially colorless. The preferred adducts are also found to be highly soluble in methanol, which is here defined as soluble to the extent of at least about 20 grams per 100 cc., and preferably at least about 50 grams per 100 cc., as will be further shown in connection with specific Examples.

Among the organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48,

o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenoxyacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17, malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethylsulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic, naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3-pyridinecarboxylic, pentanetricarboxylic, cyanoacetic.

The amine adducts are very easily made by simple mixing of the two components in solution. The product may be recovered in crystalline form, purified if desired, and redissolved for mixing with the other components and applying to the carrier. More conveniently, the adduct is prepared by adding the components to a solution of the color progenitor material and/or the binder in a mutual volatile solvent, the mixture then being applied directly to the carrier. In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to dryness, and the co-crystal adduct is washed with hexane and dried before being re-dissolved in a solution of binder and color progenitor. Alternatively, benzoic acid (0.61 gm., 0.05 mol) is dissolved in 20 gm. of 10 percent solution of cellulose nitrate in methanol, followed by addition of piperidine gm., 0.05 mol) and by 0.05 gm. of hydrindantin as color progenitor, and the solution is applied uniformly to a transparent film backing and dried, forming a colorless, clear and transparent, heat-sensitive sheet material.

Substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention. Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenylhydrazine, hexanediamine, methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine, diethylamine, diethanolamine, hydroxyethyldiethylenetriamine, isooctylamine, n-decylamine, n-methylethanolamine, tetramethylguanidine, methyldiethanolamine, 2-amino-**propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide**.

The concentration of adduct and of color progenitor in the heat-sensitive sheet materials and coatings of this invention may be widely varied but for economy is preferably not greater than that required to produce an image of adequate contrast by thermographic copying.

The following specific Examples, in which all proportions are in parts by weight unless otherwise specified, will serve further to illustrate but not to limit the invention.

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EXAMPLE 1

Co-crystal adduct of equimolar proportions of morpholine and bis(trifluoromethylsulfonyl)methane	2 parts
Indane-1,2,3-trione-2-hydrate (Ninhydrin)	0.75
Cellulose nitrate	5
Methanol	45

The adduct is soluble in methanol at 20° C. to the extent of 80 gm./100 cc.

The reactants and binder are dissolved in the solvent, and the solution is coated on 2 mil transparent heat-resistant Mylar polyester film, using a coating orifice of 2 mils, and dried. The reactants are thereby maintained in potentially coreactive association in the coating. The clear transparent colorless film product is placed against the printed surface of a typed original which is then briefly exposed through the film to intense radiation in an infra-red copying machine. A copy of the printed image appears on the film in transparent blue. On an overhead projector, the transparency projects a blue image on the white screen background.

EXAMPLE 2

Phosphomolybdic acid	9
Co-crystal adduct of phenylhydrazine and 5-chlorosalicylic acid	10
Ascorbic acid	10
Polyvinyl butyral	10
Methanol	90

Coated on clear polyester film, the solution provides a clear colorless product which forms a blue-gray image in the thermographic copying process and projects a black image with white background.

The co-crystal adduct is soluble in methanol to the extent of 58 g./100 cc.

EXAMPLE 3

Dinitroanthraquinone	3
Zinc hydrosulfite	2
Co-crystal adduct of piperidine and thiophene carboxylic acid, sol. 40 g./100 cc.	6
Polyvinyl butyral	13.4
Methanol	76

The coating on polyester film is clear and colorless, converting to dark brown upon thermographic heating at image areas.

EXAMPLE 4

Phloroglucinol	2
Sodium nitroprusside	2
Co-crystal adduct of morpholine and naphthylacetic acid, s. 32 g./100 cc.	4
Cellulose nitrate	10

The solution in methanol is applied to heat-resistant clear polyester film and dried. The heat-sensitive sheet produces a black image.

EXAMPLE 5

Bromcresol purple (colorless form)	1
Co-crystal adduct of piperidine and bromophenoxyacetic acid—s. 70 g./100 cc.	5
Cellulose nitrate	25

Applied from methanol, the composition gives purple images in the thermographic copying process.

EXAMPLE 6

A. Solution of 10 parts lead chloride in 190 parts of a 10 percent solution of cellulose nitrate in methanol.

B. Solution, in 190 parts of 10 percent solution of cellulose nitrate in methanol, of 5 parts zinc hydrosulfite and 5 parts cocrystal adduct of ethylene diamine and salicylic acid (s. 45 g./100 cc.).

Solutions A and B are combined and coated on clear polyester film at a wet coating thickness of 2 mils. The dry sheet is clear and colorless, and produces black opaque copy on a clear background in the thermographic copying process.

EXAMPLE 7

A. The co-crystal adduct of morpholine and benzoic acid (s. 70 g./100 cc.) is dissolved in a solution of cellulose nitrate in methanol and the solution coated on polyester film and dried. The product is clear and colorless.

B. Separately, polyester film is coated with a solution of acid-stabilized diazonium salt, azo dye coupler, and ethyl cellulose in ethanol, and dried, producing a clear and slightly yellowish coated film.

The composite of films A and B in face-to-face contact is locally heated at image areas in the thermographic copying process, producing a blue azo dye image on the B sheet. The copy projects as a blue image with a slightly yellowish background.

Alternatively, since the diazonium salt is decomposed by ultraviolet radiation, images may be formed by irradiating the B film through a transparency and then uniformly heating the A sheet against the B film.

Solutions A and B may alternatively be mixed together and applied as a coating on transparent film to produce a transparent heat-sensitive copy-sheet.

The diazonium salt is the zinc sulfate salt of 2,5-dibutoxymorpholinobenzene.

The azo coupler is 2,5-dichloro-1-naphthol.

EXAMPLE 8

Clear 3 mil oriented and heat-shrinkable polystyrene film is coated from a 3 mil orifice with a solution of 0.5 part of ethyl cellulose and 1.0 part of the co-crystal adduct of morpholine and myristic acid (s.> 70 g./100 cc.) in 98.5 parts of a mixture of equal volumes of methanol and ethanol. The dried product is clear and transparent. When thermographically heated at image areas, there is formed a corresponding roughened light-diffusing image which on projection appears as a dark image against a light background.

Both morpholine and myristic acid are softeners or plasticizers for polystyrene.

EXAMPLE 9

One part of the co-crystal adduct of diethylamine and 5-formylsalicylic acid (s. 32 g./100 cc.) is dissolved in 20 parts of a 10 percent solution of VYHH vinyl chloride-acetate copolymer in acetone, and the solution is applied at a thickness of 3 mils on 2 mil Mylar polyester film and dried. A further coating of 2 mils of a 13.5 percent solution of cellulose nitrate in methanol is applied and dried. The resulting clear transparent film produces light-diffusing images at thermographically heated image areas and projects dark images against a light background.

Diethylamine is a colorless liquid which boils at about 55°–56 C. At thermographically achieved temperatures, e.g. about 90°–150° C., the adduct is dissociated, the amine is vaporized, and the vinyl polymer is softened; as a result, a vesicular image is produced. The cellulose nitrate topcoat assists in preventing premature escape of the vaporized amine and in protecting the softer vinyl polymer but is not essential, particularly with somewhat thicker first coatings.

EXAMPLE 10

A solution of one part ninhydrin and three parts of the co-crystal adduct of piperidine and benzoic acid (s. 62 g./ 100 cc.) in 25 parts of water is applied to white bond paper by floating and draining. The dried sheet is tested as a heat-sensitive copy sheet in the thermographic copying process and produces a purple image on a white background.

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Wetting the sheet with methanol, acetone or other organic solvents does not cause a color reaction and the sheet after drying remains heat-sensitive.

Polyvinyl alcohol or other transparent water-soluble binder may be added to the above aqueous solution, and the mixture coated on transparent regenerated cellulose film, to produce a clear transparent heat-sensitive copy-sheet with which color projection transparencies may be thermographically prepared.

EXAMPLE 11

Colored paper having a pink tint and overprinted with a lightly inked design is coated with a first solution containing one part of hydrindantin dihydrate and two parts cellulose nitrate in 17 parts of methyl Cellosolve, and dried. A second coat of one part of co-crystal adduct of hexylamine and benzoic acid (s. 40 g./100 cc.) in 20 parts of a ten percent solution of cellulose nitrate in methanol is added and dried. The pink tint and overprinted design remain fully visible through the transparent coatings. Localized heating in the thermographic copying process produces clearly visible purple images.

Substitution for the second coat of a composition containing one part of the co-crystal adduct of hexylamine and tetrachlorobisphenol A in 20 parts of a 10 percent solution of polyvinyl butyral in trichlorethane, and wherein the adduct is present as finely divided particles, produces a light-diffusing dry surface layer which obscures the color and design of the paper backing. Replacing the binder and solvent with a system in which the adduct is soluble, for example with a solution of polyvinyl butyral in acetone, results in immediate color-forming reaction when the solution is coated over the first-applied layer containing the hydrindantin dihydrate.

The adduct of tetrachlorobisphenol A with hexylamine has a solubility in methanol of only four g./100 cc. The adduct of this acid with morpholine exhibits maximum solubility as compared with adducts of a large number of other amines, the value being 12 g./100 cc.

EXAMPLE 12

Paper is coated with a mixture of 2.5 parts of lead nitrate: thiourea complex, 2.5 parts of the co-crystal adduct of diethylamine and dinitrotoluic acid, and 10 parts of cellulose nitrate, applied from methyl alcohol and dried, to produce a heat-sensitive copy-sheet which forms black images when heated in the thermographic copying process. The solubility of the adduct is 26 g./100 cc. methanol.

What is claimed is as follows:

1. A heat-sensitive copy-sheet adapted for making reproductions of graphic originals by thermographic copying methods and having a visibly heat-sensitive layer comprising a highly methanol-soluble co-crystal adduct, heat-dissociable at thermographic copying temperature, of a basic organic amino compound and an organic acidic compound having a pKa value not greater than about 6, dissolved in a transparent organic binder, said adduct and binder being soluble in a common solvent, said binder being heat-softenable, and at least one of said compounds being vaporizable, at said temperature, to form vesicles at the heated areas within said layer.

2. The heat-sensitive copy-sheet of claim 1 wherein said layer is supported on a clear transparent film backing.

3. The heat-sensitive copy-sheet of claims 1 wherein said adduct is soluble in methanol to the extent of at least about 50 grams per 100 cc.

4. The copy sheet of claim 1 wherein said organic acidic compound is a carboxylic, sulfonic, phenolic or fluorosulfone acidic compound.

5. The copy sheet of claim 4 wherein said organic acidic compound is bis(trifluoromethylsulfonyl) methane.

6. A heat-sensitive copy-sheet adapted for making reproductions of graphic originals by thermographic copying methods and having a visibly heat-sensitive layer comprising a highly methanol-soluble co-crystal adduct, heat-dissociable at thermographic copying temperature, of a basic organic amino compound and an organic acidic compound having pKa value not greater than about 6, dissolved in a transparent organic binder, said adduct and binder being soluble in a common solvent, said layer being supported on a heat-shrinkable clear transparent film and at least one of said compounds being a softener for said film at said temperature.

7. The heat-sensitive copy-sheet of claim 6 wherein said adduct is soluble in methanol to the extent of at least about 50 grams per 100 cc.

8. The copy-sheet of claim 6 wherein said organic acidic compound is a carboxylic, sulfonic, phenolic or fluorosulfone acidic compound.

9. The copy-sheet of claim 8 wherein said organic acidic compound is bis(trifluoromethylsulfonyl) methane.

10. A heat-sensitive copy-sheet adapted for making reproductions of graphic originals by thermographic copying methods and having a visibly heat-sensitive layer comprising a highly methanol-soluble co-crystal adduct, heat-dissociable at thermographic copying temperature, of a basic organic amino compound and an organic acidic compound having a pKa value not greater than about 6, dissolved in a transparent organic binder, said adduct and binder being soluble in a common solvent, said layer including an amine-reactive color progenitor material in potentially coreactive association with said adduct and containing no free amine.

11. The heat-sensitive copy-sheet of claim 10 wherein said layer is supported on a clear transparent film backing.

12. The heat-sensitive copy-sheet of claim 10 wherein said adduct is soluble in methanol to the extent of at least about 50 grams per 100 cc.

13. The copy-sheet of claim 10 wherein said organic acidic compound is a carboxylic, sulfonic, phenolic or fluorosulfone acidic compound.

14. The copy-sheet of claim 13 wherein said organic acidic compound is bis(trifluoromethylsulfonyl) methane.

* * * * *

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EXHIBIT C

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 07/12/2016
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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
07/12/2016	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

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Office Action Summary	Application No. 14/179,862	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 4/1/16.

☐ 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 and 52-58 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 and 52-58 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: _____.

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DETAILED ACTION

Status of the Application

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

This Office Action is in response to applicant's arguments filed on April 1, 2016. Claim(s) 37-50 and 52-58 are pending and examined herein.

Response to Arguments

The outstanding nonstatutory double patenting rejection is hereby maintained as a result of Applicant's decision to hold said rejection in abeyance.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being anticipated by McCoy (CA 1148020A1) have been fully considered. Applicant argues:

> "McCoy discloses improved amino acid food additives which comprises a uniform dehydrated cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material. (McCoy, Abstract). McCoy discloses physical mixtures of multiple components in non-stoichiometric ratios. Indeed, McCoy discloses that "[g]enerally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of cocrystallizer are used." (McCoy, page 7, lines 10-15, emphasis added). The equal amounts of cocrystallizer disclosed by McCoy are equal amount by weight, not equal amount by moles."

Further, Applicant argues:

> "There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, e.g., a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase (e.g., Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004; a copy of which is provided herewith in connection with an Information Disclosure Statement). One skilled in the art would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed.

Examiner respectfully notes that as set forth on record previously and as discussed below, McCoy teaches "an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1". As pointed out by Applicant, McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed. Nonetheless, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, it is the opinion of the Examiner that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces such proportions to be possible.

Furthermore, with respect to freeze-drying, Applicant states that such a technique yields a mixture of crystalline and amorphous phase. Although a mixture is afforded, a portion of the mixture is crystalline, thereby still rendering the instant invention obvious.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered and are not fully persuasive.

Applicant argues:

> "Huffman is not analogous art as required by MPEP §2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors. With respect to the field of endeavor, the present claims are directed to methods relating to co-crystal formation with an active pharmaceutical ingredient (API) and therefore relate to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts."

With respect to this argument, Examiner respectfully notes that the instant claims are drawn to a method for designing and preparing a cocrystal, wherein the first chemical functionality is an API, with certain requirements as set forth in claim 37 and a cocrystal former. Although the claim 37 requires an API, it does not mandate that the endeavor relate to the pharmaceutical arts. The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144. Moreover, it is respectfully noted that many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic (references can be provided if requested).

Therefore, based on the foregoing reasons, said rejection is hereby maintained/modified for claim 37 and dependent claims thereon.

The rejections are maintained and made of record in the Final office action below for Applicant's convenience as necessitated by amendment.

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 claims at issue 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); and *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 a nonstatutory double patenting ground provided the reference application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form 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 http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 37-50 and 52-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 28, 37, 39-51, 53-60, and 62-66 of copending Application No. 10/378,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the copending claims are drawn to the method of designing said co-crystals. The two inventions overlap greatly in scope and the utilities are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality

as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and

nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at last one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred (page 6-7).

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and heterosynthons as required by the instant claims are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also

envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different fuctionalities, giving rise to heterosynthons. Therefore, preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds.

Examples of organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48, o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenox yacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17, malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethyisulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic,

naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3 pyridinecarboxylic, pentanetricarboxylic, cyanoacetic (column 1-2, bridging paragraph).

Huffman teaches substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Huffman teaches piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention. Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenyl hydrazine, hexanediamine, methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine , diethylamine, diethanolamine, hydroxyethyl diethylenetriamine, isooctylamine, n-decylamine, methylethanolamine, tetramethylguanidine, methyl diethanolamine, 2-amino--propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide (column 2, lines 44-68).

In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to

dryness, and the cocrystal adduct is washed with hexane and dried (column 2, lines 30-35).

Huffman does not teach the co-crystal complexes in pharmaceutical compositions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct. See *In re Dillon* 16 U.S.Q.P.2d 1897, 1900 (CAFC 1990) (en banc) ("it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that Wright suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law. ").

Therefore, it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 37-50 and 52-58 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). 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.

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/SAHAR JAVANMARD/

Examiner, Art Unit 1627

EXHIBIT D

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Pharmaceutical Patent Analyst

The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents

Örn Almarsson*[1], Matthew L Peterson[2] & Michael Zaworotko[3]



From aspirin to zoledronic acid, pharmaceutical cocrystals emerged in the past decade as a promising new weapon in the arsenal of drug development. Resurgence of interest in multicomponent crystal compositions has led to significant advances in the science of cocrystal design and discovery. These advances have built upon crystal engineering, which provides a deep understanding of supramolecular interactions between molecules that govern crystal packing and physicochemical properties of crystalline materials. Concomitantly, the patent landscape of pharmaceutical cocrystals developed rapidly in the last decade. This review presents a broad survey of patents issued in the area of pharmaceutical cocrystals. In addition, the review contains analyses of key patents in the area involving compositions and methodologies. Along the way, the main events of the past decade representing a renaissance of cocrystals of pharmaceutical materials are chronicled. Future directions in the area are discussed in light of key pending patent applications and recent publications of seminal interest.

Solid forms of active pharmaceutical ingredients

The solid form of an active pharmaceutical ingredient (API), in particular its physicochemical properties relevant to clinical performance and long-term stability, represents an important aspect of modern drug discovery, development and pharmaceutical science [1,2]. Over the course of the past century of modern drug development and manufacture, drugs such as aspirin and many antibiotics have owed their purity and storage stability to their existence as crystalline solids. Crystalline solids are solids in which the atoms, molecules or ions pack together to form a regular repeating array that extends in three dimensions. Crystalline solids are formed when a solution becomes supersaturated with crystallizing solute(s), and the vast majority of substances, if not all of them, will crystallize to form one or more crystalline phases under the right conditions. Cocrystals are a class of crystalline solids that occur when complementary molecules of different structures are crystallized to form single crystalline phases that contain stoichiometric ratios of the components. A prototypical example is a 1:1 composition cocrystal as illustrated in Figure 1. The crystalline form of a given API confers important properties to the material, such as thermodynamic solubility, melting point, shape, mechanical properties and thermal stability. Aqueous solubility and dissolution rate are particularly important in the context of drug performance since orally delivered drugs must dissolve from their dosage form within the gastrointestinal tract in order to be absorbed, first by the tissue of the intestines and ultimately into circulation. Aqueous solubility is also important for injectable drug formulations, in particular when intravenous injection is required. Because of the tight regulation of drug review and approvals across the world, detailed information on the crystalline form of an API, its synthesis, purity profile and properties are required as part of regulatory filings. Finally, and most relevant to this review, the IP associated

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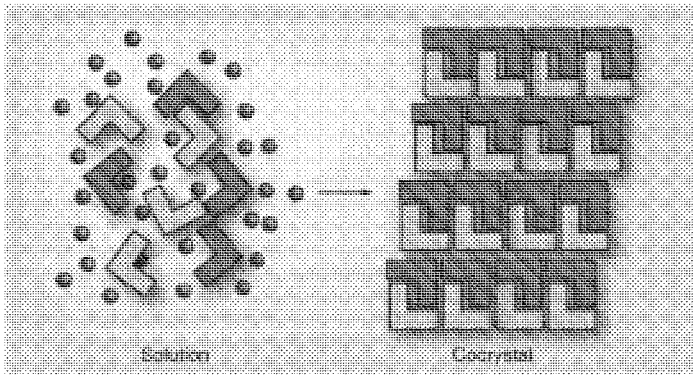


Figure 1. Stoichiometric cocrystals are formed when two complementary molecules are crystallized from solution.

with the crystalline form of an API came to the fore in the 1990s, thanks initially to high-profile patent litigation on what was at the time the best-selling drug in the world, ranitidine hydrochloride (Zantac®) [3]. Today, the characteristics and preparation of an API solid form can be of significant importance when seeking to register a new drug product using a crystalline API, and crystal forms continue to be the subject of litigations related to patent validity and infringement.

The motivation for studying cocrystals of pharmaceutical compounds

Solid-form screening in drug development has traditionally focused upon the need to find a solid form with optimal physicochemical properties, but has until recently focused almost exclusively on the generation of polymorphs, solvates, hydrates or salts of an API [4]. Pharmaceutical cocrystals [5] emerged in the last decade as an alternative class of crystal form available to pharmaceutical scientists. Despite recent emergence, pharmaceutical cocrystals are already established as an integral part of solid-form screening because they provide an opportunity to modify, sometimes with dramatic results, the physicochemical properties of an API without the need for applying medicinal chemistry, which involves covalent modification of the API. Rather, pharmaceutical cocrystals exploit the supramolecular chemistry of the API to create a new crystal form through formation of a multiple-component crystal that comprises of the API and a second compound or 'cocrystal former' (also known by various alternative names, such as 'coformer' or cocrystallizing agent). It has already been demonstrated that the aqueous solubility [6,7], physical stability [8] and mechanical properties [9] of an API can be affected by cocrystallization. Furthermore, pharmaceutical cocrystals represent an opportunity to patent new solid forms of APIs (or avoid infringement of existing patent claims on solid forms of an API). That a high proportion of new chemical entities are classified as having low solubility has, if anything, provided added impetus for solid-form screening and the study of pharmaceutical cocrystals. Pharmaceutical cocrystals can offer advantages over other solid forms as follows: salts only form for APIs that ionize (protonate or deprotonate with acid or base, respectively) in water, whereas cocrystals can be made for essentially all APIs; amorphous forms; and solvates and hydrates tend to be physically unstable during processing and on the shelf. Finally, medicinal chemistry involves chemical modification of the molecular structure of the API, requiring extensive and time-consuming toxicology and clinical testing of the resulting new molecule(s). In short, pharmaceutical cocrystals offer an opportunity to address challenges of low solubility and other physicochemical properties of APIs with relatively low cost and limited incremental risk.

History & nomenclature of cocrystals

As mentioned, cocrystals can be broadly defined as supramolecular assemblies that contain more than one type of molecule in the crystalline lattice. For the purposes of this review we more specifically define a cocrystal as follows: a multiple component crystalline solid formed in a stoichiometric ratio between two compounds that are crystalline solids under ambient conditions. At least one of these compounds is molecular (the cocrystal former) and forms supramolecular synthons(s) with the remaining component(s). If one uses this definition then cocrystals were reported as far back as the 1840s [10] and they have had various terms coined for them: addition compounds, organic molecular compounds, complexes and heteromolecular crystals [11–14]. Cocrystals are thereby distinct from solvates and hydrates if one adopts this definition. It should be noted that APIs are a natural target for cocrystal formation since the nature of APIs means that they contain exterior functional group(s) that can engage in molecular recognition events, especially hydrogen-bond formation, with biological targets. These same functional group(s) are often responsible for different crystal packing arrangements (i.e., polymorphism) and can interact with water molecules to form hydrates. However, the term cocrystal as used today did not come into widespread usage until it was popularized by MC Etter in the 1980s [15], and a pharmaceutical cocrystal, that is, a cocrystal between an API and a pharmaceutically acceptable cocrystal former, was not widely used until the 2000s. Interestingly, pharmaceutical cocrystals also have a long history in that they have been known since at least the 1930s [101]. Even earlier, glucose:sodium chloride monohydrate was described, a possible early

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example of an ionic cocrystal of a salt with a sugar [16]. In terms of nomenclature, it should be noted that there are some ambiguities; for example, there are other proposed definitions of cocrystal [17–25] and the work of Leiserowitz in the 1970s [24], as well as the compositions studied by Caira in the 1980s and 1990s [25], were referred to as complexes. Additionally, the term cocrystal is also occasionally applied to crystals of proteins with small molecules bound, for instance, within the active site of the protein. Leaving aside such issues, which are not relevant to this review, until the 2000s the motivation for the study of cocrystals of small organic molecules was oriented towards creating materials for purification or for optical, electronic and other material applications. In summary, both cocrystals and pharmaceutical cocrystals have a long history, but it is fair to assert that they had not been systematically and widely studied in the context of pharmaceutical science until the last decade.

Other solid forms of APIs

At the end of the 20th century, prior to the advent of pharmaceutical cocrystals, crystal polymorphism became a topic of major concern and highlighted the need for systematic solid-form screening of APIs, which also included the study of amorphous solid forms of APIs, with the aid of automation approaches [26]. Polymorphism in crystals is the ability of a particular chemical composition to adopt more than one type of crystal packing. Each different crystalline polymorph has its own set of properties, such as a melting point, heat of fusion and dissolution profile. Awareness of polymorphism in pharmaceutical compounds increased dramatically during the 1990s because of the aforementioned litigation on Zantac (ranitidine HCl). The need for regulatory bodies to address polymorphism was then highlighted by Norvir® (ritonavir) – an API in which catastrophic loss of drug product performance occurred due to sudden and unexpected appearance of a more stable polymorph of the drug with lower solubility than the form originally in use [27]. In addition to issues of polymorphs, crystalline hydrates created a level of concern for the same reasons. Hydrates of pharmaceutical compounds, which are special cases of solvates wherein a water molecule is included in the crystalline lattice along with the compound of interest, tend to display dynamics of water inclusion/exclusion dependent on temperature and relative humidity. Some hydrate-forming drugs have multiple hydrate forms, either as polymorphs or different levels of hydrate (e.g., mono, di- and tri-hydrate). Use of hydrates and solvates in products, while acceptable (and sometimes common, as in the case of β-lactam antibiotics [28]), is generally not preferred by innovators. From a regulatory standpoint, in the USA at least, hydrates are considered similar to polymorphs in terms of how they are treated. The US FDA guidance published in 2007 [29] states that a particular hydrate of a compound is not a different API from a non-hydrate (or alternative hydrate state). Accordingly, there exist regulatory definitions of crystal forms that do not necessarily match scientific differentiation. A similar situation has recently arisen with respect to the comparison of cocrystals with non-ionic complexes with excipients, generally regarded as safe additives or other suitable coformers, and distinction of pharmaceutical cocrystals from salts.

Design of cocrystals

Rapid advances in crystal engineering [30–32] in the 1990s facilitated a better understanding of crystal-form diversity as represented by polymorphs, salts, solvates and hydrates, and enabled the design (as distinct from high-throughput screening) of new multiple-component pharmaceutical compositions. Practitioners of methodology increasingly directed testing to targeting the functional groups in drugs. The understanding developed that an API molecules' chemical functionality can be addressed by selection of complementary functional groups from another molecule, the coformer, led to a rational approach to the development of two-component crystals. This is conceptually similar to the manner in which salt-screening targets the ionizable groups in an API and means that there is a degree of control over cocrystal composition that is not likely to be present in hydrates and solvates. This design philosophy led to the adoption of the 'synthon' approach of cocrystal discovery. The synthon as it applies to cocrystals is analogous to the term as used in the retrosynthetic approach of organic synthesis. In a sense, making cocrystals this way is a supramolecular synthetic strategy. The key to understanding and designing cocrystals of an API lies with our capability to predictably form supramolecular synthons with the API. Supramolecular synthons exist in two distinct categories: supramolecular homosynthons that are composed of identical complementary functional groups such as carboxylic acid dimers (e.g., aspirin) (Figure 2A); and supramolecular heterosynthons composed of different but complementary functional groups such as acid–weakly basic nitrogen (e.g.,aspirin–meloxicam) (Figure 2B) and acid–amide (e.g., aspirin–carbamazepine) (Figure 2C). Whereas it is quite well documented that some of these supramolecular heterosynthons are reliable for the preparation of cocrystals (i.e., they form preferentially over supramolecular homosynthons), studies related to the occurrence of a particular supramolecular heterosynthon in the presence of several competing supramolecular synthons are limited in quantity and scope. Therefore,

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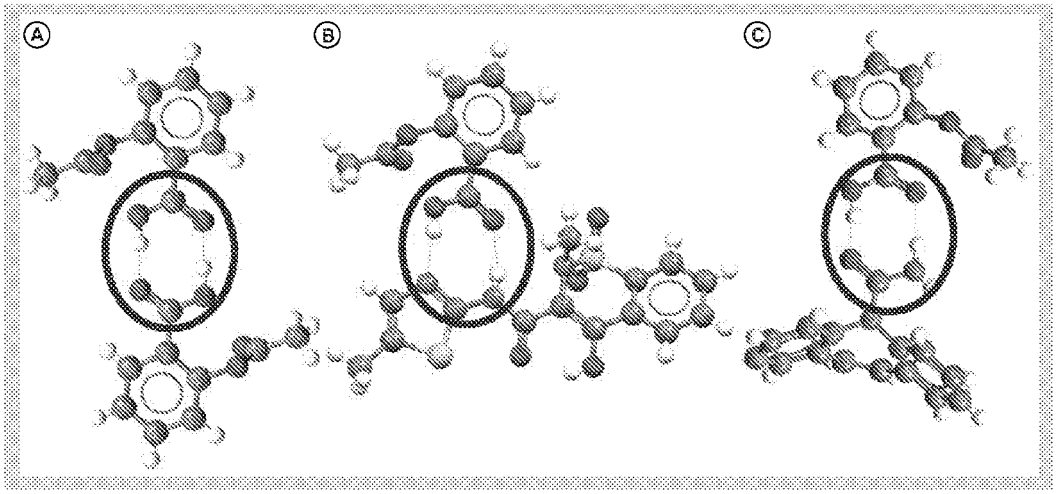


Figure 2. Synthon examples in pharmaceutical cocrystals involving carboxylic acids and amides. (**A**) The carboxylic acid–carboxylic acid supramolecular homosynthon as seen in aspirin. (**B**) The carboxylic acid–weakly basic nitrogen atom supramolecular heterosynthon as exemplified by the aspirin: meloxicam cocrystal. (**C**) The carboxylic acid–amide supramolecular heterosynthon observed in the cocrystals of aspirin and carbamazepine. The blue ovals highlight each supramolecular synthon.

APIs with multiple functional groups, although still amenable to cocrystal formation, tend to be less predictable in terms of structure and composition. To summarize the background to this article, the motivation to systematically study solid forms of APIs lies with the need to fine-tune physicochemical properties (especially modulate drug solubility, increase dissolution rate and to enhance stability), and satisfy regulatory bodies with respect to drug stability and reproducibility. This need had become apparent by the late 1990s and arose partly based on the types of compounds in development (e.g., compounds with poor aqueous solubility and other inadequate physical properties), and in part because a new level of innovation was needed at a time of productivity crisis in the pharmaceutical industry. In essence, pharmaceutical cocrystals joined the arsenal of pharmaceutical R&D as a useful new design tool – with patent prospects – to augment product design and elucidate new pharmaceutical product opportunities. Today, the fruits of almost 10 years of screening for pharmaceutical cocrystals is evidenced by the number of patent applications and issued patents for pharmaceutical cocrystals.

Pharmaceutical cocrystals: recent literature & definition

■ Primary literature

Before reviewing patents on pharmaceutical cocrystals, it is useful to survey the published literature. The first publications signaling the initiation of the pharmaceutical cocrystal era resulted from collaboration between researchers at the University of South Florida, USA, and the University of Michigan, USA. The work was also associated with patent filings, and ultimately resulted in issued claims on the compositions in this paper. A key theme in the papers was the demonstration of design and detailed structural analysis to extend considerably the crystal form diversity of aspirin and carbamazepine, an important antiepileptic drug having low aqueous solubility. These papers were quickly followed by a paper on cocrystals of itraconazole, a highly water-insoluble and poorly bioavailable (as crystalline base) antifungal agent, published by a pharmaceutical technology company, which described the utility of the cocrystal approach for dissolution enhancement. In particular, the cocrystal construct with 1,4-diacids such as succinic, fumaric and tartaric acid involved in a pair of heterosynthons with the 1,2,4-triazole group of two itraconazole molecules showed significant improvement in dissolution rate in aqueous medium compared with the crystalline free base. Additionally, the best of the cocrystals in the series matched the dissolution rate of a solid dispersion, which is an amorphous form with optimized dissolution (used in the capsule product Sporanox®). A fourth example of a publication marking the area is on cocrystals of fluoxetine HCl, an antidepressant and the active agent in Prozac®. This article, contributed by another technology company, highlighted the option of making pharmaceutical cocrystals of a salt, such that the cocrystal has three components. Modulation of solubility was observed by the inclusion of a carboxylic acid such

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as benzoic and fumaric acid to the HCl salt. The four primary literature references cited above were arguably the highest profile publications on pharmaceutical cocrystals in the first half of the decade. The subject matter reported in these publications is summarized in Table 1.

An early and key review in 2004 captured the definition of pharmaceutical cocrystals [33]. The review, now cited over 280 times, suggested that pharmaceutical cocrystals are amenable to design, and that they allow a selection of motifs that can then affect pharmaceutical properties. Pharmaceutical cocrystals were also regarded as more similar to salts than hydrates/polymorphs, given the composition types, variety and some aspects of crystal packing were seen to offer a measure of control. In contrast, polymorphs and hydrates were seen as being less amenable to design and prediction. A number of other review articles were published in the period after 2004, and these concepts have continued to be discussed and refined.

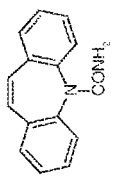
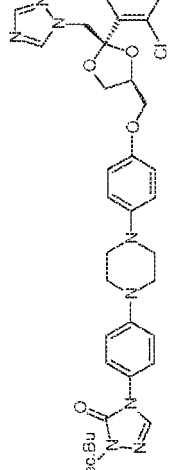
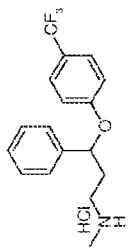
US patents on pharmaceutical cocrystals

A significant number of patent applications have been filed on pharmaceutical cocrystals, with many filed in the last decade. The US and EP patent authorities have granted patents in the area in recent years, starting with one patent from 1999 and ending (at the time of writing) with eight patents issued in 2012. With initial focus on the US-granted patents, we observe that the issued patents fall into two main categories: methodologies and compositions.

Methodology patents

The first claims to issue on pharmaceutical cocrystal methods were those in [102]. The title of the patent is 'Cocrystallization Process', and claims cover purification of chiral compounds by way of formation of cocrystals. In several cases the results are likely to be salt forms, though this has not been verified. In any event, this patent covers methodologies related to pharmaceutical cocrystals. Another cocrystallization methodology patent was filed in January 2004 and issued on November 18, 2008 [103]. The independent claim reads partially "*a method of screening for a cocrystal of a hydrochloric acid salt of an active agent.*" This patent is related to the publication on fluoxetine HCl cocrystals referred to in the previous section [7]. While claim 1 of [103] has several limitations, it allows for a range of carboxylic acids (at least four carbons) with the HCl salt of an active agent (e.g., an antidepressant drug). The inventor and assignee, SSCI, exemplified the approach with a set of carboxylic acid cocrystals of fluoxetine HCl (Table 1). The acidic -COOH function coordinates the chloride ion of an HCl salt of a basic drug. As a component of a supramolecular synthon, Cl^- appears to be a

Table 1. Chemical formulas of carbamazepine, itraconazole and fluoxetine HCl, along with lists of synthon targets in the cocrystal material and examples of coformers.

	Carbamazepine [5]	Itraconazole [7]	Fluoxetine HCl [7]
Structure			
Synthons	Amide–amide homodimer periphery (C=O acceptor and N-H donor)	1,2,4-triazole (2:1 itraconazole to diacid units)	Chloride ion (coformer hydrogen-bond donor)
Coformers	Hydrogen-bond acceptors (e.g., saccharin, nicotinamide and others)	1,4-dicarboxylic acids as hydrogen-bond donors (e.g., succinic, fumaric, tartaric and malic acids); requirement for extended conformation of the diacid (*Z-trans* configuration)	Carboxylic acids (≥4 carbon) as hydrogen-bond donors (e.g., benzoic and fumaric acid)

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ready acceptor of -OH hydrogen bond donors, affording aforementioned carboxylic acid cocrystals, alcohol solvates and hydrates. Examples were provided on solubility and dissolution effects of the cocrystals. A process patent from Cilag (part of J&J), [104], involves the use of a cocrystal for purification of the opioid tramadol. Tramadol HCl cocrystallized with topiramate, an antiepileptic, to produce enantiomerically enriched 1S,2S-tramadol HCl, illustrating the utility of a chiral auxiliary (which is incidentally also a drug) to form a specific pharmaceutical cocrystal.

Two additional cocrystal methodology patents are illustrative of the interest in processes to make pharmaceutical cocrystals. The former, [105] issued on July 27 2010 to TransForm Pharmaceuticals (at this point part of J&J) claimed "a method of producing cocrystals, comprising" steps of processing with grinding materials in small capsules within an array created by two plates and containing a ball that effected the mechanical grinding once the competed array was placed on a shaker apparatus. Mechanical grinding of powder blends with and without solvent drops, a powerful technique championed by the Jones' group at Cambridge University [34,35] had become popular within the community of cocrystal hunters by the middle of the decade. The latter patent [106] issued on 3 August 2010 to Avantium in The Netherlands claimed "*a process for inducing and/or accelerating at least one phase transformation in solid organic molecules, wherein the solid organic molecules are subjected to a tribochemical treatment.*" Cocrystals are not the sole subject of this patent, but are nonetheless explicitly named in dependent claims. The examples of innovation in methodologies relevant to cocrystal formation indicate a level of interest in protecting platform technologies to discover and make these new solid phases. The key challenge with these patents is the degree to which enforcement is practical: once a cocrystallization technology is enabled and patented, it will be difficult to prove that a specific cocrystal composition described was discovered or made using a patented process. It is therefore not surprising that composition patents and applications involving pharmaceutical cocrystals are more numerous than the methodology patents.

The landscape of issued pharmaceutical cocrystallization methodology and process patents in the USA is summarized in Table 2 [102–106]. Three of the five patents originated in companies whose business at the time was crystal form screening and characterization for pharmaceutical materials.

Composition patents

The first US patent located on the subject issued in 1999 and originated from Eli Lilly & Co. It describes compositions that can clearly be classified as pharmaceutical cocrystals: cephalosporin antibiotic complexes with parabens. The latter are excipients generally used as preservatives. The complexes were intended for purification and isolation of the hydrolytically labile β-lactam antibiotics, and thus, evidently, the concept was conceived and applied for scale-up of purification and isolation. The first composition claimed this past decade for a pharmaceutical cocrystal was issued in 2006, claiming an itraconazole form with tartaric acid and HCl. This patent has one independent claim, which in addition to naming the components comprising the cocrystal further includes a specific melting point, such that the composition in the claim is a unique species. Species claims are narrow and specific and, therefore, ostensibly easier to support and grant relative to broad composition claims. The broadest extreme of composition claim is a genus. Since cocrystals have been observed across a range of molecules for decades, a genus of pharmaceutical cocrystals is likely not a supportable patent claim at this point. The broad option of sub-genus claims, meaning the inclusion of a drug molecule or a related group of molecules plus a cocrystal former (or a group of cocrystal formers) is an alternative that has been issued in select cases. The sub-genus claim is exemplified by the itraconazole carboxylic acid cocrystals, which was issued in a later

Table 2. Methodology patents issued in the USA involving cocrystallization 2000–2010.

US patent	Date of issue	Assignee	Nonprovisional priority date	Claims	Cocrystals in claim 1	Ref.
US6570036	27 May 2003	Reuter Chemische Apparatebau KG	3 March 2000	17	Yes	[102]
US7378519	27 May 2008	Cilag GmbH Intl	16 May 2003	1	Yes	[104]
US7452555	18 November 2008	S.S.C.I., Inc.	21 January 2004	11	Yes	[103]
US7763112	27 July 2010	TransForm Pharmaceuticals, Inc.	28 April 2006	12	Yes	[105]
US7766979	3 August 2010	Avantium International B.V.	26 January 2005	20	No	[106]

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patent [107]. In essence, the independent claim allows the license holder to exclude any composition that contains the drug itraconazole and a carboxylic acid.

Table 3 [107–124] summarizes the compositions with granted claims. There are also a number of pending applications, such that the list of issued patents is likely to grow at an increasing pace over the next decade.

Two patents in Table 3, [113] and [119], contemplate compositions with variable stoiciometric ratios – in addition to the standard use of open-ended language in the claims construction. The former patent is an example of continuous variation of the coformer ratio: one coformer can be substituted in portions by an isomorphically substitutable coformer, for example uracil for 5-fluorouracil. Modafinil, a narcolepsy drug, was cocrystallized in this manner with fumaric acid and succinic acid in a system that created isomorphous cocrystals of the composition (Modafinil$_2$[fumaric acid]$_x$[succinic acid]$_{(1-x)}$), where x ranges from 0 to 1. The net result, regardless of the value of x, is a 2:1 cocrystal of modafinil and a dicarboxylic acid. An alternative label for these varying compositions is to call them solid solutions. Nomenclature aside, the approach is intriguing, because it invites tailoring of a physical property in a pharmaceutical crystal form (e.g., the melting point), by the choice of ratio of the coformer. Ordinarily, a crystal form is thought of as a discrete entity with fixed properties. The possibility of blending and selection of properties with cocrystal composition vastly increases the power of the approach.

The patent matter in [110] highlights the challenge of applying definitions of pharmaceutical cocrystals. There is occasional confusion as to whether a composition is a cocrystal or a solvate – the resolution mainly depends on how the coformer is regarded. The patent claims the acetic acid form of (-)-gossypol, a natural product with potential as an anticancer agent. The independent composition claim 1 specifies, *"A composition consisting essentially of cocrystals of (-)-gossypol with acetic acid in a molar ratio of about 1:1."* Glacial acetic acid crystallizes below room temperature at 16.6°C. Additionally, the presence of minute amounts of water in acetic acid lowers the solvents' melting point further [36]. Since glacial acetic acid is a liquid at room temperature, assuming the convention of 20°C as a lower end cut-off for the value of room temperature, the common conclusion would be that the gossypol acetic acid compound is in fact a solvate. The pharmaceutical cocrystal definition advanced in [34] excludes solvates. The exclusion was based largely on the observation that solvates are regarded as by-products of crystallization from or adventitious exposure to a solvent, and that design of solvates is less fruitful than that involving cocrystals.

The Novelix patent, covering an anticancer drug candidate rendered as a cocrystal with oxalic acid [120], provides a contrast with salt forms. Oxalate is infrequently used as a counterion in salt-form drug compounds (e.g., escitalopram oxalate, the active ingredient in the antidepressant drug Lexapro®), while oxalic acid cocrystals are well exemplified in the pharmaceutical cocrystal literature. The inventors of [120] cite as art a caffeine cocrystal with oxalic acid, reported by the Jones group in Cambridge [35]. The NVX-412 oxalic cocrystal in the patent has superior physical properties over the NVX-144 free base form of the drug candidate. Two patents from two different pharmaceutical companies involve compositions of sodium–glucose transporter type 2 (SGLT-2) inhibitors, a new drug class targeted to treat diabetes by facilitating excretion of glucose in the urine. The sugar-like drug candidate by Pfizer in [121] is PF-04971729, a drug candidate that is not described in a crystalline form by itself, this was cocrystallized with pyroglutamic acid and L-proline. The Astellas SGLT-2 compound claimed in [122] is a cocrystal of a C-glycoside with L-proline. That these two patents were issued in the same timeframe and on a similar subject matter is interesting, and speaks to the potential importance of the therapeutic class (glucose control and diabetes) as well as the utility of cocrystals in preparing crystalline, pharmaceutically acceptable forms of the drug candidates. At the time of writing, the most recent pharmaceutical cocrystal patent involves cocrystals of the anti-infective drug metronidazole and an example of an imipramine HCl cocrystal – in both cases the drug is cocrystallized with a carboxylic acid. All species claimed are defined by at least one characteristic x-ray diffraction peak. This most recent case highlights that cocrystal composition claims are being granted without the limitation of any bioperformance data (or suitable surrogate such as dissolution, or solubility), but evidently the claims in these cases are narrow species claims rather than sub-genus or genus-type claims.

Based on a brief survey of the pending applications for pharmaceutical cocrystal compositions in the USA, one should expect continued activity in 2012 and beyond. Several applications detail significant improvements in both physicochemical and bioperformance properties of the drug candidates under consideration.

Patents in countries outside the USA

Given that standards used to evaluate proposed patent claims differ between countries, it is perhaps not surprising that the area of pharmaceutical cocrystals has seen a slightly slower pace of patent activity outside the USA. Another reason for the lesser activity

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Table 3. Composition patents issued in the USA for pharmaceutical cocrystals 1999–2012[1].

US patent	Date of issue	Assignee	Compound(s)	Claims	Ref.
US6001996	14 December 1999	Eli Lilly & Co., Inc.	Complexes of (carba)-cephalosporins with parabens	2	[108]
US7078526	18 July 2006	TransForm Pharmaceuticals, Inc.	Itraconazole; tartaric cocrystal of the HCl salt having melting point of 161°C	16	[109]
US7342046	11 March 2008	The Regents of the University Of Michigan	(-)-Gossypol, acetic acid co-crystal (1:1 ratio)	13	[110]
US7446107	4 November 2008	TransForm Pharmaceuticals, Inc.	Itraconazole; cocrystals with a carboxylic acid	3	[107]
US7625910	1 December 2009	Astra Zeneca AB	AZD1152; a phosphate prodrug and maleic acid cocrystal	6	[111]
US7566805	28 July 2009	TransForm Pharmaceuticals, Inc. (Cephalon, Inc.)	Modafinil; carboxylic acid cocrystals (e.g., malonic and glycolic)	53	[112]
US7671093	2 March 2010	TransForm Pharmaceuticals, Inc.	Mixed cocrystals, 'isomorphically substitutable'	2	[113]
US7691827	6 April 2010	Eli Lilly & Co.	Gemcitabine: a prodrug cocrystallized with aromatic sulfonic acid, hydrate	6	[114]
US7803786	28 September 2010	TransForm Pharmaceuticals, Inc. and University of South Florida	Stavudine; aromatic amines such as melamine and 2-aminopyridines	15	[115]
US7927613	19 April 2011	University of South Florida/University of Michigan/ TransForm Pharmaceuticals, Inc.	Carbamazepine, celecoxib, 5-fluoro-uracil, acetaminophen, phenytoin, ibuprofen, flurbiprofen; multitude of coformers	36	[116]
US7935817	3 May 2011	Apotex Pharmachem Inc.	Adefovir dipivoxil; nicotinamide and salicylamide conformers	22	[117]
US8003700	23 August 2011	Mutual Pharmaceutical Co., Inc.	Cochicine; solid complexes, malic acid cocrystal	7	[118]
US8039475	18 October 2011	Vertex Pharmaceuticals, Inc.	Telaprevir; salicylic acid, variable stoichiometry	8	[119]
US8058437	15 November 2011	Novelix Pharmaceuticals, Inc.	(Pyrroloquinoxalinyl)pyrazinecarbo-hydrazide, oxalic acid co-crystal	12	[120]
US8080580	20 December 2011	Pfizer Inc.	SGLT-2 inhibitors, L-proline and pyroglutamic acid cocrystals	20	[121]
US8097592	17 January 2012	Astellas Pharma Inc., Kotobuki Pharmaceutical Co. Ltd.	SGLT-2 Inhibitor, L-proline cocrystal	6	[122]
US8124603	28 February 2012	Thar Pharmaceuticals	Meloxicam with various carboxylic acids, aliphatic and aromatic, and maltol and ethyl maltol	25	[123]
US8163790	24 April 2012	New Form Pharmaceuticals, Inc.	Metronidazole cocrystals with gentisic acid and gallic acid (specific X-ray reflections in each case) and a cocrystal of imipramine HCl and (+)-camphoric acid	15	[124]

[1]Through to April 2012.
SGLT-2: Sodium–glucose cotransporter subtype 2.

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Table 4. Method and compositions patents issued on pharmaceutical cocrystals in Europe, 2003–2012.

EP patent	Date of issue	Assignee	Main content of claims	US counter-part(s)
EP1156864B1 [125]	14 May 2003	Reuter Chemische Apparatebau KG	Process for isolating enantiomer components from mixtures	US6570036 [102]
EP1011838B1 [126]	24 May 2006	Reuter Chemische Apparatebau KG	Crystallization process for separating a desired substance from mixture	
EP1831237B1 [127]	20 August 2008	Eli Lilly & Co., Inc.	Amide prodrug of gemcitabine, cocrystal of the prodrug	US7691827 [114]
EP1755388B1 [128]	6 October 2010	TransForm Pharmaceuticals, Inc.	Mixed cocrystals of modafinil	US7671093 [115]
EP2139885B1 [129]	8 December 2010	Syngenta Ltd.	Cocrystals of propiconazole (an agro-chemical fungicide)	
EP2170284B1 [130]	24 August 2011	Feyecon B.V.	A method of preparing a pharmaceutical cocrystal composition	
EP2185546B1 [131]	26 October 2011	Vertex Pharmaceuticals, Inc.	Cocrystals and pharmaceutical compositions, telaprevir (VX-950)	
EP2334687B1 [132]	4 January 2012	Pfizer Inc.	SGLT-2 inhibitors, L-proline and pyroglutamic acid cocrystals	US8080580 [121]
EP2300472B1 [133]	18 January 2012	Boehringer Ingelheim Intl. GmBH	Glucocorticoid analogs, phosphoric acid and acetic acid cocrystals	
EP2114924B1 [134]	25 January 2012	Vertex Pharmaceuticals Inc.	Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvates	
EP2288606B1 [135]	15 February 2012	Bayer Pharma Ag	Rivaroxaban cocrystal with malonic acid	
EP1608339B1 [136]	21 March 2012	McNeil PPC	Celecoxib cocrystal with nicotinamide	US7927613 [116]

may be strategic decisions on the part of innovators to pursue US patents in preference to prosecuting claims in other countries. However, an increasing role of pharmaceutical cocrystals in drug development may lead to an increase in foreign patent filings. Beyond the USA and Europe, the pharmaceutical industry often pursues patent protection in countries such as Japan, Canada and Australia.

European patents in the area of pharmaceutical cocrystals

In Europe, there has so far been limited issuance of patents as yet. Patents issued in Europe on pharmaceutical cocrystals, methods as well as composition claims, are listed in Table 4 [125–136].

Five of the composition patents in Table 4 have an accompanying issued US patent counterpart.

The EPO has long taken a utilitarian (problem-solving) approach to review and allowance of patents, including crystal form patents. In contrast, the USPTO has determined the patentability of crystals on a case-by-case basis, considering the differences in physical and chemical properties of the new form relative to any previously known form. Observing recent patent case law and implementation of the Leahy–Smith America Invents Act of 2011, it is possible that a philosophical approach akin to that taken in Europe to examine crystal form patent applications will become prevalent in the USA in the near future.

Summary of the last decade of pharmaceutical cocrystals

Some points can be made in summary about the science and patent activity in pharmaceutical cocrystals. The science has advanced, the patents are arriving, but do we have product candidates arising from the technology at this point?

Scientific & patent literature on pharmaceutical cocrystals

Approximately a decade of extensive activity in the area of pharmaceutical cocrystals has been summarized in this review. The scientific literature on the topic is vast, and a number of the key papers and reviews have been included to illustrate the breadth of coverage of the topic. The patent literature on pharmaceutical cocrystals is commensurately sizable. At the time of writing, there are a number of pending applications on compositions in the category of pharmaceutical cocrystals making their way through patent prosecution. A selection of these pending cases will be discussed in the next section as examples of patents that might emerge in the next few years.

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Language of crystal forms in patents

An early (and apparently lasting) impact of the advent of pharmaceutical cocrystals is a change in the way in which crystal form types are generically named in patents and pending applications. Writers of patents have required a veritable catch basin of terms to comprehensively describe crystal forms and provide scope in their applications. The evolution of the language of crystal forms can be illustrated using a few examples of the numerous patents that have these general phrases to encompass crystal-form types. The language in pharmaceutical composition patents historically included, "the drug and any pharmaceutically acceptable salt" (e.g., [137,138]). When polymorphs became an issue in the 1990s, the general language was extended to include polymorphs, solvates and hydrates (e.g., [139,140]). Most recently, some have added the cocrystal term as part of the general description of material forms (e.g., published patent applications [141,142]). Evidently, awareness of the cocrystal possibility in these pharmaceutical form cases is prompting the addition of the cocrystal term to the generic language capturing the crystal form types that a pharmaceutical compound might adopt.

Pharmaceutical products containing cocrystals

Drug development is a painstaking, highly regulated and long process. While several options appear on the horizon, a clear-cut pharmaceutical product example involving a cocrystal is currently lacking. This situation is likely to change within the next 5–10 years as more pharmaceutical cocrystal patents issue and drugs based on pharmaceutical cocrystals as APIs make their way through clinical trials and registration. The pharmaceutical cocrystal technology has seen many applications in patents and the scientific literature, and a handful of the specific cocrystals of drug candidates are observed to be in clinical development based on data from public sources. Based on the small number of drugs approved in a given year, the approval of a cocrystal-based drug product may occur in the next few years. In general, the overall palette of drugs in regulatory review will likely continue to use a mix of technologies, cocrystals being one representative technology. Some of the candidate pharmaceutical cocrystals with a probability of becoming drugs of the future are discussed in the next section.

Current perspective on pharmaceutical cocrystals

Pharmaceutical cocrystals at the beginning of 2012

This review covers over 30 issued patents. Many applications, perhaps numbering in the hundreds, are pending in various countries and are beyond the scope of this review. So what does the future hold for pharmaceutical cocrystals and indeed for the cocrystal field in general? The chemical enterprise, including pharmaceutical drug-substance design and manufacture, faces a range of challenges over the next few decades. Cocrystals have a role to play in resolving some of these challenges, and provide an overall technological advance for the chemistry of materials. A future perspective must be comprehensive, if a bit aspirational in certain areas. The subsections below represent the areas of opportunity perceived for the coming decades of cocrystal research and development.

Cocrystals as alternative materials for pharmaceutical products of established drug molecules

There exists a range of products whose properties make them amenable for cocrystal design in order to preserve, ensure or enhance drug performance; examples include: replacing amorphous drug material with a cocrystal (to avoid perceived risk associated with non-crystalline drug in the product), substituting crystalline low-soluble drug form with cocrystal for enhanced solubility, dissolution and bio-performance, and designing bioequivalent cocrystal forms of known products to create generic equivalents or products for alternative uses to those already approved. The itraconazole cocrystals in [107] and [109] were proposed as a substitution approach to the use of an amorphous drug coated on a bead. The concept was not to improve bioavailability, which had been optimized with considerable effort through the use of a bead-coating approach. Instead, cocrystals would simplify processing by changing to a conventional dosage form design and, thus, facilitate removal of a methylene chloride solvent system required in the coating process. The Sporanox® product enjoyed significant patent protection based on the coating process, but has now become generic and, hence, it is doubtful that the cocrystal product will compete and recover the investment needed to develop the new product. Nevertheless, this general concept of replacing amorphous with crystalline material has merit. An example from recent patents is found in [119,130] by Vertex Pharmaceuticals on telaprevir, a newly approved hepatitis C viral protease inhibitor. This orally active antiviral compound has exceedingly poor bioavailability as a crystalline base compound, and is therefore presented as an amorphous dispersion prepared by spray-drying and incorporation of stabilizing polymers. The resulting amorphous drug is reportedly chemically and physically stable in the product at room temperature for years. The recently issued Incivo® (telaprevir) cocrystal patents may indicate an interest in contrasting a crystalline composition, not of the base molecule but of a well-performing pharmaceutical cocrystal. If developed, the approach may become a case of life cycle management for telaprevir and possible combinations of the drug with other antiviral agents as the therapeutic algorithm for hepatitis C infection evolves.

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Life cycle management with cocrystals

Proprietary pharmaceutical companies and generic drug manufacturers alike will undoubtedly study the recent FDA guidance on pharmaceutical cocrystals, which issued in draft form in December 2011 [37]. The guidance proposes regulatory classification of pharmaceutical cocrystals, with a main recommendation that cocrystals can be regarded as process intermediates en route to a drug product (e.g., tablet and capsule), while the labelling of the final product can remain confined to the original API. For example, if a known API is processed in a pharmaceutical operation to form a cocrystal by inclusion of an excipient (coformer), then the requirement to relabel the drug as a new API can be avoided. There are nevertheless requirements for characterization of the process and cocrystal material. In particular, two constraints are placed on sponsors who wish to employ a cocrystal in their drug product: they must define the difference in pK_a between the drug and coformer to be within range of three units, so as to rationalize the lack of proton transfer and resulting ionization; the developer must show that the cocrystal dissociates to release the free API before reaching the target site. These requirements may prove to be non-trivial in some cases.

Product enhancement, enabling bioperformance

Arguably the most technically challenging applications of cocrystals could prove to be the act of improving bioperformance for difficult-to-formulate drug candidates. Occasionally, a compound with excellent pharmacological activity and safety can pose a major formulation challenge from the perspective of bioperformance. For example, attaining sufficient overall exposure of an oral dose may require extraordinary formulation efforts, such as those described for itraconazole and telaprevir in previous sections. A patented example of a development compound benefiting dramatically from a cocrystal form is AMG-517, a TrpV1 antagonist that was in development by Amgen, Inc. as a putative pain drug. Published patent application [143] describes the enhancement of oral exposure to this water-insoluble compound by a sorbic acid cocrystal. The effect of the cocrystal on bioavailability was particularly striking in preclinical studies (oral pharmacokinetics in rat) [38]. The boosting effect observed on bioavailability has significant practical impact, since the doses required for qualification and definition of a margin of safety for the drug candidate far exceed those envisioned in clinical use. In the absence of the cocrystal, the super-exposures may never be attained, and hence the true *in vivo* toxicology profile of a compound may be obscured. In summary, a cocrystal can benefit a clinical product and, perhaps even more strikingly, a toxicology formulation.

The use of a cocrystal form to bring about an intravenous-to-oral switch is exemplified in a recently published patent application [144]. The compound in question, zoledronic acid, a bone-resorption inhibitor, is water-soluble but not optimally permeable for absorption from the gut. In addition, compounds in this class are irritating to the esophagus and stomach lining. A cocrystal approach was employed to increase oral bioavailability and a coating was also applied to allow the compound to be absorbed only once the drug form is past the stomach.

Scale-up & manufacture of cocrystals in batch mode

As useful cocrystal materials are discovered, aspects of their development into useful products will gain importance. Of primary importance will be the ability to reproducibly manufacture the materials in large quantities. Some progress in this area has already been demonstrated. For example, in some cases traditional solvent-based crystallization can be used to prepare large batches of cocrystals. Detailed knowledge of the phase diagram involving the drug, coformer(s) and solvent is essential in these cases. Though not yet exemplified, the grinding method used for screening may well be a candidate for scale-up in batch mode, either as a unit operation to create a new API form or in order to generate an *in situ* cocrystal en route to a drug product. In addition, by reducing solvent use, a practitioner is fulfilling one of the goals of green chemistry.

Cocrystals in the context of continuous processing

The modern pharmaceutical enterprise has depended on batch manufacturing through the 20th century, and manufacturing groups have been surprisingly slow to adopt concepts from continuous process engineering. In contrast to pharma, chemical companies employ continuous processing extensively in high-volume chemical manufacture. As part of a push to improve manufacture in the pharmaceutical industry, the FDA and other regulatory bodies have been pursuing the Critical Path Initiative and Quality-by-Design in the last decade. The push is starting to generate activity and funding in continuous processing. As an example, Novartis Pharmaceuticals has sponsored a large continuous processing initiative, the main contributors to which are at the Massachusetts Institute of Technology. Cocrystals have been shown in recent publications to be good candidate compositions for certain unit operations that fit with continuous processing.

While there is limited patent activity, a few publications in the literature have introduced continuous processing examples with cocrystals. For example, large amounts of cocrystals were prepared solvent-free

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(or essentially without use of solvent) using twin screw extrusion [39]. This type of processing has been common in polymer production, but is less extensively applied in pharmaceutical manufacture. Spray-drying, a technique often used to prepare amorphous materials, was used in the preparation of several cocrystals [40]. In another example, demonstrating the utility of cocrystals in modern chemical transformations, a cocrystal with lower solubility than either of the parent compounds was used to precipitate the product in a fermentation reaction [41]. Each of the techniques described above can be utilized as batch operations or as continuous (or semicontinuous) manufacturing operations.

■ Synthesis with cocrystals green chemistry opportunities

Cocrystals offer the potential to eliminate the need for use of solvent in a chemical reaction and thereby reduce the cost of materials used in processing and all of the costs of dealing with solvent waste. Such 'cocrystal controlled solvent-free synthesis' [42] approaches have already demonstrated that high yield solvent-free synthesis can be accomplished in several classes or reaction through two strategies: the use of coformers to serve the role of a template for aligning reactive groups (e.g., photodimerization of olefins [32]), and the formation of cocrystals from two reactive coformers followed by application of stress (e.g., condensation [43]).

Future perspective

The future outlook for pharmaceutical cocrystals indicates promise in the following areas:

- Reformulation of existing drugs for improved performance;
- Life cycle management with recently approved drugs;
- Enabling novel development compounds: bioperformance and purification;
- Scale-up: both batch mode and continuous;
- Green chemistry and synthesis with cocrystals as intermediates.

The regulatory arena is beginning to deal with the appearance of pharmaceutical cocrystals as a class of materials. Examples are the FDA guidance published in December 2011 [37], as well as a recent literature report from the FDA on carbamazepine saccharin [44], one of the prototypes of the class as it emerged in a systematic way in the past decade. In regard to the patent landscape for pharmaceutical cocrystals, we should expect to see continued and likely accelerating activity in various regions, as is likely to continue to be the case for solid forms in general [45]. The target compounds and uses will likely reflect some or all of the areas in the above future outlook. And perhaps further opportunities will be identified in the current decade.

Disclaimer

This review describes the opinions and observations of the authors as scientists in the field of pharmaceutical crystal engineering, and does not necessarily represent the viewpoints of the authors' employers. No legal opinions or advice are provided herein.

Executive summary

Background

- Solid forms of active pharmaceutical ingredients (APIs) are important to the function of products. Physicochemical properties of compounds are determined by the crystal structure.
- The motivation for studying cocrystals of pharmaceutical compounds comes from the need to optimize properties, such as solubility, dissolution rate and bioavailability. There are also patenting motivations for studying cocrystals in the context of drugs and drug candidates. For regulatory review, the solid form of a drug candidate must be well characterized and described.

History & nomenclature of cocrystals

- Cocrystals have been long known, but not until recently have they been studied systematically for pharmaceutical compounds. Alternative names include complexes and multicomponent crystals. This review excludes cocrystals of drugs with proteins; the focus is on the drug compound and its compositions with cocrystal formers (abbreviated as 'coformers').
- Other solid forms of APIs include the pure form, solvates and salt forms. A salt comes from proton transfer to or from a drug substance with an oppositely charged counterion to balance charge of the ionized drug. Cocrystals do not have this requirement, and cocrystals of salts exist. Any of the possible crystal form types are subject to potential polymorphism – the appearance of multiple crystal forms of the same chemical composition having different properties from one another.
- Design of cocrystals is a great opportunity for pharmaceutical compounds. Rapid advances in crystal engineering and characterization capabilities have given the field of pharmaceutical cocrystals a big boost in the last decade. Making cocrystals represents a supramolecular synthetic strategy: synthesis of new compounds with the desired pharmacological agent as part of distinct non-covalent crystal compositions.

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Executive summary (cont.)

Pharmaceutical cocrystals: recent literature & definition

- The primary literature surveyed includes multiple citations from the 20th century. The beginning of the 21st century saw a section of key papers highlighting the potential of pharmaceutical cocrystals to tailor and improve performance of compounds like carbamazepine, fluoxetine HCl and itraconazole.

US patents on pharmaceutical cocrystals

- Methodology patents – five US patents and two EP – patents are discussed. The key challenge with methodology and process patents on pharmaceutical cocrystals (and crystal forms in general) is the degree to which enforcement is practical. Composition patents are more prevalent in the field of pharmaceutical cocrystals.
- Composition patents: 18 US patents have been issued in the past decade (based on our survey through to April 2012). A large number of pending applications are in process, and only a few of these are mentioned in this review. Composition claims range from very specific (a particular form of a specific cocrystal composition characterized by a physical property) to sub-genus claims (any cocrystal of a particular drug with a class of coformers).

Patents in countries outside the USA

- European patents in the area of pharmaceutical cocrystals are not yet as numerous as patents in the USA, but there remains significant ongoing activity. Ten European patents have been issued to date, and most EP patents have pending or issued US counterparts.

Summary of the last decade of pharmaceutical cocrystals

- The language in pharmaceutical composition patents historically included 'the drug and any pharmaceutically acceptable salt'. In the 1990s, the general language was extended to include polymorphs, solvates and hydrates. Most recently, some have added the cocrystal term as part of the general description of material forms.
- While several options appear on the horizon, a clear-cut pharmaceutical product example involving a cocrystal is currently lacking. The signs are that this will change within the next decade.

Current perspective on pharmaceutical cocrystals

- Cocrystals as alternative materials for pharmaceutical products of established drug molecules. A range of products exist for which structure and properties make them amenable for cocrystal design in order to preserve, ensure or enhance drug performance. Examples include:
  - Replacing amorphous drug material with a cocrystal to avoid perceived risk associated with non-crystalline drug in the product;
  - Substituting crystalline low-soluble drug form with cocrystal for enhanced solubility, dissolution and bioperformance;
  - Designing bioequivalent cocrystal forms of known products.
- Life cycle management with cocrystals: proprietary pharmaceutical companies and generic drug manufacturers alike will undoubtedly study (and perhaps also comment on) the recent US FDA guidance on pharmaceutical cocrystals, which was issued in draft form in December 2011.
- Product enhancement, enabling bio-performance: a key use of pharmaceutical cocrystals is to improve bioperformance (e.g., bioavailability, rate of absorption) for difficult-to-formulate drug candidates. The use of a cocrystal form to bring about an intravenous-to-oral reformulation is also exemplified.
- Scale-up and manufacture of cocrystals in batch mode relies on engineering capability and physical understanding of the cocrystal at hand. In principle (and in practice) traditional solvent-based crystallization can be developed to prepare large batches of cocrystals. A successful crystallization process must be based on detailed knowledge of the phase diagram (solubility and temperature dependence of solubility) involving the drug, coformer(s) and solvent.
- Cocrystals in the context of continuous processing; the modern pharmaceutical enterprise has depended on batch manufacturing through the 20th century, with slow adoption of concepts from continuous process engineering. As part of a push to improve manufacture in the pharmaceutical industry, the FDA and other regulatory bodies have been pursuing the Critical Path Initiative and Quality-by-Design in the last decade. Recent activity and funding in continuous processing is exemplified by the Novartis/MIT continuous processing initiative.

Synthesis with cocrystals & green chemistry opportunities

- Cocrystals offer the potential to eliminate the need for use of solvent in a chemical reaction and, thereby, reduce the cost of materials used in processing and all costs associated with dealing with solvent waste. Such 'cocrystal-controlled solvent-free synthesis' approaches have been demonstrated in literature recently.

Future perspective

- The future outlook for pharmaceutical cocrystals indicates promise in the following areas:
  - Reformulation of existing drugs for improved performance;
  - Life cycle management with recently approved drugs;
  - Enabling novel development compounds: bioperformance and purification;
  - Scale-up: batch mode and continuous;
  - Green chemistry and synthesis with cocrystals as intermediates.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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Understanding Lyophilization Formulation Development

Frank Kofi Bedu-Addo

The author covers the fundamentals of lyophilization and provides case studies about the development of lyophilized biopharmaceutical products and the importance of biophysical characterization in formulation and the lyophilization process.

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Lyophilization or freeze-drying is often used to stabilize various pharmaceutical products, including virus vaccines, protein and peptide formulations, liposome, and small-chemical drug formulations (1–4).

Often a pharmaceutical product may be susceptible to physical and chemical degradation when stored as a ready-to-use solution. The goal of the formulations scientist is to identify the right formulation conditions, the right excipients in optimal quantities, and the right dosage form to maximize stability, biological activity, safety, and marketability of a particular product.

Desired characteristics of a lyophilized product

A lyophilized product should possess certain desirable characteristics, including

- long-term stability
- short reconstitution time
- elegant cake appearance
- maintenance of the characteristics of the original dosage form upon reconstitution, including so-

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lution properties; structure or conformation of proteins; and particle-size distribution of suspensions
- isotonicity upon reconstitution (in some cases, also for bulk solution).

The lyophilization process

The lyophilization process consists of three stages: freezing, primary drying, and secondary drying.

Freezing. During this stage the formulation is cooled. Pure crystalline ice forms from the liquid, thereby resulting in a freeze concentration of the remainder of the liquid to a more viscous state that inhibits further crystallization. Ultimately, this highly concentrated and viscous solution solidifies, yielding an amorphous, crystalline, or combined amorphous–crystalline phase.

Primary drying. The ice formed during freezing is removed by sublimation at subambient temperatures under vacuum. This step traditionally is carried out at chamber pressures of 40–400 Torr and shelf temperatures ranging from −30 °C to +10 °C. Through out this stage, the product is maintained in the solid state below the collapse temperature of the product in order to dry the product with retention of the structure established in the freezing step. The collapse temperature is the glass transition temperature (T_g) in the case of amorphous products or the eutectic temperature (T_e) for crystalline products.

Secondary drying. The relatively small amount of bound water remaining in the matrix is removed by desorption. During this stage, the temperature of the shelf and product are increased to promote adequate desorption rates and achieve the desired residual moisture.

Possible destabilizing effects of the lyophilization process

Freezing. Freezing damage can occur with labile products such as liposomes, proteins, and viruses (5,6). Initial ice-crystal size depends on the relative contributions of nucleation and crystal growth of ice. A rapid nucleation and growth rate resulting from a large degree of supercooling leads to a larger number of small ice crystals, which in turn presents a large ice–water interface (7). Exposure of proteins to this ice–water interface can lead to denaturation. Freezing stresses also can disrupt the liposome bilayer and emulsion structure.

The freezing step will determine the structure of the final dried cake as well as the drying rate. Small ice crystals produce pores with lower volume–surface area, thus resulting in lower diffusive flux and slower sublimation rates (7).

Drying. Removal of the hydration shell from proteins and products such as liposomes during drying in the absence of the appropriate stabilizers can cause destabilization of the protein structure and fusion of liposomes (8,9). Extremely low water content in the final product can result in destabilization, and optimal water content should be determined (10). The desired residual moisture must be correlated to stability during long-term storage as

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part of development studies.

Excipients in a lyophilized formulation

The design of a lyophilized formulation is dependent on the requirements of the active pharmaceutical ingredient (API) and intended route of administration. A formulation may consist of one or more excipients that perform one or more functions. Excipients may be characterized as buffers and pH adjusters, bulking agents, stabilizers, and tonicity modifiers.

Buffers. Buffers are required in pharmaceutical formulations to stabilize pH. In the development of lyophilized formulations, the choice of buffer can be critical. Phosphate buffers, especially sodium phosphate, undergo drastic pH changes during freezing (6,11,12). A good approach is to use low concentrations of a buffer that undergoes minimal pH change during freezing such as Tris, citrate, and histidine buffers (13).

Bulking agents. The purpose of the bulking agent is to provide bulk to the formulation. This is important in cases in which very low concentrations of the active ingredient are used. Crystalline bulking agents produce an elegant cake structure with good mechanical properties. However, these materials often are ineffective in stabilizing products such as emulsions, proteins, and liposomes but may be suitable for small-chemical drugs and some peptides (14,15). If a crystalline phase is suitable, mannitol can be used. Sucrose or one of the other disaccharides can be used in a protein or liposome product.

Stabilizers. In addition to being bulking agents, disaccharides form an amorphous sugar glass and have proven to be most effective in stabilizing products such as liposomes and proteins during lyophilization (1,8,9,16). Sucrose and trehalose are inert and have been used in stabilizing liposome, protein, and virus formulations. Glucose, lactose, and maltose are reducing sugars and can reduce proteins by means of the mailard reaction (17–19).

Two hypothesis have been postulated to explain the stabilizing effects of the disaccharides.

- The water replacement hypothesis: Disaccharides have been found to interact with these products by hydrogen bonding similarly to the replaced water.
- The vitrification hypothesis: Disaccharides form sugar glasses of extremely high viscosity. The drug and water molecules are immobilized in the viscous glass, leading to extremely high activation energies required for any reactions to occur (8,9,16,20,21).

Tonicity adjusters. In several cases, an isotonic formulation might be required. The need for such a formulation may be dictated by either the stability requirements of the bulk solution or those for the route of administration. Excipients such as mannitol, sucrose, glycine, glycerol, and sodium chloride are good tonicity adjusters. Glycine can lower the glass-transition temperature if it is maintained in the amorphous phase. Tonicity modifiers also can

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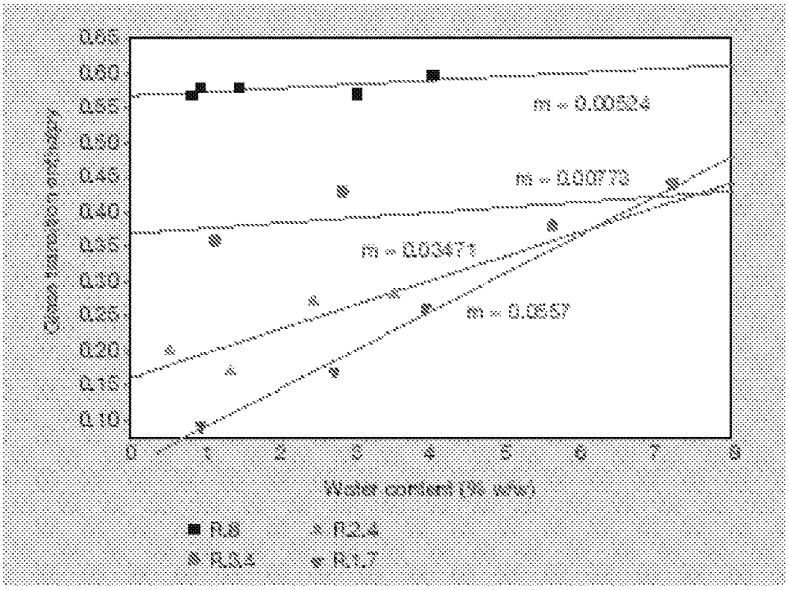


Figure 1: Effect of water content on glass-transition enthalpy. Plot of enthalpy versus water content for four formulations having various sugar/lipid ratios (*R*).

be included in the diluent rather than the formulation.

Glass-transition temperature and its significance

When heated, sugar glasses undergo a second-order transition from a rigid state to a viscoelastic rubbery state. The temperature at which the vitreous transformation occurs is the glass-transition temperature (T_g). When a product exceeds the T_g value, the rigid glass softens to become a highly viscous rubbery material and collapses. The T_g value of a formulation can be determined by differential scanning calorimetry (DSC), and the collapse temperature is measured by freeze-drying microscopy (22–24). Primary drying is always performed at the highest possible temperature while maintaining the product below the collapse temperature. A 5 °C increase in product temperature can lead to a decrease in drying time by a factor of two (13).

The dried amorphous product material also has a T_g value. As water is removed during secondary drying, T_g increases. Storage below T_g is important for several products to maintain the rigid-glass structure and hence stability of the product (25,26).

Formulation example 1: development of a lyophilized liposome formulation

Preformulation studies were performed to select optimal pH, ionic strength, and excipients to optimize stability of the drug and lipids (F.K. Bedu-Addo, R. Coe, S. Bhamadi-

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Table I: Effect of water content and sugar–lipid ratio on liposome stability.

	Average liposome size (nm)		
Residual water content (%)	**Sugar:lipid ratio 3.4**	**Sugar:lipid ratio 2.1**	**Sugar:lipid ratio 1.7**
7.2	108	-	-
4.8	111	132	-
3.9	-	-	151
3.5	-	138	-
3.0	104	145	-
2.7	105	-	177
1.0	124	-	177

patti, and J. Pawelchak, The Liposome Co., 1997). A diacyl phosphatidylcholine was used as the matrix lipid, cholesterol was included in the formulation to improve rigidity of the bilayer, and a negatively charged lipid was included to improve blood circulation time. Mannitol was selected as the bulking agent, and maltose was a stabilizer. Dynamic light scattering and microscopy were used to monitor liposome fusion and disintegration. Lipid and drug stability were monitored by reverse-phase high- performance liquid chomatography (RP-HPLC). Water content was evaluated by Karl Fisher titration.

Lipid and drug concentrations were determined on the basis of the required dosage, therefore optimal sugar:lipid ratios were investigated by altering maltose concentrations. Maltose concentrations of 200, 125, and 100 mg/mL were investigated, thus resulting in sugar:lipid weight ratios of 3.4, 2.1, and 1.7, respectively. The effect of water content between 1 and 9% also was investigated.

Glass-transition enthalpy was evaluated using DSC to obtain a quantitative estimate of glass structure existing in the formulation. As shown in Figure 1, the effect of water content on glass content was dependent on the maltose:lipid ratio. Glassy structure content decreased with a decrease in water content. This effect diminished as the sugar:lipid ratio was increased. The T_g value, as measured by DSC, increases linearly with water content. T_g, which is an indicator of the rigidity of the sugar glass, also increased with an increase in the sugar:lipid ratio. Liposome stability increased linearly with an increase in the amount of glassy structure existing in the formulation. Fusion leading to increase in particle size was observed at lower maltose:lipid ratios as water content was decreased. At a 1.7 ratio, liposome disintegration was observed below 2.7% water (see Table I).

Fusion leading to an increase in liposome size and potential drug leakage was observed at the lower maltose:lipid ratios and water con-

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tent. A maltose: lipid ratio of 3.4 provided good stability during lyophilization. The T_g value and glass-transition enthalpy were good indicators of liposome stability.

Formulation example 2: development of a lyophilized protein formulation

A study was conducted to develop a lyophilized protein formulation (F.K. Bedu-Addo, R. Moreadith, and S. Advant, Diosynth-RTP/Thrombogenics Ltd, 2000).The first step in developing any formulation is determining the solubility and liquid stability at various pH, ionic strength, and excipient conditions conducted as part of the preformulation study. At this stage, it is necessary to have the right analytical tools to fully characterize the product. In the case of proteins, one must also understand the effects of various potential formulation conditions and excipients on conformation and conformational stability. This is typically achieved using biophysical techniques such as circular dichroism (CD), fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry, and fluorescence spectroscopy (27–32). FTIR can also be used to evaluate protein structure in the dried cake (27).

On the basis of the results of a preformulation study, five formulations were developed and evaluated using a conservative lyophilization cycle:

- Formulation 1 contained a disaccharide and no crystalline bulking agent.
- Formulation 2 contained a low ratio of disaccharide to bulking agent.
- Formulation 3 contained a high ratio of disaccharide to bulking agent with 0.005% of a nonionic surfactant.
- Formulation 4 contained a high ratio of disaccharide to bulking agent with 0.01% of a nonionic surfactant
- Formulation 5 contained a high ratio of disaccharide to bulking agent with no nonionic surfactant

A nonionic surfactant was included in two of the formulations because in some cases, even in the presence of the appropriate stabilizers, a surfactant is required to inhibit aggregation upon reconstitution (33,34). Studies also have shown that the long-term stability of a lyophilized protein formulation and also the tendency to form aggregates upon reconstitution correlates with the extent of deviation from the protein's native conformation.

Deamidation and oxidation were evaluated by RP-HPLC, formation of insoluble aggregates by UV400, soluble aggregate formation by size exclusion chromatography (SEC), protein concentration by UV280 and conformational change by CD.

Formulation 2 underwent significant conformational change during freezing and resulted in 2% aggregates by SEC. All formulations except Formulation 1 exhibited some conformational change during the freezing step. No further conformational changes were observed during drying, no chemical changes were observed in any formulation. No in-

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soluble aggregates were observed during reconstitution.

Formulation 1 exhibited the longest drying and reconstitution times and also had the least elegant-looking cake structure. Formulations 3 and 4 containing surfactant did not provide any advantages over Formulation 5 and were eliminated. Formulations containing a crystalline bulking agent provided an elegant cake. Formulation 5 was selected. The very minor differences between the formulations were expected because preformulation studies had been performed to identify optimal conditions and the formulations optimized with respect to pH, buffer, stabilizer and bulking agent before lyophilization.

Effects of the formulation on the lyophilization process

One must understand that the process will be determined by the formulation. For example, the use of disaccharides will result in a low collapse temperature, which causes primary drying to be performed at low temperatures and implying a long process. A large volume fill or high solids content in the formulation will provide increased resistance to mass transfer, hence a longer process (35).

The process also can determine the properties of the formulation. The freezing process can influence crystallization of excipients such as mannitol and glycine (36–39). Incomplete crystallization will depress the collapse temperature.

Significant crystallization of the bulking agent will reduce drying time. However, large amounts of crystalline bulking agent can reduce stabilizing effects of the amorphous stabilizer especially with proteins.

Summary

Always optimize the formulation (pH, buffer, ionic strength, stabilizers) to provide maximum stability of the bulk solution before lyophilization as well as dried product upon long term storage.

Select the right excipients (amount and type) to provide product stability and efficient drying, For example, a dried small-chemical drug might be stable in only a crystalline bulking agent, whereas a dried protein product may require an amorphous stabilizer.

Select the lyophilization process to allow maximum drying efficiency while maintaining product integrity.

Understand the effect of each step of the process on the formulation to design the right process for the product.

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Novartis v. Regents, IPR2023-01346
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Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
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:	U0157.70023US02

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:				
PET. REVIVE ABANDON APP, DELAY PYMT-RESP	2453	1	850	850
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 5 months with $0 paid	2255	1	1500	1500
Miscellaneous:				
		Total in USD ($)		**2350**

Electronic Acknowledgement Receipt	
EFS ID:	30046450
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	U0157.70023US02
Receipt Date:	10-AUG-2017
Filing Date:	13-FEB-2014
Time Stamp:	16:35:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2350
RAM confirmation Number	081117INTEFSW16381200
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: 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	U015770023US02-TRN-DFC.pdf	25087 708f00ab82794aaa556d36946e1017cb7fe baced	no	1
Warnings:					
Information:					
2	Extension of Time	U015770023US02-EXT-DFC.pdf	23621 29a1ae972827bb7d4f15d79d5ed7a9edbb 52d0ca	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	U015770023US02-FEE-DFC.pdf	31425 f004c5b24ec5e1813e7f7a6ef13e9b602d34 3d08	no	1
Warnings:					
Information:					
4	Petition for review by the Office of Petitions	U015770023US02-PET-DFC.pdf	26823 fac21c366f171e246700e0a823648d9be7c4 bbf4	no	2
Warnings:					
Information:					
5	Petition for review by the Office of Petitions	U015770023US02-PETREV-DFC.pdf	27413 9911c30c659571462dc9a0f3237642408ae 63f4d	no	2
Warnings:					
Information:					
6	Appeal Brief Filed	U015770023US02-ABRF-DFC.pdf	6455039 9c55c5c35d5c6e274e1f7000df789c2cde24 a08b	no	102
Warnings:					
Information:					

7	Fee Worksheet (SB06)	fee-info.pdf	32955 57c1b930da3e1e21825ce1cd2ceb61d73076d085	no	2
Warnings:					
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			Total Files Size (in bytes):	6622363	

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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)

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	Sahar Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

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
- [x] 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
- [x] 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		
Date	August 10, 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: August 10, 2017 Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

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PTO/AIA/22 (03-13)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) U0157.70023US02
Application Number 14/179,862-Conf. #7725	Filed February 13, 2014
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT	
Art Unit 1627	Examiner Sahar Javanmard

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	$
☒ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$ 1,500.00

☒ 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/	August 10, 2017
Signature	Date
David F. Cauble	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 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: August 10, 2017 Electronic Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

5641289.1

FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	Sahar Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[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 ($)2,350.00

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	
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 ($)**		**Fee Paid ($)**
_____	- 41 or HP =	_____	x	_____	=	_____

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

Indep. Claims		**Extra Claims**		**Fee ($)**		**Fee Paid ($)**
_____	- 3 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): 2255 Extension for response within fifth month	1,500.00
2453 Petition for revival of an abandoned application	850.00

SUBMITTED BY

Signature	/David F. Cauble/	Registration No. (Attorney/Agent)	73,490	Telephone	617.646.8000
Name (Print/Type)	David F. Cauble			Date	August 10, 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: August 10, 2017 Electronic Signature: /Chelsea E. Dowling/ (Chelsea E. Dowling)

5641287.1

Office of Petitions: Routing Sheet

4700

Application No. 14179862

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

- [X] **GRANTED**
- [ ] **DISMISSED**
- [ ] **DENIED**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 08/22/2017

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
08/22/2017	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

UM00000583
NOVARTIS EXHIBIT 1016
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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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In re Application of	:	
ZAWOROTKO et al.	:	
Application No. 14/179,862	:	DECISION ON PETITION
Filed: 02/13/2014	:	
Attorney Docket No. U0157.70023US02	:	

This is a decision on the petition under 37 CFR 1.181 filed August 10, 2017, to withdraw the holding of abandonment in the above-identified application. This is also a decision on the petition under 37 CFR 1.137(a) filed August 10, 2017, to revive the application.

On January 12, 2017, applicants timely submitted a notice of appeal, a notice of appeal fee, a request for a three-month extension of time, and a $700 extension of time fee in response to the final Office action mailed July 12, 2016. The filing of the notice of appeal set a two-month period, plus extensions of time, from January 12, 2017 (the date of receipt of the notice of appeal), for applicants to submit an appeal brief. On July 19, 2017, the Office mailed a Notice of Abandonment.

On August 10, 2017, applicants filed a petition under 37 CFR 1.181 to withdraw the holding of abandonment, a petition under 37 CFR 1.137(a) to revive the application, an $850 petition fee, an appeal brief, a request for a five-month extension of time, and a $1,500 extension of time fee.

In support of the petition under 37 CFR 1.181, applicants assert that they could extend the two-month deadline for filing an appeal brief up to an additional five months. Therefore, applicants could file a timely appeal brief with a five-month extension of time on or before August 12, 2017. Applicants aver that they timely filed the appeal brief within the extendable period on August 10, 2017. Applicants contend the Office mailed the Notice of Abandonment in error.

Upon a review of the record, the Office concurs with applicants' assertion. On January 12, 2017, applicants timely submitted a notice of appeal, a notice of appeal fee, and a three-month extension of time within the extendable period set forth in the final Office action mailed July 12, 2016. Applicants were required to submit an appeal brief in accordance with 37 CFR 41.37 within two months from the notice of appeal receipt date of January 12, 2017. The period for filing of the appeal brief was extendable under 37 CFR 1.136. The record shows that applicants timely filed the appeal brief on August 10, 2017, within a five-month extension of time and fee.

The petition to withdraw the holding of abandonment is **granted.** The application is restored to pending status in view of the fact that applicants filed a timely appeal brief on August 10, 2017. In view of the decision granting the petition under 37 CFR 1.181 and the determination that the application was not in fact abandoned, the petition under 37 CFR 1.137(a) to revive the

application is unnecessary. Accordingly, the petition under 37 CFR 1.137(a) is **dismissed** as inappropriate. As the Office has not considered the petition to revive on the merits, the USPTO will refund the $850 petition fee.

This matter is being referred to Technology Center Art Unit 1627 for further action in view of the timely filing of the appeal brief.

Telephone inquiries concerning this decision may be directed to the undersigned at (571) 272-3211.

/Christina Tartera Donnell/

Christina Tartera Donnell
Attorney Advisor
Office of Petitions

Office of Petitions: Decision Count Sheet

Mailing Month: 8

Application No.: 14179862

14179862

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: Christina Donnell

Count (1) - Palm Credit 14179862

Decision: GRANT

FINANCE WORK NEEDED
☐ Select Check Box for YES

GRANT

Decision Type: 525 - 37 CFR 1.181 for W/D HOLDING OF ABANDONMEI

525

Notes:

Count (2)

Decision: DISMISSED

FINANCE WORK NEEDED
☐ Select Check Box for YES

DISMISSED

Decision Type: 502 - 37 CFR 1.137(b) - REVIVAL BASED ON UNINTENTIO

502

Notes: please enter 502 petition code filed 08/10/17

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: *8/17/2017*

Office of Petitions Internal Document - Ver. 5.0

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Aug 22, 2017 10:34:21 AM

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	PET.DEC.TC	08/22/2017	U0157.70023US02
	PET.OP.DEC	08/22/2017	U0157.70023US02

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 12/08/2017
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/08/2017	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):

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UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Application Number: 14/179,862
Filing Date: 13 Feb 2014
Appellant(s): Zaworotko et al.

David Cauble
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 10, 2017.

(1) Grounds of Rejection to be Reviewed on Appeal

Every ground of rejection set forth in the Office action dated July 12, 2016 from which the appeal is taken is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

The obviousness-type double patenting rejection of claims 37-50 and 52-58 as provisionally rejected over claims 25, 28, 37, 39-51, 53-60, and 62-66 over copending Application No. 10/378,956 is hereby withdrawn because the copending application has since been abandoned.

MAINTAINED REJECTIONS

The following ground(s) of rejection are applicable to the appealed claims.

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.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at last one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer

to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred (page 6-7).

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and heterosynthons as required by the instant claims are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different fuctionalities, giving rise to heterosynthons. Therefore, preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Claims 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds.

Examples of organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48, o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-

chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenox yacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17, malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethyisulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic, naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3 pyridinecarboxylic, pentanetricarboxylic, cyanoacetic (column 1-2, bridging paragraph).

Huffman teaches substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Huffman teaches piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention. Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-

n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenyl hydrazine, hexanediamine, methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine , diethylamine, diethanolamine, hydroxyethyl diethylenetriamine, isooctylamine, n-decylamine, methylethanolamine, tetramethylguanidine, methyl diethanolamine, 2-amino--propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide (column 2, lines 44-68).

In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to dryness, and the cocrystal adduct is washed with hexane and dried (column 2, lines 30-35).

Huffman teaches an example of a cocrystal adduct of piperidine and benzoic acid in water (column 4, Example 10).

Huffman does not teach the co-crystal complexes in pharmaceutical compositions.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct. See *In re Dillon* 16 U.S.Q.P.2d 1897, 1900 (CAFC 1990) (en banc) ("it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed

compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that Wright suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law. ").

Therefore, it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

(2) Response to Argument

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being anticipated by McCoy (CA 1148020A1) have been fully considered. Applicant argues:

> The Examiner considers the claimed invention to be within the scope of McCoy because McCoy teaches cocrystallizer/amino acid compositions having weight ratios of from 0.9:1 to 6:1. There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, *e.g.*, a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. Nor does McCoy suggest that it would be advantageous to select a stoichiometric ratio from the range of weight ratios. In fact, McCoy teaches that the criteria for selecting the optimum amount of cocrystallizer is whether there is "enough to enable successful dehydration of the amino acid co-crystallizer solution." Based on this teaching, the skilled person would not be motivated to modify McCoy by utilizing a stoichiometric ratio of amino acid to cocrystallizer, and as such could not have envisioned the claimed invention.

Further, Applicant argues:

> McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material." One of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase *(e.g.,*Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004; a copy of which was submitted with the Information Disclosure Statement of April 1, 2016, and which is enclosed herewith as *Exhibit E*. One skilled in the ait would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed.

Examiner respectfully notes that as set forth on record previously and as discussed below, McCoy teaches "an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1". As pointed out by Applicant, McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed. Nonetheless, the range disclosed for the ratio between cocrystallizer and edible amino acid salt would encompass a cocrystal that is also stoichiometrically proportional. Therefore, it is the opinion of the Examiner that although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the range of 0.9:1 to about 6:1 embraces such proportions to be possible.

Furthermore, with respect to freeze-drying, Applicant states that such a technique yields a mixture of crystalline and amorphous phase. Although a mixture is afforded, a portion of the mixture is crystalline, thereby still rendering the instant invention obvious.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered and are not fully persuasive.

Applicant argues:

> "Huffman is not analogous art as required by MPEP §2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors. With respect to the field of endeavor, the present claims are directed to methods relating to co-crystal formation with an active pharmaceutical ingredient (API) and therefore relate to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts."

With respect to this argument, Examiner respectfully notes that the instant claims are drawn to a method for designing and preparing a cocrystal, wherein the first chemical functionality is an API, with certain requirements as set forth in claim 37 and a cocrystal former. Although the claim 37 requires an API, it does not mandate that the endeavor relate to the pharmaceutical arts. The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144. Moreover, it is respectfully noted that many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic (references can be provided if requested). Furthermore, Huffman teaches an example of a cocrystal adduct of piperidine and benzoic acid in water (column 4, Example 10), thereby fulfilling the limitation of a pharmaceutically acceptable carrier.

Conclusion

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SAHAR JAVANMARD/
Primary Examiner, Art Unit 1627

Conferees:

/SREENIVASAN PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

/JOHANN R RICHTER/
Supervisory Patent Examiner, Art Unit 1617

Requirement to pay appeal forwarding fee. In order to avoid dismissal of the instant appeal in any application or ex parte reexamination proceeding, 37 CFR 41.45 requires payment of an appeal forwarding fee within the time permitted by 37 CFR 41.45(a), unless appellant had timely paid the fee for filing a brief required by 37 CFR 41.20(b) in effect on March 18, 2013.

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REQUEST FOR ORAL HEARING BEFORE THE PATENT TRIAL AND APPEAL BOARD	Docket Number (Optional) U0157.70023US02

In re Application of	Michael J. Zaworotko *et al.*
Application Number	14/179,862-Conf. #7725
Filed	February 13, 2014
For	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Art Unit	1627
Examiner	Sahar Javanmard

Applicant hereby **requests an oral hearing** before the Patent Trial and Appeal Board in the appeal of the above-identified application.

The fee for this Request for Oral Hearing is (37 CFR 41.20(b)(3)) $ 1,300.00

[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: $ 650.00

[ ] Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____

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

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[x] Payment made via EFS-Web.

[ ] A petition for an extension of time under 37 CFR 1.136(b) (PTO/SB/23 or equivalent) is enclosed. For extensions of time in reexamination proceedings, see 37 CFR 1.550.

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[ ] 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

Telephone Number 617.646.8000

Date February 7, 2018

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Novartis v. Regents, IPR2023-01346
Page 555 of 725

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Sahar Javanmard
Art Unit:	1627

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Dated: February 7, 2-18 Electronic Signature for: /Trish McDonald/

REPLY BRIEF

Patent Trial and Appeal Board
US Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313–1450

Dear Commissioner:

This Reply Brief is filed within two (2) months of the Examiner's Answer, mailed on December 8, 2017 (hereinafter "the Answer"), and is in furtherance of the Appeal Brief, filed on August 10, 2017 (hereinafter "the Appeal Brief").

The Appeal Forwarding fee required under 37 C.F.R. § 41.20(b)(4) is being paid by credit card using the credit card payment option of the USPTO's Electronic Filing System.

I. INTRODUCTION

The Examiner's Answer maintains the grounds of rejection of claims 37-50 and 52-58 as previously summarized on pages 10-12 of the Appeal Brief, and as summarized below.

Claims 37-50 and 52-58 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over McCoy (CA 1148020A1).

Claims 37-50 and 52-58 are further rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Huffman (U.S. Patent No. 3,664,858).

II. ARGUMENTS

A. The Examiner has not established a *prima facie* case of obviousness

i. McCoy

The Examiner acknowledges that McCoy does not disclose the specific examples of homo- and heterosynthons required by the claims, and does not disclose the identification of a synthon from the crystal structure. The Examiner further acknowledges that McCoy teaches the use of a cocrystallizer in a weight ratio, and not in stoichiometric proportions. Nonetheless, the Examiner holds that the claimed pharmaceutical compositions are obvious, arguing that "cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy".[1] Appellant disagrees and maintains that it would not have been obvious to select a stoichiometric ratio from the range of weight ratios suggested in McCoy.

Specifically, McCoy discloses cocrystallizer/amino acid compositions having weight ratios of from 0.9:1 to 6:1.[2] There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, *e.g.*, a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. Nor does McCoy suggest that it would be advantageous to select a stoichiometric ratio from the range of weight ratios. In fact, McCoy teaches that the criteria for selecting the optimum amount of cocrystallizer is whether there is "'enough' to enable successful dehydration of the amino acid co-crystallizer solution."[3] Based on this teaching,

[1] Page 6 of the Answer
[2] McCoy page 7
[3] *Id.*

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the skilled person would not be motivated to modify McCoy by utilizing a stoichiometric ratio of amino acid to cocrystallizer, and as such could not have envisioned the claimed invention.

In the Examiner's Answer, the Examiner acknowledges that McCoy teaches "by weight" and not in "stoichiometric proportions" as instantly claimed.[4] However, the Examiner is of the opinion that "although McCoy does not teach specific examples of an API and co-crystal former in stoichiometric proportions, the [weight] range of 0.9:1 to about 6:1 embraces such [stoichiometric] proportions to be possible."[5] As discussed in the Appeal Brief, the Examiner has not identified an express teaching, or preferred embodiments, of McCoy that would motivate the skilled artisan to select stoichiometric ratios of co-crystals according to the present claims. In fact, as discussed above, an express teaching of McCoy relates to the criteria of successful dehydration, wherein "preferably, equal [mass] amounts of amino acid and cocrystallizer are used." In addition, the Examiner has not identified the teaching of a similar property or use (*e.g.*, formation of a homo- or heterosynthon structure) that motivate the skilled artisan to prepare co-crystals according to the present claims.

At least for the foregoing reasons, the Examiner has not established a *prima facie* case for the obviousness of the claimed invention over McCoy, and Appellant respectfully requests reconsideration and reversal of the rejection of claims 37-50 and 52-58 under § 103(a).

ii. Huffman

As discussed in the Appeal Brief, the Examiner has not established a prima facie case for rejecting the claims as being unpatentable over Huffman because (a) Huffman is not a proper reference for use in an obviousness rejection, (b) the Examiner has not met their burden of articulating the reasons for rejecting each and every limitation of the pending claims, and (c) one of ordinary skill in the art would not have a reasonable expectation of success in forming a co-crystal of an API having maintained activity and/or improved properties.

Huffman discloses heat-sensitive copy-sheet coatings,[6] and that such coatings and copy-sheets are useful in the preparation of projection transparencies.[7] Huffman is not analogous art as

[4] Page 11 of the Answer
[5] *Id.*
[6] Huffman at Abstract
[7] *Id.* at column 1, lines 1-11

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required by MPEP § 2141.01(a) because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors.

With respect to the field of endeavor, each appealed claim, indeed the entire specification, is directed to a pharmaceutical composition comprising a co-crystal including an active pharmaceutical ingredient (API), and therefore relates to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts.

With respect to the problem faced and whether the reference is reasonably pertinent to that problem, as described throughout the Application, "[u]ndesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs" and crystalline self-assemblies may improve such characteristics, but "many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase" and "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."[8] The present application provides, as a solution to this problem, the "design of new pharmaceutical solid phases, such as multiple-component phases, using co-crystal formers that are complementary in the sense of supramolecular chemistry, *i.e.*, they form supramolecular synthons with pharmaceutical molecules or ions."[9] These multiple-component solids "exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction", which "can afford improved drug solubility, dissolution rate, stability and bioavailability, for example."[10]

In contrast, the problem faced in Huffman is that when heating prior art copy-sheets, "the sheet causes dissociation of the adduct with liberation of amine and formation of color-bodies."[11] The solution provided by Huffman is "to produce clear transparent films and coatings containing heat-dissociable amine adducts in non-particulate form" as this coating "does not obscure desired colors or markings on the underlying carrier" and produces "excellent projection transparencies."[12]

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[8] U.S. Application No. 14/179,862, paragraphs [0003] and [0004].
[9] *Id.* at paragraph [0009]
[10] *Id.* at paragraph [0039]
[11] Huffman column 1, lines 28-33
[12] *Id.* at column 1, liens 34-40

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Producing excellent projection transparencies that do not obscure desired colors or markings is not reasonably pertinent to problem described in the instant application. The inventors would not have considered producing excellent projection transparencies that do not obscure desired colors or markings in solving the problem described in the instant application, which relates to the lack of rational design of crystalline pharmaceuticals, which was hampered by the multiple phases formed by most drugs. As a result, Huffman is not analogous art under MPEP § 2141.01(a) and is not a proper reference for use in an obviousness rejection. For this reason alone, the rejection under 103(a) should be withdrawn.

Even assuming that Huffman was a proper reference for use in an obviousness rejection, which Appellant asserts is not the case, the Examiner has not met their burden in articulating the reason for rejecting the claims based on Huffman alone, as Huffman provides no teaching or suggestion to make co-crystals, as recited in the present claims. Huffman makes salts rather than co-crystals. Huffman discloses mixtures of amines and acids, *e.g.*, carboxylic acids. Indeed, one of ordinary skill in the art will readily appreciate that the amines disclosed in Huffman will deprotonate the carboxylic acids disclosed in Huffman to make salts. The present claims recite co-crystals.

Furthermore, Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition. Indeed, the Examiner acknowledges that Huffman does not teach the co-crystal complexes in pharmaceutical compositions.[13] The Examiner's reason for arriving at the claimed subject matter, which relates to pharmaceutical compositions including an active pharmaceutical ingredient (API), is that "it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct."[14] The Examiner provides no evidence or rationale to support this conclusory statement. Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition comprising a co-crystal of an active pharmaceutical ingredient. As a result, Huffman does not teach or suggest each and every limitation of the claims and therefore does not render the claims obvious.

[13] Page 9 of the Answer
[14] *Id.*

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In addition, the Examiner states that "if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claim are met."[15] The Examiner states that "the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight." Appellant respectfully disagrees, and submits that the recitation of an API comprising a first chemical functionality should be given patentable weight. Appellant maintains that the present specification supports an interpretation of the claim terms "active pharmaceutical ingredient" and "API" as referring to a biologically active pharmaceutical entity having a therapeutic effect on a human or animal, such pharmaceutical entities having prophylactive, palliative, and/or curative effects.[16] In accordance with this interpretation, an API is not defined according to an intended use, but rather according to its properties, and as such should be afforded patentable weight.

Moreover, Appellant maintains that the present specification supports an interpretation where the claim term "wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former" denotes an actual state that fundamentally ties the formation of the supramolecular synthon to the physical characteristics of the API. As a result, the disputed claim language reaches well beyond merely describing an intended use since the claims actively recite an actual configuration, *e.g.*, non-covalent hydrogen bonding between an API and a complementary co-former. In further support of the patentable weight of the term "API," Appellant submits that one of ordinary skill in the art would not have had a reasonable expectation of success in forming a co-crystal with an API. Additionally, one of ordinary skill in the art would not have had a reasonable expectation that a co-crystal of an API would be useful, *e.g.*, maintain activity and/or have improved properties. Indeed, combining an API with a co-crystal co-former could have had a negative impact on the activity of the API, including decreased solubility, dissolution rate, stability, and/or bioavailability. However, the teachings of the instant application demonstrate the unpredictable finding that APIs could not only be used in co-crystals, but that the co-crystals exhibit improved characteristics as compared to the API alone.

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[15] Page 7 of the Answer
[16] U.S. Application No. 14/179,862, *e.g.*, at paragraph [0048]

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In the Examiner's Answer, the Examiner asserts that despite the fact that the claims require an API, they "[do] not mandate that the endeavor relate to the pharmaceutical arts" and "it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant".[17] As discussed above, Appellant maintains that the term API should be afforded patentable weight. Indeed, the Examiner provides no reasoning why one of ordinary skill in the art would interpret the claims as merely reciting an intended use, as opposed to a state which ties the formation of the supramolecular synthon to the physical characteristics of the API. In addition, the Examiner has failed to support their assertion that one of ordinary skill in the art would look to Huffman to arrive at the claimed invention, as Huffman provides no teaching or suggestion to make co-crystals, much less co-crystals comprising an API as recited in the claims.

At least for the foregoing reasons, the Examiner has not established a *prima facie* case for the obviousness of the claimed invention over Huffman, and Appellant respectfully requests reconsideration and reversal of the rejection of claims 37-50 and 52-58 under 35 U.S.C. § 103(a).

III. CONCLUSION

The foregoing clearly demonstrates that the rejections of all of the claims are erroneous and should be reversed.

The Appellant believes that any fee due with this Reply Brief has been timely paid. However, if any fee is outstanding, please charge Deposit Account No. 23/2825 under Docket No. U0157.70023US02, from which the undersigned is authorized to draw.

Dated: February 07, 2018

Respectfully submitted,

By /David F. Cauble/
David F. Cauble, Ph.D
Registration Number: 73,490
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[17] Page 12 of the Answer

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Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
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/Trish McDonald
Attorney Docket Number:	U0157.70023US02

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:				
REQUEST FOR ORAL HEARING	2403	1	650	650
APPEAL FORWARDING FEE	2413	1	1120	1120

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1770**

Electronic Acknowledgement Receipt	
EFS ID:	31730078
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Trish McDonald
Filer Authorized By:	David F. Cauble
Attorney Docket Number:	U0157.70023US02
Receipt Date:	07-FEB-2018
Filing Date:	13-FEB-2014
Time Stamp:	16:47:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1770
RAM confirmation Number	020818INTEFSW16500600
Deposit Account	232825
Authorized User	Wolf Greenfield
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	U015770023US02-TRN-DFC.pdf	25245 884720012d88a140c77f5d6fe39e828cbb8a3872	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US02-FEE-DFC.pdf	31366 99cad8aec02b2427ef63771a1f74c5ecdb37d798	no	1
Warnings:					
Information:					
3	Request for Oral Hearing	U015770023US02-ROH-DFC.pdf	22736 0e773290412b0af1fba14832af8e877d7992b51f7	no	1
Warnings:					
Information:					
4	Reply Brief Filed	U015770023US02-RBRF-DFC.pdf	47928 0a16c8dbc011bfe2d9c8454fd60f98d14fbf2d18	no	7
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32318 c43e526846a9cf04f52cd4a2a1c8d5bd18f6fce6	no	2
Warnings:					
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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

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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	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	Sahar Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

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
- [ ] 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
- [x] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Request for Oral Hearing

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/David F. Cauble/		
Printed name	David F. Cauble		
Date	February 7, 2018	Reg. No.	73,490

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Dated: February 7, 2018 Electronic Signature for: /Trish McDonald/

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FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	Sahar Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[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 ($)1,770.00

METHOD OF PAYMENT (check all that apply)

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

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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	280	140*	70	600	300	150	720	360	180	
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 _____ - 41 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

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

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

Indep. Claims _____ - 3 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

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 _____ - 100 = _____ /50 = _____ (round **up** to a whole number) x Fee ($) _____ = Fee Paid ($) _____

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): 2403 Request for oral hearing 650.00

2413 Forwarding an appeal in an application 1,120.00

SUBMITTED BY					
Signature	/David F. Cauble/	Registration No. (Attorney/Agent)	73,490	Telephone	617.646.8000
Name (Print/Type)	David F. Cauble			Date	February, 7, 2018

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 02/13/2018

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
02/13/2018	ELECTRONIC

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

Appeal No: 2018-003325
Application: 14/179,862
Appellant: Michael J. Zaworotko et al.

Patent Trial and Appeal Board Docketing Notice

Application 14/179,862 was received from the Technology Center at the Board on February 09, 2018 and has been assigned Appeal No: 2018-003325.

In all future communications regarding this appeal, please include both the application number and the appeal number.

The mailing address for the Board is:

PATENT TRIAL and APPEAL BOARD
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P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

Telephone inquiries can be made by calling 571-272-9797 and referencing the appeal number listed above.

By order of the Patent Trial and Appeal Board.

DAG

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	AP_DK_M	02/13/2018	U0157.70023US02

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 05/21/2019
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/21/2019	ELECTRONIC

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

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

Appeal No:	2018-003,325
Appellant:	Michael J. Zaworotko et al.
Application No:	14/179,862
Hearing Room:	A
Hearing Docket:	A
Hearing Date:	Friday, July 26, 2019
Hearing Time:	01:00 PM
Location:	**Madison Building - East Wing** **600 Dulany Street, 9th Floor** **Alexandria, Virginia 22313-1450**

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Appeal No:	2018-003,325
Appellant:	Michael J. Zaworotko et al.
Application No:	14/179,862
Hearing Room:	A
Hearing Docket:	A
Hearing Date:	Friday, July 26, 2019
Hearing Time:	01:00 PM
Location:	**Madison Building - East Wing** **600 Dulany Street, 9th Floor** **Alexandria, Virginia 22313-1450**

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David F. Cauble	73,490
Typed or Printed Name of Attorney/Agent/Appellant	Registration No.
/David F. Cauble/	June 11, 2019
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NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346

Electronic Acknowledgement Receipt

EFS ID:	36262238
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	U0157.70023US02
Receipt Date:	11-JUN-2019
Filing Date:	13-FEB-2014
Time Stamp:	12:12:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	U015770023US02-TRN-DFC.pdf	26428 454a488ff780313bbe1f032eabb4e15f5afc0ca2	no	1
Warnings:					

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2	Waiver of Hearing by Appellant	U015770023US02-WAIVEHEARING-DFC.pdf	111771 fd57e1384243eb6d6f4d8afdfe045f434521 9f4a	no	2
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Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Attorney Docket Number	U0157.70023US02

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Signature	/David F. Cauble/		
Printed name	David F. Cauble, PhD, JD		
Date	June 11, 2019	Reg. No.	73,490

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 08/06/2019

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EXAMINER	
JAVANMARD, SAHAR	

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1627	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MICHAEL J. ZAWOROTKO,
NAIR RODRIGUEZ-HORNEDO, and BRIAN MOULTON

Appeal 2018-003325[1]
Application 14/179,862
Technology Center 1600

Before FRANCISCO C. PRATS, JOHN G. NEW, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a pharmaceutical composition that contains a crystal composed of a pharmaceutical compound and a second compound. The Examiner entered two rejections for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] Appellants identify the Regents of the University of Michigan and the University of South as the real parties in interest in this appeal. Appeal Br. 3.

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STATEMENT OF THE CASE

Appellants' invention involves forming a crystal by combining a pharmaceutically active compound with a second compound, termed a "co-crystal former[]." *See* Spec. ¶¶ 8–9. The Specification explains that preparing a crystal composed of a pharmaceutical compound and a co-crystal former "can afford improved drug solubility, dissolution rate, stability and bioavailability, for example." *Id.* ¶ 39.

The Specification discloses:

> Examples of multiple-component crystals of the subject invention include, but are not limited to, acet[a]minophen/4,4′-bipyridine/water, phenytoin/pyridone, aspirin/4,4'-bipyridine, ibuprofen/4,4′-dipyridyl, flurbiprofen/4,4′-dipyridine, 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/tremesic 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.

Id.; *see also id.* ¶¶ 56–178 (Examples 1–19 describing formation of crystals listed in ¶ 39 by co-dissolving pharmaceutical compounds and crystal co-formers in solvent and then slowly evaporating solvent from the composition).

As to the terminology used in the appealed claims, the Specification explains "crystals are *de facto* examples of self-assembly, *i.e.*[,] crystals are

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comprised from a series of molecular recognition events or *supramolecular synthons*." *Id.* ¶ 2 (citation omitted).

The Specification explains further that a crystal co-former may include a functional group that is identical to a functional group on the pharmaceutical compound also present in the two-component or multiple-component salt. *See id.* ¶ 9. In the situation where a crystal is formed from a pharmaceutical compound and a crystal co-former having an identical functional group, that association is termed a "homosynthon[]." *See id.* ("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.").

Claim 37 illustrates the appealed subject matter and reads as follows:

> 37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former and each supramolecular synthon comprising an API homosynthon 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,
>
> wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,
>
> wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, and
>
> wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical

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> functionality of the API and the second chemical functionality of the co-former.

Appeal Br. 25.

The following grounds of rejection are before us for review:

(1) Claims 37–50 and 52–58, under 35 U.S.C. § 103(a) as being unpatentable over McCoy[2] (Ans. 3–6); and

(2) Claims 37–50 and 52–58, under 35 U.S.C. § 103(a) as being unpatentable over Huffman[3] (Ans. 6–10).

OBVIOUSNESS—MCCOY

In rejecting Appellants' claims over McCoy, the Examiner first determined that the term "API" in the claims was not entitled to any patentable weight because the term was merely directed to an intended use of the recited ingredient. Ans. 4–5. The Examiner then summarized the disclosures in McCoy, including the formation of co-crystals of amino acids with a variety of different co-crystallizer materials. *Id.* at 5–6.

Based on those disclosures, the Examiner concluded that it would have been obvious "to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different [functionalities], giving rise to heterosynthons." *Id.* at 6. Therefore, the Examiner reasoned, "preparing and identifying the cocrystals, as required by

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[2] CA 1 148 020 (issued June 14, 1983).
[3] US 3,664,858 (issued May 23, 1972).

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the limitations of the instant claims, are well within the scope of the teachings of McCoy." *Id.*

We reverse this rejection.

As an initial matter, we find that the Examiner erred in determining that the term "API" in Appellants' claims should not be afforded patentable weight. It is well settled that during examination, the PTO must interpret terms in a claim using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Under that standard, "words of the claim are generally given their ordinary and accustomed meaning, *unless it appears from the specification . . . that they were used differently by the inventor*." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (emphasis added).

In other words, in "the situation in which a patent applicant has elected to be a lexicographer by providing an explicit definition in the specification for a claim term . . ., the definition selected by the patent applicant controls." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998).

Here, Appellants' Specification expressly defines "'active pharmaceutical ingredient (API)'" as "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." Spec. ¶ 48. Because that broad definition encompasses the amino acids included

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in the co-crystals described in McCoy (*see, e.g.*, McCoy, abstract), the Examiner does not persuade us that under the correct standard of claim interpretation, it is proper to accord the term API no patentable weight.

We are also not persuaded that the Examiner has articulated a prima facie case of obviousness with sufficient specificity. Our reviewing court has directed as follows:

> In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. [The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.

In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations omitted, bracketed material in original).

In the present case, Appellants' claims, as exemplified by claim 1 reproduced above, require the API to be combined with a co-crystal former to form a crystal that contains "an API homosynthon." Appeal Br. 25.

Therefore, to meet the requirements of claim 1, the prior art must teach or suggest forming a crystal composed of (1) an active pharmaceutical ingredient (API) and (2) a second ingredient that contains at least one functional group that is identical to a functional group present on the API molecule. *See* Spec. ¶ 9 (explaining that, when a crystal is formed from a pharmaceutical compound and a crystal co-former having an identical functional group such as an acid or amide moiety, that association is termed a "homosynthon[]").

We acknowledge the Examiner's assertions that the compositions of Appellants' claims are within the scope of McCoy's teachings, and that a

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skilled artisan would have envisioned compositions encompassed by Appellants' claims from McCoy's disclosures. Ans. 6.

The Examiner, however, does not identify from the many possible combinations of ingredients disclosed by McCoy which *specific* combination of amino acid and cocrystallizer material taught or suggested by the reference would result in a crystal in which the API (amino acid) and cocrystallizer would have at least one identical functional group, as required by Appellants' claims. Nor does the Examiner explain *why any particular* combination of amino acid and cocrystallizer taught or suggested by McCoy would have a common identical functional group, or what that common identical functional group might be.

Absent some articulation of the specific combination of amino acid and cocrystallizer material disclosed in McCoy that would provide a crystal encompassed by Appellants' claims, and an explanation why at least two members of that particular combination contain an identical functional group that would provide a homosynthon encompassed by Appellants' claims, we are not persuaded that the Examiner has provided a sufficiently specific evidentiary basis allowing us to sustain the rejection. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."). Accordingly, for the reasons discussed, we reverse the Examiner's rejection of claims 37–50 and 52–58 for obviousness over McCoy.

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OBVIOUSNESS—HUFFMAN

In rejecting Appellants' claims over Huffman, the Examiner cited Huffman as teaching crystal adducts of amines with aromatic hydroxy compounds. Ans. 7. The Examiner noted Huffman's teachings that numerous different organic compounds were useful in its adducts, and in stoichiometric amounts. *Id.* at 7–9. The Examiner particularly noted Huffman's disclosure of forming a crystal adduct containing equimolar amounts of salicylic acid and piperidine, as well as a crystal containing piperidine and benzoic acid. *Id.* at 9.

The Examiner conceded that Huffman differed from Appellants' claims in that "Huffman does not teach the co-crystal complexes in pharmaceutical compositions." *Id.*

The Examiner reasoned, however, that it "would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct." *Id.* (citing *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990)).

We reverse this rejection as well. We acknowledge the statement in *Dillon* cited by the Examiner:

> [I]t is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from *the prior art* that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that [*In re*] *Wright*[, 848 F.2d 1216 (Fed. Cir. 1988)] suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a *prima facie* obviousness rejection is not supported if no reference shows or

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> suggests the newly-discovered properties and results of a claimed structure is not the law.

In re Dillon, 919 F.2d at 693.

All of Appellants' independent claims, however, recite pharmaceutical compositions that contain a pharmaceutically acceptable carrier in addition to the crystal also recited in the claims. *See* Appeal Br. 25 (claim 1); *id.* at 26 (claim 41); *id.* at 28 (claim 52); *id.* at 29 (claim 53).

Therefore, in addition to explaining why Huffman would have suggested preparing a two-component crystal encompassed by Appellants' claims, to demonstrate that the claimed compositions are unpatentable under § 103, the Examiner must also explain why a skilled artisan would have considered it obvious to combine that crystal with a pharmaceutical carrier to form a pharmaceutical composition. We are not persuaded that the Examiner has explained adequately why a skilled artisan would have combined the ingredients required by the Appellants' claims to produce a pharmaceutical composition encompassed by the claims.

The Examiner contends that Huffman does disclose combining its crystals with pharmaceutically acceptable ingredients, such as water. Ans. 12 (citing Huffman, Example 10). The composition disclosed in Huffman's Example 10, however, also contains ninhydrin, and rather than being a pharmaceutical composition, is instead applied to a sheet of paper and used in a thermographic copying process. *See* Huffman, 4:70–75. We are not persuaded that the Examiner has explained adequately why adding water to a crystal-containing composition that also contains ninhydrin, for ultimate use in a thermographic copying process, would have suggested including

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Huffman's crystals in a pharmaceutical composition alongside a pharmaceutically acceptable carrier.

The Examiner contends that "many of the acids taught in Huffman are in fact commonly employed in the pharmaceutical art, namely acids of ascorbic, succinic, malonic, oxalic, glyoxylic, and glycolic." Ans. 12.

Rather than using those acids to form crystals employed in pharmaceutical compositions, however, Huffman uses those acids in combination with amines to form crystals ultimately deployed in thermographic copying processes. *See* Huffman, 1:1–2:22.

Therefore, given that thermographic copying was the sole utility disclosed by Huffman for its crystals, the fact that some of the crystals' components were also known to be useful in pharmaceutical compositions does not persuade us that Huffman would have motivated a skilled artisan to include the crystals in pharmaceutical compositions, alongside a pharmaceutically acceptable carrier, as recited in Appellants' claims. Accordingly, aside from the fact that the Examiner has not explained specifically why Huffman's acid/amine combination teaches or suggests a crystal composed of a homosynthon, we are not persuaded that Huffman teaches or suggests a composition having all of the claimed ingredients.

Indeed, given that thermographic copying is the sole utility disclosed by Huffman for its crystals, we agree with Appellants that the Examiner has not explained adequately why Huffman should be considered analogous art. *See* Ans. 12.

Regarding the use of analogous art in obviousness rejections, our reviewing court has stated:

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> Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.

In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

In the present case, as noted above, Huffman's field of endeavor is the preparation of compositions useful for thermographic copying on heat-sensitive sheets (*see* Huffman, 1:1–68), whereas Appellants' 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." Spec. ¶ 7.

We are not persuaded, therefore, that Huffman is from the same field of endeavor as Appellants' invention. We agree with Appellants, moreover, that the Examiner has not explained adequately why Huffman's preparation of compositions that are advantageous when used in thermographic copying processes would have been considered reasonably pertinent to Appellants' problem of preparing multi-component pharmaceutical compositions. That Huffman may have employed acids that are also useful in preparing pharmaceutical compositions (*see* Ans. 12) does not persuade us that the problems faced by Huffman involve any of the same considerations faced when preparing multi-component pharmaceutical compositions.

In sum, for the reasons discussed, we reverse the Examiner's rejection of claims 37–50 and 52–58 for obviousness over Huffman.

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SUMMARY

For the reasons discussed, we reverse both of the Examiner's obviousness rejections.

REVERSED

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To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Aug 06, 2019 03:34:28 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
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UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	APDR	08/06/2019	U0157.70023US02

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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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

NOTICE OF ALLOWANCE AND FEE(S) DUE

23628 7590 11/20/2019
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER
JAVANMARD, SAHAR

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/20/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

TITLE OF INVENTION: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	02/20/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23628 7590 11/20/2019
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

TITLE OF INVENTION: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	02/20/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
JAVANMARD, SAHAR	1627	424-400000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 11/20/2019

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 11/20/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Notice of Allowability	Application No. 14/179,862	Applicant(s) Zaworotko et al.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (FITF) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 8/6/19.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/SAHAR JAVANMARD/
Primary Examiner, Art Unit 1627

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Continuation of 3. The allowed claim(s) is/are: 37-50 and 52-58 (renumbered as 1-21)

NOVARTIS EXHIBIT 1016
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DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Reasons for Allowance

The claimed invention of "a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former and each supramolecular synthon comprising an API homosynthon 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, wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding, wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, and wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former" is novel and non-obvious. The closest prior art is due to Huffman (US Patent 3,664,858) of record. Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds. Huffman uses said complexes in combination with

amines to form crystals in thermographic copying processes not in pharmaceutical compositions as required by the instant claims. Huffman is considered non-analogous art.

Additionally, the abandonment of application 10/378,956 overcomes the outstanding obviousness-type double patenting rejection.

Thus the claimed invention is rendered neither anticipated nor obvious.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 37-50 and 52-58 are allowed.

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571)270-3280. The examiner can normally be reached on Monday-Friday, 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/SAHAR JAVANMARD/
Primary Examiner, Art Unit 1627

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/179,862	Zaworotko et al.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/21/2014	10/20/2014	09/29/2015	07/08/2016	11/13/2019				
	1	-	-	-	-	-				
	2	-	-	-	-	-				
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	4	-	-	-	-	-				
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	34	-	-	-	-	-				
	35	-	-	-	-	-				
	36	-	-	-	-	-				
1	37	✓	✓	✓	✓	=				
2	38	✓	✓	✓	✓	=				
3	39	✓	✓	✓	✓	=				
4	40	✓	✓	✓	✓	=				
5	41	✓	✓	✓	✓	=				
6	42	✓	✓	✓	✓	=				

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/179,862	Zaworotko et al.
	Examiner	**Art Unit**
	SAHAR JAVANMARD	1627

CLAIM		DATE								
Final	Original	03/21/2014	10/20/2014	09/29/2015	07/08/2016	11/13/2019				
7	43	✓	✓	✓	✓	=				
8	44	✓	✓	✓	✓	=				
9	45	✓	✓	✓	✓	=				
10	46	✓	✓	✓	✓	=				
11	47	✓	✓	✓	✓	=				
12	48	✓	✓	✓	✓	=				
13	49	✓	✓	✓	✓	=				
14	50	✓	✓	✓	✓	=				
	51	✓	-	-	-	-				
15	52	✓	✓	✓	✓	=				
16	53	✓	✓	✓	✓	=				
17	54	✓	✓	✓	✓	=				
18	55	✓	✓	✓	✓	=				
19	56		✓	✓	✓	=				
20	57		✓	✓	✓	=				
21	58		✓	✓	✓	=				

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	Examiner	Art Unit
	SAHAR JAVANMARD	1627

CPC - Searched*		
Symbol	**Date**	**Examiner**
C07D223/26; 275/06; 213/82; 213/79; 213/69; 213/22; 213/06; 233/74	10/16/2019	SJ
C06C317/04; 233/75; 233/03; 205/57; 69/157; 63/307; 61/135; 57/58; 57/30; 53/124; 53/08; 53/02; 47/544; 233/25; 51/43; 51/412	10/16/2019	SJ
A61K47/32; 47/10; 31/616; 31/55; 31/4166; 31/192; 31/167; 9/1652	10/16/2019	SJ

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
424	400	4/4/2014	SJ
	updated 10/2014		SJ

* 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**
EAST (searched inventor names)	4/4/2014	SJ
EAST (keyword search)	4/4/2014	SJ
updated 10/2014		SJ
Google Patents (searched:organic acids amines adducts crystals)	12/12/2014	SJ
updated	10/16/2019	SJ

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	Examiner	Art Unit
	SAHAR JAVANMARD	1627

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C07D	223/26; 275/06; 213/82; 213/79; 213/69; 213/22; 213/06; 233/74	11/13/2019	SJ
C06C	317/04; 233/75; 233/03; 205/57; 69/157; 63/307; 61/135; 57/58; 57/30; 53/124; 53/08; 53/02; 47/544; 233/25; 51/43; 51/412	11/13/2019	SJ
A61K	47/32; 47/10; 31/616; 31/55; 31/4166; 31/192; 31/167; 9/1652	11/13/2019	SJ

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	Examiner	Art Unit
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CPC						
Symbol					Type	Version
C07D	/	223	/	26	F	2013-01-01
A61K	/	9	/	1652	I	2013-01-01
A61K	/	31	/	167	I	2013-01-01
A61K	/	31	/	192	I	2013-01-01
A61K	/	31	/	4166	I	2013-01-01
A61K	/	31	/	55	I	2013-01-01
A61K	/	31	/	616	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
A61K	/	47	/	32	I	2013-01-01
C07C	/	51	/	412	I	2013-01-01
C07C	/	51	/	43	I	2013-01-01
C07C	/	233	/	25	I	2013-01-01
C07D	/	233	/	74	I	2013-01-01
C07C	/	47	/	544	I	2013-01-01
C07C	/	53	/	02	I	2013-01-01
C07C	/	53	/	08	I	2013-01-01
C07C	/	53	/	124	I	2013-01-01
C07C	/	57	/	30	I	2013-01-01
C07C	/	57	/	58	I	2013-01-01
C07C	/	61	/	135	I	2013-01-01
C07C	/	63	/	307	I	2013-01-01
C07C	/	69	/	157	I	2013-01-01
C07C	/	205	/	57	I	2013-01-01
C07C	/	233	/	03	I	2013-01-01
C07C	/	233	/	75	I	2013-01-01
C07C	/	317	/	04	I	2013-01-01
C07D	/	213	/	06	I	2013-01-01
C07D	/	213	/	22	I	2013-01-01
C07D	/	213	/	69	I	2013-01-01
C07D	/	213	/	79	I	2013-01-01
C07D	/	213	/	82	I	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	21	
/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627	13 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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	Examiner	**Art Unit**
	SAHAR JAVANMARD	1627

CPC						
Symbol					**Type**	**Version**
C07D	/	275	/	06	I	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
C07C	/	51	/	412	I	1	1	2013-01-01
C07C	/	53	/	06	I	1	2	2013-01-01
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C07C	/	53	/	10	I	2	2	2013-01-01
C07C	/	51	/	412	I	3	1	2013-01-01
C07C	/	57	/	30	I	3	2	2013-01-01
C07C	/	51	/	412	I	4	1	2013-01-01
C07C	/	61	/	135	I	4	2	2013-01-01
C07C	/	51	/	43	I	5	1	2013-01-01
C07C	/	57	/	30	I	5	2	2013-01-01
C07C	/	51	/	43	I	6	1	2013-01-01
C07C	/	53	/	06	I	6	2	2013-01-01
C07C	/	51	/	43	I	7	1	2013-01-01
C07C	/	61	/	135	I	7	2	2013-01-01
C07C	/	51	/	43	I	8	1	2013-01-01
C07C	/	53	/	10	I	8	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627	13 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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	Examiner	**Art Unit**
	SAHAR JAVANMARD	1627

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07D223/26	/	223	/	26
A61K9/16	/	9	/	16
A61K31/167	/	31	/	167
A61K31/192	/	31	/	192
A61K31/4166	/	31	/	4166
A61K31/55	/	31	/	55
A61K31/616	/	31	/	616
A61K47/10	/	47	/	10
A61K47/32	/	47	/	32
C07C51/41	/	51	/	41
C07C51/43	/	51	/	43
C07C233/25	/	233	/	25
C07D233/74	/	233	/	74
C07C47/544	/	47	/	544
C07C53/02	/	53	/	02
C07C53/08	/	53	/	08
C07C53/124	/	53	/	124
C07C57/30	/	57	/	30
C07C57/58	/	57	/	58
C07C61/135	/	61	/	135

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627	13 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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	14/179,862	Zaworotko et al.
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CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627	13 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28	1	37	10	46	18	55		
	2		11		20		29	2	38	11	47	19	56		
	3		12		21		30	3	39	12	48	20	57		
	4		13		22		31	4	40	13	49	21	58		
	5		14		23		32	5	41	14	50				
	6		15		24		33	6	42		51				
	7		16		25		34	7	43	15	52				
	8		17		26		35	8	44	16	53				
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NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/SAHAR JAVANMARD/ Primary Examiner, Art Unit 1627	13 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	278588	(C07D223/26 or C07D275/06 or C07D213/82 or C07D213/79 or C07D213/69 or C07D213/22 or C07D213/06 or C07C317/04 or C07C233/75 or C07C233/03 or C07C205/57 or C07C69/157 or C07C63/307 or C07C61/135 or C07C57/58 or C07C57/30 or C07C53/124 or C07C53/08 or C07C53/02 or C07C47/544 or C07D233/74 or C07C233/25 or C07C51/43 or C07C51/412 or A61K47/32 or A61K47/10 or A61K31/616 or A61K31/55 or A61K31/4166 or A61K31/192 or A61K31/167 or A61K9/1652).cpc.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2019/11/13 11:06
L2	3068	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2019/11/13 11:07
L3	413	L1 L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2019/11/13 11:07
L4	24619	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2019/11/13 11:07
L5	132	L3 L4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2019/11/13 11:07
L6	142792	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2019/11/13 11:08

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L7	67	L5 L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2019/11/13 11:08
L8	0	L7 @PD< "20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2019/11/13 11:08
S2	2	("6559293").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/07/30 09:53
S3	1	aspirin cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:28
S4	1	almarrson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S5	246	almarsson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S6	280	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S7	5	S5 S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30
S8	1303795	crystal	US-PGPUB; USPAT; USOCR; FPRS;	NEAR	OFF	2008/09/12 14:30

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			EPO; JPO; DERWENT			
S9	102	S5 S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30
S10	17	aspirin crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:36
S11	1	wo "0151919"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:51
S12	1	wo "0142222"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:59
S13	4182	supramolecul$2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S14	31445	aspirin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S15	157	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:00
S16	5	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/12 15:00
S17	2200	active pharmaceutical ingredient	US-PGPUB; USPAT;	ADJ	OFF	2008/09/12 15:02

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			USOCR; FPRS; EPO; JPO; DERWENT			
S18	19	S13 S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:02
S19	2	heterosynthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:04
S20	47880	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 08:31
S21	1329	co crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 08:31
S22	126	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:31
S23	18	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 08:31
S24	2	S22 and @pd< "20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:45
S25	283	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/30 08:48
S26	18	S20 S25	US-	AND	OFF	2008/09/30

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			PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT			08:48
S27	57	co crystal.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 09:39
S28	14	S27 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:39
S29	458	Pharmaceutical co adj crystal compositions drugs	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S30	543	Pharmaceutical co adj crystal composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S31	543	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S32	29	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 09:56
S33	47	S31 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S34	119	crystal engineering	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	ADJ	OFF	2008/09/30 10:03

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			DERWENT			
S35	32	S34 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:03
S36	29	S34 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S37	4	S36 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S38	228231	crystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S39	7179	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S40	200	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 10:26
S41	132	S40 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S42	106	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/30 10:26
S43	64	S42 and @pd< "20030303"	US-PGPUB; USPAT; USOCR;	AND	OFF	2008/09/30 10:27

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			FPRS; EPO; JPO; DERWENT			
S44	472	cocrystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S45	41	S20 S44	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S46	9	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S47	5	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S48	5	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S49	77	(40/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S50	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S51	9	(("7452555") or ("7446107") or ("7205413") or ("7078526")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 06:23
S52	4	("2003/0224006").URPN.	USPAT	OR	OFF	2009/08/31 06:38
S53	3	("2665277").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:13
S54	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR;	ADJ	OFF	2009/08/31 07:18

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			FPRS; EPO; JPO; DERWENT			
S55	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:18
S56	607	S54 S55	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:18
S57	335	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2009/08/31 07:19
S58	13	S56 S57	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:19
S59	27058	hydrogen bond	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:20
S60	28	S56 S59	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:20
S61	58	co-crystal former	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:21
S62	14	S55 S61	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:22
S63	2904	active pharmaceutical ingredient	US-PGPUB;	ADJ	OFF	2009/08/31 08:44

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S64	791	S63 crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S65	20	S63 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S66	2904	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:58
S67	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 08:58
S68	607	S67 S66	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S69	210	S68 CRYSTAL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S70	4	(("7452555") or ("7446106") or ("7205413") or ("7078526")).PN.	USPAT	OR	OFF	2009/09/28 10:26
S71	95	phosphate hemihydrate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 14:42
S72	54110	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS;	OR	OFF	2009/09/28 14:42

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			EPO; JPO; DERWENT			
S73	5	S72 S71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 14:42
S74	2	((("3028420") or ("5521207")).PN.	USPAT	OR	OFF	2009/09/28 14:52
S75	19	API cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 15:02
S76	0	ep "0548028"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 15:46
S77	6	supramolecular synthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 22:18
S78	20	US-2711411-$.DID. OR US-4198507-$.DID. OR US-4368197-$.DID. OR US-4994604-$.DID. OR US-5177262-$.DID. OR US-5332834-$.DID. OR US-5338644-$.DID. OR US-5380867-$.DID. OR US-5412094-$.DID. OR US-5523090-$.DID. OR US-5614342-$.DID. OR US-5998413-$.DID. OR US-6001996-$.DID. OR US-6268385-$.DID. OR US-6570036-$.DID. OR US-20030162226-$.DID. OR US-20030166581-$.DID. OR US-20030224006-$.DID. OR US-20040019211-$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:04
S79	20	US-20040106053-$.DID. OR US-20040106055-$.DID. OR US-20040171062-$.DID. OR US-20040176335-$.DID. OR US-20050070551-$.DID. OR US-20050181041-$.DID. OR US-20050169982-$.DID. OR US-20050252649-$.DID. OR US-20050256127-$.DID. OR US-6559293-$.DID. OR US-6699840-$.DID. OR US-20040053853-$.DID. OR US-3536809-$.DID. OR US-3598123-$.DID. OR US-3845770-$.DID. OR US-3916899-$.DID. OR US-4008719-$.DID. OR US-4267179-$.DID. OR US-4764604-$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:07

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S80	15	US-4916134-$.DID. OR US-5006513-$.DID. OR US-5059595-$.DID. OR US-5073543-$.DID. OR US-5120548-$.DID. OR US-5354556-$.DID. OR US-5414997-$.DID. OR US-5474997-$.DID. OR US-5591767-$.DID. OR US-5633015-$.DID. OR US-5639476-$.DID. OR US-5661151-$.DID. OR US-5674533-$.DID. OR US-5707975-$.DID. OR US-5733566-$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:08
S81	35195	bipyridine phthalaldehyde nicotinamide saccharrin pyridinecarboxylic adj acid nitroisophthalic adj acid adamantanetetracarboxylic adj acid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:11
S82	59011	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:12
S84	2951	S81 S82	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S85	1424	co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S86	39	S84 S85	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S87	147955	(active pharmaceutical ingredient) or API	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:29
S88	725	S87 S81	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:29
S89	35	S88 S85	US-PGPUB;	AND	OFF	2010/06/17 10:29

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S90	3689	(active pharmaceutical ingredient)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:31
S91	143	S81 S90	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S92	23	S91 S85	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S93	11	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S94	6	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S95	5	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S96	14	S93 S94 S95	US-PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S97	103	S85 S81	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 11:41
S98	14	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S99	6	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S100	5	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S101	17	S98 S99 S100	US-PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S102	160	ferrocene co-crystal	US-PGPUB;	AND	ON	2013/07/26 12:46

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S103	0	S102 and @pd< "20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2013/07/26 12:46
S104	2	S102 and @pd< "20030301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2013/07/26 12:47
S105	24	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S106	8	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S107	7	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S108	27	S105 S106 S107	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/04/04 13:43
S109	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/04/04 13:44
S110	0	S108 S109	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/04/04 13:44
S111	10	S108 and cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/04/04 13:44
S112	12	gb "2169601"	US-PGPUB; USPAT; USOCR;	ADJ	ON	2014/04/04 14:46

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			FPRS; EPO; JPO; DERWENT			
S113	2	("5631250").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/04/07 10:07
S114	4	GB "1297261"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2014/04/07 10:20
S115	0	("("6559293" | "2711411" | "20040106052" | "20040171062" | "4267179" | "4916134" | "5059595" | "5120548" | "5332834" | "5354556" | "5661151" | "5674533" | "6001996" | "2665277" | "5994365" | "20070026078" | "20070293674" | "4853379" | "5935933" | "5952187" | "6287295" | "5635535" | "6294186" | "4504614" | "5190583" | "20030162226" | "4008719" | "5073543" | "5412094" | "5591767" | "7078526" | "7205413" | "20020107250" | "20020119193" | "5242942" | "5641512" | "5753693" | "6294192" | "6365185" | "6403640" | "6420394" | "6488962" | "5006513" | "5177262" | "5338644" | "5474997" | "6268385" | "7446107" | "20020034542" | "20060223794" | "20090088443" | "5324351" | "5384327" | "5631250" | "5703232" | "5760007" | "5932598" | "5998380" | "6613790" | "6770705" | "20030224006" | "20040053853" | "20040106055" | "20050256127" | "3916899" | "4368197" | "4994604" | "5733566" | "6570036" | "5023092" | "7452555" | "20020071857" | "20070021510" | "3970651" | "4513006" | "5286493" | "5736541" | "6132420" | "6342249" | "6413965" | "7459449" | "20030096014" | "20040019211" | "20040106053" | "3536809" | "3598123" | "5414997" | "5523090" | "5998413" | "6699840" | "20020006951" | "20020015735" | "20070015841" | "5466823" | "5972986" | "6201010" | "6283953" | "6319903" | "6503884" | "20100331285" | "4385138" | "4442244" | "5358982" | "20040176335" | "20050181041" | "5380867" | "5633015" | "5639476" | "20020013357" | "20020037925" | "4008321" | "5273760" | "5356467" |	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2014/04/07 11:10

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		"5472712" | "5633272" | "5985902" | "6054136" | "6270787" | "6333050" | "7132579" | "6376616" | "20050070551" | "20050169982" | "20050252649" | "3845770" | "5614342" | "3020420" | "20070059356" | "6071537" | "6156781" | "6245357" | "6323266" | "6348458" | "6368626" | "6375978" | "6579895" | "6913830" | "20050070551" | "4198507" | "4764604" | "5707975" | "5521207" | "20020042446" | "20030069190" | "20060134198" | "4925674" | "4927855" | "5366738" | "5510496" | "5563165" | "5760068" | "6191117" | "6384034").PN.").PN.				
S116	0	(("6559293" | "2711411" | "20040106052" | "20040171062" | "4267179" | "4916134" | "5059595" | "5120548" | "5332834" | "5354556" | "5661151" | "5674533" | "6001996" | "2665277" | "5994365" | "20070026078" | "20070293674" | "4853379" | "5935933" | "5952187" | "6287295" | "5635535" | "6294186" | "4504614" | "5190583" | "20030162226" | "4008719" | "5073543" | "5412094" | "5591767" | "7078526" | "7205413" | "20020107250" | "20020119193" | "5242942" | "5641512" | "5753693" | "6294192" | "6365185" | "6403640" | "6420394" | "6488962" | "5006513" | "5177262" | "5338644" | "5474997" | "6268385" | "7446107" | "20020034542" | "20060223794" | "20090088443" | "5324351" | "5384327" | "5631250" | "5703232" | "5760007" | "5932598" | "5998380" | "6613790" | "6770705" | "20030224006" | "20040053853" | "20040106055" | "20050256127" | "3916899" | "4368197" | "4994604" | "5733566" | "6570036" | "5023092" | "7452555" | "20020071857" | "20070021510" | "3970651" | "4513006" | "5286493" | "5736541" | "6132420" | "6342249" | "6413965" | "7459449" | "20030096014" | "20040019211" | "20040106053" | "3536809" | "3598123" | "5414997" | "5523090" | "5998413" | "6699840" | "20020006951" | "20020015735" | "20070015841" | "5466823" | "5972986" | "6201010" | "6283953" | "6319903" | "6503884" | "20100331285" | "4385138" | "4442244" | "5358982" | "20040176335" | "20050181041" | "5380867" | "5633015" | "5639476" | "20020013357" | "20020037925" | "4008321" | "5273760" | "5356467" | "5472712" | "5633272" | "5985902" |	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/04/07 11:10

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		"6054136" | "6270787" | "6333050" | "7132579" | "6376616" | "20050070551" | "20050169982" | "20050252649" | "3845770" | "5614342" | "3020420" | "20070059356" | "6071537" | "6156781" | "6245357" | "6323266" | "6348458" | "6368626" | "6375978" | "6579895" | "6913830" | "20050070551" | "4198507" | "4764604" | "5707975" | "5521207" | "20020042446" | "20030069190" | "20060134198" | "4925674" | "4927855" | "5366738" | "5510496" | "5563165" | "5760068" | "6191117" | "6384034").PN.").PN.				
S117	467	("6559293" | "2711411" | "20040106052" | "20040171062" | "4267179" | "4916134" | "5059595" | "5120548" | "5332834" | "5354556" | "5661151" | "5674533" | "6001996" | "2665277" | "5994365" | "20070026078" | "20070293674" | "4853379" | "5935933" | "5952187" | "6287295" | "5635535" | "6294186" | "4504614" | "5190583" | "20030162226" | "4008719" | "5073543" | "5412094" | "5591767" | "7078526" | "7205413" | "20020107250" | "20020119193" | "5242942" | "5641512" | "5753693" | "6294192" | "6365185" | "6403640" | "6420394" | "6488962" | "5006513" | "5177262" | "5338644" | "5474997" | "6268385" | "7446107" | "20020034542" | "20060223794" | "20090088443" | "5324351" | "5384327" | "5631250" | "5703232" | "5760007" | "5932598" | "5998380" | "6613790" | "6770705" | "20030224006" | "20040053853" | "20040106055" | "20050256127" | "3916899" | "4368197" | "4994604" | "5733566" | "6570036" | "5023092" | "7452555" | "20020071857" | "20070021510" | "3970651" | "4513006" | "5286493" | "5736541" | "6132420" | "6342249" | "6413965" | "7459449" | "20030096014" | "20040019211" | "20040106053" | "3536809" | "3598123" | "5414997" | "5523090" | "5998413" | "6699840" | "20020006951" | "20020015735" | "20070015841" | "5466823" | "5972986" | "6201010" | "6283953" | "6319903" | "6503884" | "20100331285" | "4385138" | "4442244" | "5358982" | "20040176335" | "20050181041" | "5380867" | "5633015" | "5639476" | "20020013357" | "20020037925" | "4008321" | "5273760" | "5356467" | "5472712" | "5633272" | "5985902" | "6054136" | "6270787" | "6333050" |	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/04/07 11:12

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		"7132579" | "6376616" | "20050070551" | "20050169982" | "20050252649" | "3845770" | "5614342" | "3020420" | "20070059356" | "6071537" | "6156781" | "6245357" | "6323266" | "6348458" | "6368626" | "6375978" | "6579895" | "6913830" | "20050070551" | "4198507" | "4764604" | "5707975" | "5521207" | "20020042446" | "20030069190" | "20060134198" | "4925674" | "4927855" | "5366738" | "5510496" | "5563165" | "5760068" | "6191117" | "6384034").PN.				
S118	18	S117 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/04/07 11:13
S119	189	carbamazepine DMSO co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/12/12 13:15
S120	8	carbamazepine DMSO co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	ON	2014/12/12 13:16
S121	0	S119 and @PD<"20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/12/12 13:19
S122	147	transform pharmaceuticals.as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2014/12/12 13:27
S123	6	S122 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/12/12 13:27
S124	18	WO "2004078161"	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2014/12/12 13:53

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			EPO; JPO; DERWENT			
S125	1611	carbamazepine.ti. or carbamazepine.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/12/12 14:03
S126	8069	aspirin.ti. or aspirin.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/12/12 14:03
S127	22	S125 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/12/12 14:04
S128	2	("6559293").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S129	9	aspirin cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S130	22	almarrson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S131	935	almarsson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S132	1409	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S133	31	S131 S132	US-PGPUB; USPAT;	AND	OFF	2015/09/29 10:03

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			USOCR; FPRS; EPO; JPO; DERWENT			
S134	2681771	crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S135	447	S131 S134	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S136	31	aspirin crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S137	25	wo "0151919"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S138	13	wo "0142222"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S139	13907	supramolecul$2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S140	68662	aspirin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S141	698	S139 S140	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S142	8	S139 S140	US-	WITH	OFF	2015/09/29

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			PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT			10:03
S143	13255	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S144	148	S139 S143	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S145	10	heterosynthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S146	106773	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S147	4858	co crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S148	694	S146 S147	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S149	85	S146 S147	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2015/09/29 10:03
S150	2	S148 and @pd< "20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	AND	OFF	2015/09/29 10:03

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			DERWENT			
S151	1409	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S152	266	S146 S151	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S153	464	co crystal.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S154	80	S153 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S155	2083	Pharmaceutical co adj crystal compositions drugs	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S156	2497	Pharmaceutical co adj crystal composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S157	2497	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S158	99	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2015/09/29 10:03
S159	48	S157 and @pd< "20030303"	US-PGPUB; USPAT; USOCR;	AND	OFF	2015/09/29 10:03

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			FPRS; EPO; JPO; DERWENT			
S160	846	crystal engineering	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S161	36	S160 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S162	487	S160 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S163	4	S162 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S164	426683	crystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S165	17905	S146 S164	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S166	413	S146 S164	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2015/09/29 10:03
S167	152	S166 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S168	236	S146 S164	US-PGPUB;	WITH	OFF	2015/09/29 10:03

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S169	82	S168 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S170	984	cocrystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S171	190	S146 S170	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S172	30	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S173	9	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S174	8	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S175	78	(40/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S176	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S177	12	(("7452555") or ("7446107") or ("7205413") or ("7078526")).PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S178	23	("2003/0224006").URPN.	USPAT	OR	OFF	2015/09/29 10:03
S179	12	("2665277").PN.	US-PGPUB;	OR	OFF	2015/09/29 10:03

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S180	13255	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S181	106773	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S182	2807	S180 S181	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S183	1409	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2015/09/29 10:03
S184	65	S182 S183	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S185	51165	hydrogen bond	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S186	201	S182 S185	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S187	592	co-crystal former	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03

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S188	139	S181 S187	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S189	13255	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S190	3533	S189 crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S191	164	S189 cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S192	13255	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S193	106773	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S194	2807	S193 S192	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S195	1050	S194 CRYSTAL	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S196	4	(("7452555") or ("7446106") or ("7205413") or ("7078526")).PN.	USPAT	OR	OFF	2015/09/29 10:03
S197	167	phosphate hemihydrate	US-PGPUB; USPAT;	ADJ	OFF	2015/09/29 10:03

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			USOCR; FPRS; EPO; JPO; DERWENT			
S198	106773	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S199	12	S198 S197	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S200	2	(("3028420") or ("5521207")).PN.	USPAT	OR	OFF	2015/09/29 10:03
S201	218	API cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S202	10	ep "0548028"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S203	37	supramolecular synthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S204	20	US-2711411-$.DID. OR US-4198507-$.DID. OR US-4368197-$.DID. OR US-4994604-$.DID. OR US-5177262-$.DID. OR US-5332834-$.DID. OR US-5338644-$.DID. OR US-5380867-$.DID. OR US-5412094-$.DID. OR US-5523090-$.DID. OR US-5614342-$.DID. OR US-5998413-$.DID. OR US-6001996-$.DID. OR US-6268385-$.DID. OR US-6570036-$.DID. OR US-20030162226-$.DID. OR US-20030166581-$.DID. OR US-20030224006-$.DID. OR US-20040019211-$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2015/09/29 10:03
S205	20	US-20040106053-$.DID. OR US-20040106055-$.DID. OR US-20040171062-$.DID. OR US-20040176335-$.DID. OR US-20050070551-$.DID. OR US-20050181041-$.DID. OR US-	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2015/09/29 10:03

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		20050169982-$.DID. OR US-20050252649-$.DID. OR US-20050256127-$.DID. OR US-6559293-$.DID. OR US-6699840-$.DID. OR US-20040053853-$.DID. OR US-3536809-$.DID. OR US-3598123-$.DID. OR US-3845770-$.DID. OR US-3916899-$.DID. OR US-4008719-$.DID. OR US-4267179-$.DID. OR US-4764604-$.DID.				
S206	15	US-4916134-$.DID. OR US-5006513-$.DID. OR US-5059595-$.DID. OR US-5073543-$.DID. OR US-5120548-$.DID. OR US-5354556-$.DID. OR US-5414997-$.DID. OR US-5474997-$.DID. OR US-5591767-$.DID. OR US-5633015-$.DID. OR US-5639476-$.DID. OR US-5661151-$.DID. OR US-5674533-$.DID. OR US-5707975-$.DID. OR US-5733566-$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2015/09/29 10:03
S207	66573	bipyridine phthalaldehyde nicotinamide saccharrin pyridinecarboxylic adj acid nitroisophthalic adj acid adamantanetetracarboxylic adj acid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S208	106773	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetominophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S209	6081	S207 S208	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S210	4288	co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S211	130	S209 S210	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S212	289117	(active pharmaceutical ingredient) or API	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03

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S213	1853	S212 S207	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S214	115	S213 S210	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S215	13255	(active pharmaceutical ingredient)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2015/09/29 10:03
S216	537	S207 S215	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S217	85	S216 S210	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S218	30	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S219	9	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S220	8	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S221	33	S218 S219 S220	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S222	389	S210 S207	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2015/09/29 10:03
S223	30	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S224	9	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03

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S225	8	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S226	33	S223 S224 S225	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S227	324	ferrocene co-crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2015/09/29 10:03
S228	0	S227 and @pd<"20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2015/09/29 10:03
S229	2	S227 and @pd<"20030301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2015/09/29 10:03
S230	30	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S231	9	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S232	8	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2015/09/29 10:03
S233	33	S230 S231 S232	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/09/29 10:03
S234	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S235	0	S233 S234	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2015/09/29 10:03
S236	13	S233 and cocrystal	US-PGPUB; USPAT;	AND	ON	2015/09/29 10:03

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			USOCR; FPRS; EPO; JPO; DERWENT			
S237	14	gb "2169601"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2015/09/29 10:03
S238	4	("5631250").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03
S239	4	GB "1297261"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2015/09/29 10:03
S240	0	("("6559293" | "2711411" | "20040106052" | "20040171062" | "4267179" | "4916134" | "5059595" | "5120548" | "5332834" | "5354556" | "5661151" | "5674533" | "6001996" | "2665277" | "5994365" | "20070026078" | "20070293674" | "4853379" | "5935933" | "5952187" | "6287295" | "5635535" | "6294186" | "4504614" | "5190583" | "20030162226" | "4008719" | "5073543" | "5412094" | "5591767" | "7078526" | "7205413" | "20020107250" | "20020119193" | "5242942" | "5641512" | "5753693" | "6294192" | "6365185" | "6403640" | "6420394" | "6488962" | "5006513" | "5177262" | "5338644" | "5474997" | "6268385" | "7446107" | "20020034542" | "20060223794" | "20090088443" | "5324351" | "5384327" | "5631250" | "5703232" | "5760007" | "5932598" | "5998380" | "6613790" | "6770705" | "20030224006" | "20040053853" | "20040106055" | "20050256127" | "3916899" | "4368197" | "4994604" | "5733566" | "6570036" | "5023092" | "7452555" | "20020071857" | "20070021510" | "3970651" | "4513006" | "5286493" | "5736541" | "6132420" | "6342249" | "6413965" | "7459449" | "20030096014" | "20040019211" | "20040106053" | "3536809" | "3598123" | "5414997" | "5523090" | "5998413" | "6699840" | "20020006951" | "20020015735" | "20070015841" | "5466823" |	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2015/09/29 10:03

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		"5972986" | "6201010" | "6283953" | "6319903" | "6503884" | "20100331285" | "4385138" | "4442244" | "5358982" | "20040176335" | "20050181041" | "5380867" | "5633015" | "5639476" | "20020013357" | "20020037925" | "4008321" | "5273760" | "5356467" | "5472712" | "5633272" | "5985902" | "6054136" | "6270787" | "6333050" | "7132579" | "6376616" | "20050070551" | "20050169982" | "20050252649" | "3845770" | "5614342" | "3020420" | "20070059356" | "6071537" | "6156781" | "6245357" | "6323266" | "6348458" | "6368626" | "6375978" | "6579895" | "6913830" | "20050070551" | "4198507" | "4764604" | "5707975" | "5521207" | "20020042446" | "20030069190" | "20060134198" | "4925674" | "4927855" | "5366738" | "5510496" | "5563165" | "5760068" | "6191117" | "6384034").PN.").PN.				
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To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Nov 20, 2019 03:36:33 AM

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	NOA	11/20/2019	U0157.70023US02

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PRINTER RUSH
(PTO ASSISTANCE)

Application: 14179862	Examiner: Javanmard	GAU: 1627
From:	Location: IDC	Creation Date: 01/21/2020

Week Date: 11/25/2019

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	02/13/2014	[ ] Foreign Priority
[X] CLM	04/01/2016	[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

1. Please initial/line through citations on IDS 2/13/14.
2. Renumbered claims 2-4, 6-8, and 14 (original claims 38-40, 42-44, and 50) depend on renumbered claim 15 (original claim 52). A claim can not depend on a subsequent renumbered claim.
Thank you.

[XRUSH] Response:

Initials: _____

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/179,862	Zaworotko et al.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14/179,862	Zaworotko et al.
	Examiner	**Art Unit**
	SAHAR JAVANMARD	1627

CLAIM		DATE								
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FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 1 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

1627 Sahar Javanmard

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
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		5,273,760		Oshlack et al.	12-28-1993
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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. 10/378,956, 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. /S.J./

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
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		5,324,351		Oshlack et al.	06-28-1994
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		5,760,068		Talley et al.	06-02-1998

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. 10/378,956, 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).

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FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	3	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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				FIRST NAMED INVENTOR: Michael J. Zaworotko	
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NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346

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	*	ZAMAN, M. B. et at "Linear hydrogen-bonded molecular tapes in the cocrystals of squaric acid with 4,4'-dipyridylacetylene and 1,2-bis(4-pyridyl) ethylene" *Acta Cryst.*, 2001, pp. 621-624, Vol. C57.	
	*	ZAMAN, M.B. et al. "Crystal Engineering Using Anilic Acids and Dipyridyl Compounds through a New Supramolecular Synthon" *J. Org. Chem.*, 2001, 66:5987-5995.	
	*	ZAWOROTKO, M. J. "Crystal Engineering of Diamondoid Networks", *Chem. Soc. Rev.*, 1994, pp. 283-288, Vol. 23.	
	*	ZAWOROTKO, Michael J., "Binary Crystals by Design," Abstracts of Papers, 23rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, IEC-030.	
	*	ZERKOWSKI, J. et al. "Design of organic structures in the solid state: hydrogen-bonded molecular "tapes"[1]" *J. Am. Chem. Soc.*, 1990, pp. 9025-9026, Vol. 112.	
	*	ZERKOWSKI, J. et al. "Design of organic structures in the solid state: molecular tapes based on the network of hydrogen bonds present in the cyanuric acid•melamine complex" *J. Am. Chem. Soc.*, 1994, pp. 2382-2391, Vol. 116.	
	*	ZERKOWSKI, J. et al. "Investigations into the robustness of secondary and tertiary architecture of hydrogen-bonded crystalline tapes" *Chem. Mater*, 1994, pp. 1250-1257, Vol. 6.	
	*	ZERKOWSKI, J. et al. "New varieties of crystalline architecture produced by small changes in molecular structure in tape complexes of melamines and barbiturates" *J. Am. Chem. Soc.*, 1994, pp. 4305-4315, Vol. 116.	
	*	ZERKOWSKI, J. et al. "Polymorphic packing arrangements in a class of engineered organic crystals" Chem. Mater., 1997, pp. 1933-1941, Vol. 9.	
	*	ZERKOWSKI, J. et al. "Solid-state structures of "Rosette" and "Crinkled Tape" motifs derived from the cyanuric acid-melamine lattice" *J. Am. Chem. Soc.*, 1992, pp. 5473-5475, Vol. 114.	
	*	ZERKOWSKI, J. et al. "Steric control of secondary, solid-state architecture in 1:1 complexes of melamines and barbiturates that crystallize as crinkled tapes" *J. Am. Chem. Soc.*, 1994, pp. 4298-4304, Vol. 116.	
	*	ZHANG, R. et al. "Atmospheric new particle formation enhanced by organic acids" *Science*, June 4, 2004, pp. 1487-1490 with additional supporting online material, Vol. 304.	

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. 10/378,956, 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. /S.J./

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	27	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

	*	ZHU, H. et al. "Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 1. theophylline" *International Journal of Pharmaceutics*, 1996, pp. 151-160, Vol. 135.	

[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:
/Sahar Javanmard/	04/07/2014

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. 10/378,956, 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. /S.J./

NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346

PRINTER RUSH
(PTO ASSISTANCE)

Application: 14179862	Examiner: Javanmard	GAU: 1627
From:	Location: IDC	Creation Date: 01/21/2020

Week Date: 11/25/2019

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	02/13/2014	[ ] Foreign Priority
[X] CLM	04/01/2016	[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

1. Please initial/line through citations on IDS 2/13/14.
2. Renumbered claims 2-4, 6-8, and 14 (original claims 38-40, 42-44, and 50) depend on renumbered claim 15 (original claim 52). A claim can not depend on a subsequent renumbered claim.
Thank you.

[XRUSH] Response:

Issues resolved.

Initials: /S.J/

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

UM00000726
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 679 of 725

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	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Attorney Docket Number	U0157.70023US02

Total Number of Pages in This Submission

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] 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):

  Part B - Issue Fee Transmittal

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	February 19, 2020	Reg. No.	73,490

7964026.1

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Cathy Nicholson	(Typed or printed name)
/Cathy Nicholson/	(Signature)
Filed via EFS Web on February 19, 2020	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

TITLE OF INVENTION: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500.00			$500.00	02/20/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
S. Javanmard	1627	

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Wolf, Greenfield & Sacks, P.C.
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE or COUNTRY)
University of South Florida	Tampa, Florida
The Regents of the University of Michigan	Ann Arbor, Michigan

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 23/2825

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /David F. Cauble/ Date February 19, 2020

Typed or printed name David F. Cauble, PhD, JD Registration No. 73,490

7964027.1

Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
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:	U0157.70023US02

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:				
UTILITY APPL ISSUE FEE	2501	1	500	500

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**500**

Electronic Acknowledgement Receipt	
EFS ID:	38630437
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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:	U0157.70023US02
Receipt Date:	19-FEB-2020
Filing Date:	13-FEB-2014
Time Stamp:	15:11:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$500
RAM confirmation Number	E20202IF11351185
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	U015770023US02-TRN-DFC.pdf	24419 3103eaeda0e4d2090080ccdd8e04c5d00da2 98df9	no	1
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	U015770023US02-ISSFEE-DFC.pdf	37460 fadb348fffce55d08473c7674e643873db04 e40c	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30651 b5489d0ba171e45ad3b91ecf3c74ae383ea b1f51	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	92530		

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.

PRINTER RUSH
(PTO ASSISTANCE)

Application: 14179862	Examiner: Javanmard	GAU: 1627
From:	Location: IDC	Creation Date: 02/20/2020

Week Date: 11/25/2019

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	02/13/2014	[ ] Foreign Priority
[ ] CLM		[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

2nd QUERY

Please initial/line through citations on page 2 of 30 (IDS 02/13/2014).

[XRUSH] Response:

Initials: _____

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

UM00000733
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 686 of 725

PRINTER RUSH
(PTO ASSISTANCE)

Application: 14179862	Examiner: Javanmard	GAU: 1627
From:	Location: IDC	Creation Date: 02/20/2020

Week Date: 11/25/2019

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[X] IDS	02/13/2014	[ ] Foreign Priority
[ ] CLM		[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

2nd QUERY

Please initial/line through citations on page 2 of 30 (IDS 02/13/2014).

[XRUSH] Response:

Considered.

Initials: /S.J/

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

UM00000734
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 687 of 725

DOCKET NO.: U0157.70023US02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

Madam:

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 within three months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. § 1.53(d).

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J/

NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 688 of 725

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	Michael J. Zaworotko et al.	U0157.70023US01

†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.

European Search Report for Application No. EP 03711407.1 mailed November 22, 2006 (U0157.70023EP00)
International Search Report for Application No. PCT/US2003/06662 mailed October 24, 2003 (U0157.70023WO00)
***Office Action dated 04/13/2011 in U.S. Application No. 12/861,203**
***Notice of Reasons for Rejection dated 10/08/2009 for Japanese Application No. 2003-572946**

*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. 10/378,956, 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).

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J/

UM00000736
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 689 of 725

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 filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825 under Docket No. U0157.70023US02 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /Edward R. Gates/
Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US02
Date: February 13, 2014
xNDDx

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J/

UM00000737
NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346
Page 690 of 725

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	1	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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		
		2,554,816		Clapp et al.	05-29-1951
		2,665,277		Homeyer et al.	01-05-1954
		2,711,411		Holbert et al.	06-21-1955
		2,980,679		Gianfranco	04-18-1961
		3,028,420		Petrow et al.	04-03-1962
		3,536,809		Schaller et al.	04-09-1991
		3,598,123		Zaffaroni	08-10-1971
		3,845,770		Theeuwes et al.	11-05-1974
		3,916,899		Theeuwes et al.	11-04-1975
		3,970,651		Kaplan et al.	07-20-1976
		4,008,321		Kamishita et al.	02-15-1977
		4,008,719		Theeuwes et al.	02-22-1977
		4,198,507		Barry et al.	04-15-1980
		4,267,179		Heeres et al.	05-12-1981
		4,368,197		Shefter et al.	01-11-1983
		4,513,006		Maryanoff et al.	04-23-1995
		4,764,604		Muller	08-16-1988
		4,792,569		Maryanoff et al.	12-20-1988
		4,853,379		Shroot et al.	08-01-1989
		4,916,134		Heeres et al.	04-10-1990
		4,925,674		Giannini et al.	05-15-1990
		4,927,855		Lafon	05-22-1990
		4,994,604		Tung et al.	02-19-1991
		5,006,513		Hector et al.	04-09-1991
		5,023,092		DuRoss	07-11-1991
		5,059,595		Le Grazie	10-22-1991
		5,073,543		Marshall et al.	12-17-1991
		5,120,548		McClelland et al.	06-09-1992
		5,177,262		Taylor et al.	01-15-1993
		5,242,942		Costanzo et al.	09-07-1993
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NOVARTIS EXHIBIT 1016
Novartis v. Regents, IPR2023-01346

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
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NOVARTIS EXHIBIT 1016
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NOVARTIS EXHIBIT 1016
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FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	25	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 26 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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Sheet	27	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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NOVARTIS EXHIBIT 1016
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Page 717 of 725

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	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 1 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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
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Change(s) applied to document, /A.J./ 3/ 1/2020		3,536,809		Schaller et al.	10/1970 ~~04-09-1991~~
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Sheet 2 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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Change(s) applied to document.
/A.J./
3/6/2020

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 03/25/2020

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

EXAMINER	
JAVANMARD, SAHAR	

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1627	

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Novartis v. Regents, IPR2023-01346
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600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

In re Application of
Zaworotko et al.
Application No. 14/179,862
Filed: 02/13/2014
Attorney Docket No. U0157.70023US02

DECISION ON PETITION

ACCEPTANCE OF COLOR DRAWINGS

This is a decision on the Petition to Accept Color Drawings under 37 C.F.R 1.84 (a) (2), received in the United States Patent and Trademark Office (USPTO) on 13 February 2014.

The petition is **GRANTED**.

A grantable petition under 37 C.F.R. 1.84(a) (2) must meet the following requirements:

1. Payment of the fee set forth under 37 C.F.R. 1.17(h),
2. Submission of three (3) sets of color drawings, or one (1) set of color drawings if filed by EFS-Web, and
3. The first paragraph of the brief description of the drawings in the Specification contains the required language pertaining to colored drawings.

A review of U.S. Patent and Trademark records indicates that each of the above three requirements have been satisfied. Accordingly, the petition under 37 C.F.R. 1.84(a)(2) is GRANTED.

Telephone inquiries relating to this decision may be directed to the undersigned in the Office of Data Management at 571-272-4200 .

/BETTY J POWELL/
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	04/28/2020	10633344	U0157.70023US02	7725

23628 7590 04/08/2020

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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 69 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

University of South Florida, Tampa, FL;
The Regents of the University of Michigan, Ann Arbor, MI;
Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
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14179862	ISSUE.NTF	04/08/2020	U0157.70023US02

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