UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CONCERT PHARMACEUTICALS, INC.
Petitioner

v.

INCYTE CORPORATION
Patent Owner

Case No: Unassigned
U.S. Patent No. 9,662,335

Title: HETEROARYL SUBSTITUTED PYRROLO[2,3-B] PYRIDINES AND PYRROLO[2,3-B] PYRIMIDINES AS JANUS KINASE INHIBITORS

Petition for Post-Grant Review
Under 35 U.S.C. §§321-328 and 37 C.F.R. §42.200 *et seq*.

TABLE OF CONTENTS

LIST OF EXHIBITS

Concert Exhibit #	***Description***
1001	Rodgers, *et al*., "Heteroaryl Substituted Pyrrolo[2,3-B] Pyridines And Pyrrolo[2,3-B] Pyrimidines As Janus Kinase Inhibitors," U.S. Patent No. 9,662,335 (filed June 3, 2016; issued May 30, 2017)
1002	Declaration of Dr. Michael T. Crimmins
1003	Curriculum Vitae for Dr. Michael T. Crimmins
1004	Silverman, I., *et al*., " Deuterated Derivatives of Ruxolitinib," WO 2013/188783 (filed on June 14, 2013; published on December 19, 2013)
1005	Jakafi® Product Label, *in* 2016 Physicians' Desk Reference, 70th ed., pp. 1157-1165
1006	File History for U.S. Application No. 14/711,576 (filed May 13, 2015)
1007	File History for U.S. Application No. 14/274,948 (filed May 12, 2014)
1008	File History for U.S. Application No. 14/020,505 (filed September 6, 2013)
1009	File History for U.S. Application No. 13/076,220 (filed March 30, 2011)
1010	File History for U.S. Application No. 12/549,170 (filed August 27, 2009)
1011	File History for U.S. Application No. 11/637,545 (filed December 12, 2006)
1012	U.S. Provisional Application No. 60/859,404 (filed November 16, 2006)
1013	U.S. Provisional Application No. 60/856,872 (filed November 3, 2006)
1014	U.S. Provisional Application No. 60/850,625 (filed October 10, 2006)
1015	U.S. Provisional Application No. 60/810,231 (filed June 2, 2006)
1016	U.S. Provisional Application No. 60/749,905 (filed December 13, 2005)
1017	File History for U.S. Application No. 15/173,057

Concert Exhibit #	***Description***
1018	Blake, M., *et al*., "Studies with Deuterated Drugs," *J. Pharm. Sci*., 64(3):367-91 (1975)
1019	Gant, T., "Using Deuterium in Drug Discovery," *J. Med. Chem*., 57(9):3595-11 (2014)
1020	Filer, C., "Isotopic Fractionation of Organic Compounds in Chromatography," *J. Labelled Cpd. Radiopharm.* 42(2):169-97 (1999)
1021	Kushner, D., *et al*., "Pharmacological uses & perspectives of heavy water & deuterated compounds," *Can. J. Physiol. Pharmacol.* 77(2):79-88 (1999)
1022	Naicker, S., *et al*., "Deuterated Rapamycin Compounds, Method and Uses Thereof," U.S. Patent No. 6,939,878 (filed January 9, 2004; issued September 6, 2005)
1023	Foster, A., "Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design," *Advances in Drug Research* 14:1-40 (1985)
1024	Hallén, B., *et al*., "Single-Dose Pharmacokinetics of Terodiline, Including a Stable Isotope Technique for Improvement of Statistical Evaluations," *Biopharmaceutics & Drug Disposition*, 9:229-50, (1988)
1025	Atzrodt, J., *et al*., "The Renaissance of H/D Exchange," *Angew. Chem. Int. Ed.* 46:7744 – 65 (2007)
1026	Giles, R., *et al*., "Hydrogen–deuterium exchange of aromatic amines and amides using deuterated trifluoroacetic acid," *Tetrahedron Letters* 56(5):747–49 (2015)
1027	Sundararaman, P. *et al.*, "Optical Rotatory Dispersion Studies. 133[1.] Deuterium Octant Contributions in Cyclohexanones," *J. Org. Chem*. 45(26): 5231-36 (1980)
1028	Kennedy, N. and Cohen, T., "The Stereoselective Reductions of Ketones to the Most Thermodynamically Stable Alcohols Using Lithium and Hydrated Salts of Common Transition Metals," *J. Org. Chem.* 80(16): 8134 -41 (2015)
1029	"Chapter 3: Labelling with Deuterium and Tritium," Hanson, J.R., *in* The Organic Chemistry of Isotopic Labelling, pp. 40-61, Cambridge, UK: RSC Publishing (2011)

Concert Exhibit #	***Description***
1030	Földesi, A., *et al*., "The Synthesis of Deuterionucleosides," *Nucleosides, Nucleotides & Nucleic Acids* 19:1615-56 (2000)
1031	Tung, R., *et al*., "Substituted Xanthine Derivatives," U.S. Patent No. 8,952,016 (filed September 1, 2010; February 10, 2015)
1032	Gant, T., *et al*., "Substituted N-Aryl Pyridinones," U.S. Patent No. 8,383,823 (filed June 20, 2008; issued February 26, 2013)
1033	Gant, T., *et al*., "Substituted Phenethylamines With Serotoninergic and/or Norepinephrinergic Activity," U.S. Patent No. 7,456,317 (filed November 30, 2006; issued November 25, 2008)
1034	Navarro, I., *et al*., "Insect Desaturases as Unique Analytical Tools To Unravel the Stereochemical Course of the Reduction of Vicinal Ditosylates with Lithium Aluminum Deuteride, " *Angew. Chem. Int. Ed.* 38: 162-166 (1999)
1035	Jones, A., *et al*., "HPLC Isotope Effects and Macrocycles: The Case of Echinocandin B," *Journal of Labelled Compounds and Radiopharmaceuticals* XXXI(4):297-303 (1992)
1036	Mulzer, J., *et al*., "A Mechanistically Unusual Base Induced [1,3]-H-Shift in Homoallylic Ethers," *Tetrahedron Lett*. 38(31):5469-72 (1997)
1037	Baldwin, J. and Black, K., "Stereoselective Preparation of *trans* -2,3-Dideuterioprop-2-en-1-ol," *J. Org. Chem.* 48(13): 2778-79 (1983)
1038	Dauphin, G., *et al*., "Microbiological Synthesis of Optically Active 3-Deuterio-cycloalkanones," *JCS Chem. Comm.* 7:318-19 (1980)
1039	Dauphin, G., *et al*., "Microbiological Synthesis and Circular Dichroism of Optically Active 2-Deuterio-Cycloalkanones," *Tetrahedron Lett*. 21(44): 4275-78 (1980)
1040	Hong, P, *et al*., "Size-Exclusion Chromatography for the Analysis of Protein Biotherapeutics and their Aggregates," *J. Liq. Chromatogr. Relat. Technol.* 35: 2923-50 (2012)
1041	Yarnell, A., "Heavy Hydrogen Drugs Turn Heads, Again," *Chemical & Engineering News* pp.36, 38-39 June 22, 2009
1042	Hine, J., *et al*., "Stereoselective Bifunctional Catalysis of Dedeuteration of Cyclopentanone-*2,2,5,5-d*$_4$ by (1*R*,2*S*,3*R*,4*R*)-3-Dimethylaminomethyl-1, 7, 7 -trimethyl-2-norbornanamine[1]," *J. Am. Chem. Soc*. 102(13):4403-09 (1980)

Concert Exhibit #	***Description***
1043	Liu, *et al*., "Processes And Intermediates For Making a JAK Inhibitor," U.S Patent No. 8,987,443 (filed March 5, 2014; issued March 24, 2015)
1044	Sing, L., *et al*., "Demonstration of a Conformational Isotope Effect In Deuterium Substituted Cyclopentanones," *Tetrahedron* 37: 181-89 (1981)
1045	"Chapter 3: Hydrogen," Greenwood and Earnshaw, *in* Chemistry of the Elements 2nd Ed. pp. 32-67 Oxford: Butterworth Heinemann (1997)
1046	Deutsch, J. and Mandelbaum, A., "The Synthesis of 2,2-d_2-cyclohexanone and 2,2-d_2-cyclopentanone," *Tetrahedron Letters* 17(13): 1351-52 (1969)
1047	"Chapter 7: Isolation and Purification of Compounds," Pedersen, S.F. & Myers, A.M., *in* Understanding the Principles of Organic Chemistry: A Laboratory Course, pp. 89-140, United States: Cengage Learning (2011)
1048	"Technique 3 Crystallization: Purification of Solids," Pavia, Lampman & Kriz, *in* Introduction to Organic Laboratories Techniques, 3rd ed., pp.522-645, United States: Saunders College Publishing (1988)
1049	Cartoni, G. and Ferreti, I., "Separation of Isotopic Molecules by High-Performance Liquid Chromatography," *J. Chromatography* 122: 287-91 (1976)
1050	"Ch. 2 Mechanism of Retention," Scott, R.P.W., *in* Chromatographic Science Series Vol. 70: Techniques and Practice of Chromatography pp. 27-67, New York: Marcel Dekker, Inc. (1995)
1051	Kimata, K., *et al*., "Direct Chromatographic Separation of Racemates on the Basis of Isotopic Chirality," *Anal. Chem.* 69: 2610-12 (1997)
1052	Czarnik, A., "Deuterium-Enriched Atorvastatin," U.S. Patent No. 7,745,480 (filed April 4, 2008; issued June 29, 2010)
1053	Excerpt from *Academic Press Dictionary of Science and Technology*, Academic Press, Inc., p. 1154 (1992)
1054	"Chapter 34: Mass Spectrometry," Streitwieser, A., Heathcock, C. & Kosower, E., *in* Introduction to Organic Chemistry 4th ed. pp. 1179-1200, New York: Macmillan Publishing Company (1992)

I. INTRODUCTION

Concert Pharmaceuticals, Inc. submits this Petition for Post-Grant Review seeking cancellation of claims 1-6 of U.S. Patent No. 9,662,335 ("the '335 patent"), issued to Incyte Corporation. CON1001.

This Petition, supported by the testimony of Dr. Michael Crimmins (CON1002), who is an expert with over 30 years of synthetic organic chemistry experience, demonstrates why the '335 patent—and every application in the priority chain to which the '335 patent claims benefit—fails to adequately describe and enable the full scope of the vast genus of deuterated ruxolitinib analogs now claimed. As a direct consequence, the '335 patent is PGR-eligible because the '335 patent claims cannot claim priority benefit to a filing date *before* June 3, 2016. The challenged claims should also be cancelled under 35 U.S.C. §112(a) because they overreach the disclosure of the '335 patent.

More than 10 years after Incyte filed its earliest priority application—and just one month after Concert announced initiation of Phase 1 clinical testing of a deuterated ruxolitinib analog (CTP-543) to treat alopecia areata—Incyte cobbled together disparate and unrelated aspects of its disclosure to file claims to cover Concert's clinical drug candidate. Those claims issued in the '335 patent and encompass a vast genus of deuterated analogs of ruxolitinib, where one or more of the 18 hydrogen atoms in ruxolitinib are replaced by deuterium.

The challenged claims encompass this vast genus of *more than* 500,000 (claims 1 and 2) and *more than* 250,000 (claims 3-6) individual deuterated analogs, as well as various mixtures of such analogs, far exceeding what Incyte possessed or enabled. The striking lack of blaze marks in the '335 patent specification pointing to *any* deuterated ruxolitinib analog underscores Incyte's use of hindsight to piece together Concert's invention from the '335 patent's scant disclosure. The deuterated ruxolitinib analogs Incyte now claims were never described as an integrated whole. Instead, the various elements of the claimed compounds appear only as undistinguished members among laundry-lists scattered throughout the specification: ruxolitinib is one of the many trillion compounds encompassed by Formula I, and among the 600 or so compounds in the Examples, and deuterium is one of 21 isotopes and radionuclides. Nothing in the specification guides the skilled artisan to combine these unrelated disclosures, or to focus on the specific elements claimed by Incyte. Incyte's *post hoc* combination of disparate parts of a specification is prohibited by the written description requirement of 35 U.S.C. §112(a), justifying institution of trial and cancellation of the challenged claims. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336 (Fed. Cir. 2013).

Having failed through its written description to guide one of skill in the art to the genus of compounds it now claims, Incyte likewise failed to disclose any

method of making the myriad deuterated ruxolitinib analogs. The specification is devoid of any specific guidance or examples of how to deuterate any compound of Formula I, let alone ruxolitinib, and the knowledge in the field was not sufficient to supplement the lacking disclosure in the '335 patent. With the deuterium substitution chemistry available in 2016, and even today, the skilled artisan cannot make at least 95% of the claimed analogs. At best, the skilled artisan with knowledge of all of the chemical techniques known at the time for making deuterated compounds could have made only a tiny fraction of the claim scope. This failure violates the enablement requirement of 35 U.S.C. §112(a), further justifying institution of trial and cancellation of all challenged claims. *See Storer v. Clark*, No. 2015-1802, 2017 WL 2661863 (Fed. Circ. June 21, 2017).

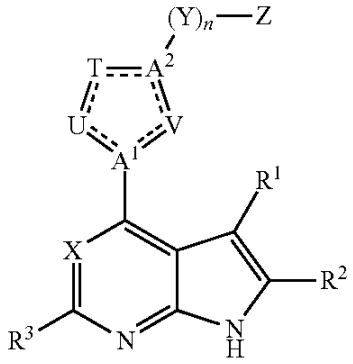
Finally, intervening prior art (WO 2013/188783 A1; "Silverman" (CON1004)), anticipates challenged claims 1-4, providing a third ground for cancelling these claims.

Therefore, Petitioner requests institution of PGR and cancellation of the challenged claims under 35 U.S.C. §§112(a) and 102(a)(1).

II. SUMMARY OF THE '335 PATENT AND CHALLENGED CLAIMS

The '335 patent, which shares an identical specification with each of the parent applications beginning with U.S. Appl. No. 11/637,545 (CON1011), relates

to a vast genus of heteroaryl substituted pyrrolo[2,3-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrimidines that fall within Formula I:



(I)

CON1001, 7:1-27, CON1006, 7-12; CON1007, 7-12; CON1008, 7-12; CON1009, 7-12; CON1010, 7-12; CON1011, 7-12.[1] Formula I encompasses *many trillions* of potential compounds based on the substituent group options for A^1, A^2, T, U, V, X, Y, Z, R^1, R^2, and R^3 recited at col. 7-27 of the patent.[2] CON1001, 7:1–27; CON1002, ¶¶25, 141, 158.

[1] For all cited patents, the number before the colon refers to the column number, and the number(s) after the colon refer to line number(s).

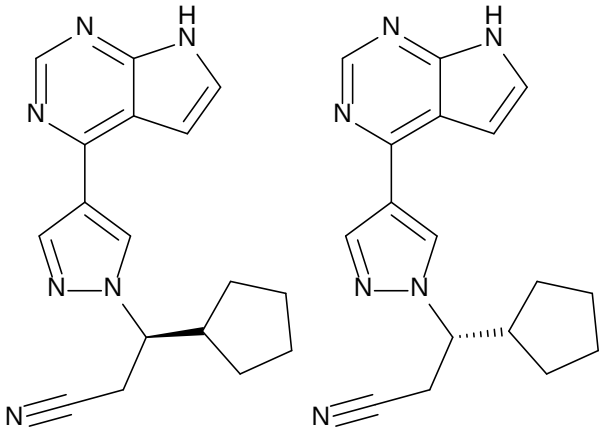
[2] The number of potential compounds encompassed by Formula I is estimated by multiplying the number of options listed under each substituent group, i.e., $A^1 * A^2 * T * U * V * X * Y * Z * R^1 * R^2 * R^3$. CON1002, ¶25.

The '335 patent also discloses hundreds of compounds (about 600 compounds in Examples 1-750), among them ruxolitinib. CON1001, 69:5–366:6; CON1002, ¶¶26, 31, 142, 158; *see also* CON1005, 1161. However, every one of these compounds has isotopes only in their natural isotopic abundance. CON1001, 69:5-366:6; CON1002, ¶¶27, 142. The '335 patent does not describe a single compound having an isotopic replacement, let alone ruxolitinib with deuterium substitution. CON1001, 69:5–366:6; CON1002, ¶¶27, 142, 160. The '335 patent only mentions deuterium as an example of an isotope of hydrogen, and includes it in a lengthy list of other potential isotopes, which "include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I, and ^{131}I." CON1001, 68:4-9; *see also* 32:60-64; CON1002, ¶¶27, 142, 160-161.

The '335 patent provisional applications have a substantially similar disclosure. *See* CON1002, ¶¶157-164; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111. They too disclose Formula I, and hundreds of compounds in the Examples (increasing from approximately 230 to 530 compounds from Appl. Nos. 60/749,905 to 60/859,404), one of which is ruxolitinib. *See* CON1002, ¶¶157-164; CON1012, 6-11, 52-221; CON1013, 6-11, 52-221; CON1014, 6-10, 50-219; CON1015, 6-10, 43-157; CON1016, 6-9, 27-28.

However, as in the parent applications, every compound in the provisional applications has hydrogen only in its natural isotopic abundance. *See id*. None of the provisional applications describes a single compound having an isotopic replacement, let alone ruxolitinib with deuterium substitution. *See id*. Like the parent applications, the provisional applications mention deuterium only as an example of an isotope of hydrogen, and include it in a lengthy list of other potential isotopes. CON1002, ¶¶157-164; *see* CON1012, 29; CON1013, 29; CON1014, 27; CON1015, 21; CON1016, 16.

Independent claim 1 recites "[a] compound, which is 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, wherein *one or more hydrogen atoms are replaced by deuterium*; or a pharmaceutically acceptable salt thereof." CON1001, 366:14-34 (emphasis added); CON1002, ¶¶18-23, 75-80. Independent claims 3 and 5 differ from claim 1 only in that they recite the (3R) and (3S) enantiomers, respectively, of the compound of claim 1. *Id.* These (3R) and (3S) enantiomers are depicted below:



(3R) (3S)

See CON1001, 109:1-20; CON1002, ¶23. Claims 2, 4, and 6, which depend from claims 1, 3, and 5, respectively, additionally recite a pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. CON1001, 366:14-34; CON1002, ¶¶18-23; 75-80.

The '335 patent claims were cobbled together by taking one compound (ruxolitinib, the propanenitrile compound named in claim 1[3]) and one isotope

[3] Technically, "ruxolitinib" is the name given to the non-isotopically enriched (3R) form of the propanenitrile compound. For ease of reference, this Petition uses "ruxolitinib" to refer to the non-isotopically enriched named compound of claim 1 that includes its (3R) and (3S) enantiomers, unless otherwise designated with particularity.

(deuterium) from the broad and disparate disclosures of potential compounds and isotopes. CON1001, 7:1-27, 32:60-64, 67:56-68:16, 69:7-366:6, 366:14-34; CON1002, ¶¶18-27, 157-158. Although ruxolitinib is among the approximately 600 compounds in Examples 1-750, the '335 patent does not provide any guidance or experimental data suggesting that ruxolitinib is superior to the others or would be considered a lead compound CON1002, ¶¶26, 157-158; *see* CON1001, 69:5–366:6. Nor does the '335 patent provide any guidance or experimental data suggesting that deuterated analogs of the disclosed compounds are particularly preferred. CON1002, ¶¶24-27, 157-158; *see* CON1001, 69:5–366:6.

Ruxolitinib contains 18 hydrogen atoms, one or more of which are replaced by deuterium according to the '335 patent claims. CON1001, 366:14-34; CON1002, ¶¶77-79, 82-84. The challenged claims do not specify the number of hydrogen atoms to be replaced, the positions of the hydrogen atoms that are to be replaced, or any specific combinations of replacements. CON1001, 366:14-34; CON1002, ¶¶75-80. By requiring one or more hydrogen atoms to be replaced by deuterium, the number of substitution patterns of deuterium is so broad and complex that claim 1 covers a very large genus. CON1001, 366:14-34; CON1002, ¶¶75-80, 82-84, 91, 99, 150. Claims 3 and 5, reciting the (3R) and (3S) enantiomers, respectively, are barely more limited. *Id*. The claim breadth results from the number of hydrogen atoms that can be replaced, the number of potential

combinations for replacement, and because it also encompasses mixtures of the deuterated ruxolitinib analogs having any deuterium substitution pattern. *Id*.

III. BACKGROUND

Isotopes are variants of an element that have the same number of protons, but differ in the number of neutrons in their nuclei. CON1002, ¶32; CON1054, 1184; CON1022, 2:32-34. Many elements, such as hydrogen, carbon, and nitrogen, exist in multiple isotopic forms. *Id*.

Hydrogen is an element that has three naturally-occurring isotopes: 1) protium (which makes up >99.9% of naturally occurring hydrogen); 2) deuterium; and 3) tritium. CON1002, ¶33; CON1019, 3596, 3605; CON1033, 5:51-55; CON1054, 1184. A protium atom has a single proton and a single electron, while a deuterium atom has a single proton, a single electron, as well as a single neutron. CON1002, ¶33; CON1018, 368; CON1019, 3596, 3599; CON1022, 2:31-34. Thus, a protium atom and a deuterium atom differ by a single neutron, which increases the molecular weight of a compound by 1 g/mol for each deuterium atom replacement of a hydrogen atom. CON1002, ¶¶33-34; CON1018, 368; CON1019, 3595-3596, 3599, 3608; CON1022, 2:31-34; CON1053, 1154. The term "hydrogen" is used herein to refer to natural abundance hydrogen, which is essentially protium. Because hydrogen and deuterium differ from each other by only a single neutron, analogs of compounds that differ by only a few deuterium

atoms have nearly identical physical properties. CON1002, ¶¶32-34; CON1018, 368, 365; CON1019, 3596-3600; CON1020, 169, 186; CON1022, 2:31-34; CON1053, 1154; CON1054, 1183-1185. These properties include size, polarity, vapor pressure, and solubility. *See id*.

Recrystallization, chromatography, distillation, extraction, and sublimation are known separation techniques available to a person of ordinary skill in the art (POSA) today, as well as before June 3, 2016. These separation techniques rely on differences in physical properties like size, polarity, vapor pressure, and solubility. A POSA using such techniques would generally be unsuccessful in separating analogs that differ by only a few deuterium atoms. Without the ability to separate such analogs, a POSA would not have been able to make at least 95% of the distinct analogs encompassed by the claims, as well as the vast majority of mixtures of those analogs. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183;

CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

IV. CLAIM CONSTRUCTION

Challenged claims 1-6 must be given their broadest reasonable interpretations ("BRI") in light of the specification of the '335 patent. 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-2146 (2016). For the purposes of this PGR only, the following claim construction is submitted. If a term is not explicitly construed below, its plain and ordinary meaning should be applied.

All of the challenged claims recite or require that "one or more hydrogen atoms" of ruxolitinib are replaced by deuterium. CON1001, 366:14-34. Ruxolitinib contains 18 hydrogen atoms. CON1001, 109:1-110:38; CON1002, ¶¶75-79. The BRI for "one or more hydrogen atoms" means any one or any combination of the 18 hydrogen atoms of ruxolitinib may be replaced with deuterium. This BRI flows from the claims themselves and from the specification. CON1001, 366:14-31; CON1002, ¶¶75-79.

Although the claims specify that "one or more hydrogen atoms" are replaced, the claims and specification are silent as to the number of hydrogen atoms to be replaced or the positions of the hydrogen atoms to be replaced.

CON1001, 109:1-110:38; 366:14-34; CON1002, ¶¶75-79. The '335 patent specification does not indicate that any replacement patterns are "preferred," nor does it exclude any hydrogen atoms from potential replacement. CON1001, 109:1-110:38; 366:14-34; CON1002, ¶¶77-79. Thus, there is no basis in the claims or specification to limit the scope of the challenged claims to any subset of hydrogen atom replacements. *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("Without any claim term that is susceptible of clarification by the written description, there is no legitimate way to narrow the property right."). A POSA would consider *each* hydrogen atom as replaceable independently of one another and in any combination. CON1002, ¶77.

The claims thus cover a broad genus of all possible deuterated ruxolitinib analogs. CON1001, 366:14-34; CON1002, ¶¶75-79, 82-84, 91, 150. Discussed below, the genus encompasses a vast number of deuterated ruxolitinib analogs—*more than* 500,000 analogs in claims 1 and 2 and *more than* 250,000 analogs in each of claims 3-6, as well as a nearly infinite number of mixtures of those analogs. *Id*.

V. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. §42.204(b) AND RELIEF REQUESTED

Claims 1-6 are eligible for PGR and are unpatentable for lack of enablement and written description. Additionally, claims 1-4 are unpatentable as anticipated.

Accordingly, Concert requests institution of PGR and cancellation of claims 1-6 on the following grounds:

Ground	*Claims*	*Legal Basis*
1	1-6	Lack of enablement
2	1-6	Lack of written description
3	1-4	Anticipated by Silverman (CON1004)

The grounds are not redundant because each provides a different statutory basis under which the challenged claims are unpatentable.

This petition is supported by the declaration of Dr. Michael Crimmins (CON1002). Dr. Crimmins is an expert in the field of synthetic organic chemistry, especially stereoselective synthetic organic chemistry, and has been for at least 30 years. CON1002, ¶¶6-13; CON1003.

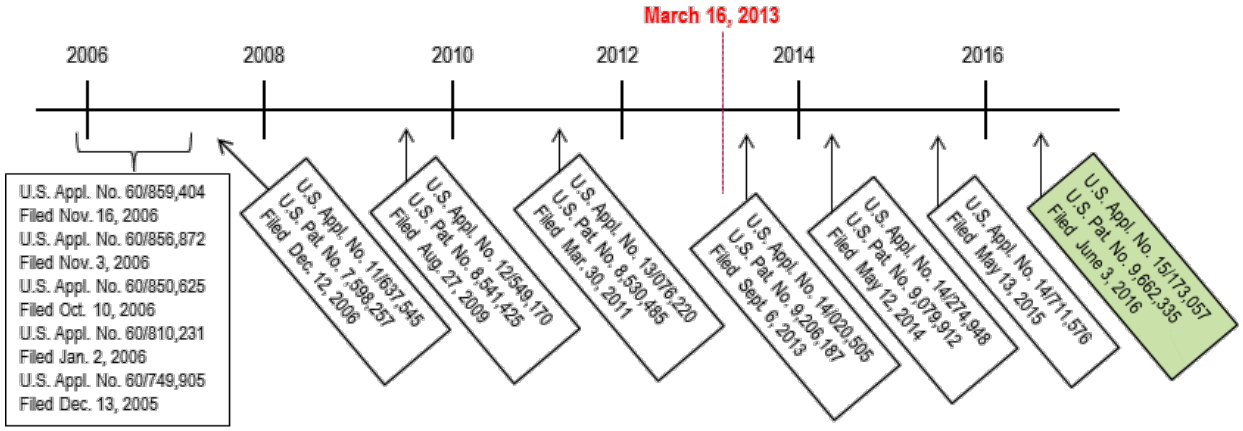
A. The '335 patent is PGR-eligible

U.S. Appl. No. 15/173,057 ("the '057 application"), which issued as the '335 patent, is a transitional application[4] and is eligible for PGR. This is because "the

[4] A transitional application is one filed on or after March 16, 2013, but claiming the benefit of a filing date before March 16, 2013 under 35 U.S.C. §§119, 120, 121, or 365. *See Inguran LLC v. Premium Genetics*, PGR2015-00017, Paper 8, at *10 (P.T.A.B. Dec. 22, 2015) (citing MPEP §§2159.03–2159.04); *see also*

['335] patent contains, . . . at least one claim that was not disclosed in compliance with the written description and enablement requirements of §112(a) *in the earlier application* for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *Inguran LLC v. Premium Genetics*, PGR2015-00017, Paper 8, at *11-16 (P.T.A.B. Dec. 22, 2015) (emphasis added); *see also* AIA §3(n)(1); 35 U.S.C. §100(i); *U.S. Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 17, at *8 (P.T.A.B. Jan. 29, 2016).

Shown below, the '335 patent claims the benefit of several parent and provisional applications. Each of the parent applications, beginning with U.S. Appl. No. 11/637,545, shares the same specification with the '335 patent.



See CON1001, face page.

U.S. Endodontics, LLC v. Gold Standard Instruments, LLC, PGR2015-00019, Paper 17, at *8 n.3 (P.T.A.B. Jan. 29, 2016).

None of the challenged claims were adequately enabled or described in the parent or provisional applications as detailed below in §§V.B and V.C Thus, the '335 patent is PGR-eligible because the challenged claims are not entitled to claim priority benefit to an application filed before June 3, 2016. *See* 35 U.S.C. §100(i)(1)(a); *Inguran*, Paper 8, at *11; *Dr. Reddy's Labs., Ltd. v. Helsinn Healthcare S.A.*, Paper 12, at *9-10 (P.T.A.B. Aug. 17, 2016); AIA §3(n)(1).

1. The '335 patent claims are not enabled and not entitled to claim the priority benefit of an application filed before June 3, 2016

The earlier-filed parent and provisional applications do not enable the challenged claims. *See* 35 U.S.C. §§119(e), 120. Enablement requires that, as of the effective filing date of the patent, a POSA could make and use the full scope of the claimed invention without undue experimentation. *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013); *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1380-81 (Fed. Cir. 2012). Here, the earlier-filed parent and provisional applications fall far short of enabling a POSA to practice the full scope of the claimed invention. *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

As discussed in detail below in Ground 1 and as supported by Dr. Crimmins (CON1002), a balancing of the *Wands* factors demonstrates that it would have required undue experimentation to practice anything more than a tiny fraction of

the scope of the challenged claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Specifically, it would have required undue experimentation to *make* the vast majority of the claimed deuterated ruxolitinib analogs because the '335 patent specification, which is the same as the earlier-filed parent applications, does not describe or teach how to synthesize and/or isolate even a single embodiment within the scope of the claims. The provisional applications are likewise devoid of an enabling disclosure. CON1002, ¶¶15, 38-74, 94-140, 154-156, 164-165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289;

CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

When coupled with the absence of teachings in the art of methods for making at least 95% of the compounds in the claimed genus, it is clear that a POSA would have needed to attempt the same type of "iterative, trial-and-error process to practice the claimed invention" that was deemed non-enabling in *ALZA Corp. v. Andrx Pharmaceuticals, LLC*, 603 F.3d 935, 938, 941 (Fed. Cir. 2010) (finding that because "the field of ascending release dosage forms was not mature at the time the [asserted] patent was filed," "the preparation of such dosage forms was not routine"). Even then, a POSA could not have made at least 95% of the claimed genus because the disclosure in the earlier-filed parent and provisional applications "and knowledge of the prior art, would not have . . . led [the POSA] to make the target compound[s]." *Storer*, 2017 WL 2661863 *9.

Therefore, for the reasons discussed in Ground 1, the challenged claims are neither enabled by nor entitled to the priority benefit of *any* application in the '335 patent's priority chain. 35 U.S.C. §§119(e), 120; *Inguran*, PGR2015-00017, Paper 8, at *11-16. Thus, the earliest effective filing date of the challenged claims is no earlier than June 3, 2016 (the actual filing date of the '335 patent). For this reason, the challenged claims are PGR-eligible.

2. The '335 patent claims lack written description and cannot claim the priority benefit of an application filed before June 3, 2016

None of the earlier-filed parent and provisional applications adequately describes the challenged claims as required by 35 U.S.C. §112(a). *See* 35 U.S.C. §§119(e), 120; *In re Daniels*, 144 F.3d 1452, 1456 (Fed. Cir. 1998); *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997). When earlier-filed applications fail to adequately describe the claimed invention, the challenged patent is only entitled to its actual filing date. *See* 35 U.S.C. §100(i)(1)(a); *Lockwood*, 107 F.3d at 1571-1572; *In re NTP, Inc.*, 654 F.3d 1268, 1276-1277 (Fed. Cir. 2011) (finding that a patent is entitled to the priority date of an earlier-filed continuation application only if, *inter alia*, "the written description of the earlier filed application discloses the invention claimed in the later filed application sufficient to satisfy the requirements of § 112"); *Inguran*, PGR2015-00017, Paper 8, at *11-16.

The challenged claims cover a genus of distinct compounds in which one or more of the 18 hydrogen atoms of ruxolitinib are replaced with a deuterium atom. CON1001, 366:14-34; CON1002, ¶¶77-79, 82-84. "To satisfy the written description requirement, the blaze marks directing the skilled artisan to [the claimed compound] must be in the *originally filed disclosure*." *Purdue Pharma, L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000) (emphasis added).

Yet, as discussed in detail below in Ground 2, the '335 patent specification, which is the same as the earlier-filed parent applications, fails to describe *a single* compound with a hydrogen atom replaced by deuterium, let alone ruxolitinib with a hydrogen atom replaced by deuterium. CON1001, 7:1-27, 69:7-366:6; CON1002, ¶¶16, 25, 88-164, 166, 178; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267. Moreover, the generic disclosure of, *inter alia*, many trillions of potential compounds or approximately 600 exemplified compounds and many different potential isotopic substitutions in the '335 patent does not direct a skilled person to a *deuterated ruxolitinib* analog. CON1001, 7:1-27, 32:60-64; 68:4-28; 69:7-366:6; CON1002, ¶¶24-27, 88-164, 178; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267. The provisional applications also lack blaze marks to a *deuterated ruxolitinib* analog. *See* CON1002, ¶¶164, 166; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111.

Based on the evidence provided with this Petition and supported by Dr. Crimmins' declaration (CON1002), Federal Circuit precedent dictates finding that the challenged claims lack written description in the earlier-filed parent

applications, each of which shares the same specification as the '335 patent, and in the earlier-filed provisional applications. *See Lockwood*, 107 F.3d at 1571-72; *NTP*, 654 F.3d at 1276-77. Therefore, the challenged claims are not entitled to the priority benefit of *any* application in the '335 patent's priority chain, and their earliest effective filing date is no earlier than June 3, 2016 (the actual filing date of the '335 patent). 35 U.S.C. §§100(i)(1)(a), 119(e), 120; *Inguran*, PGR2015-00017, Paper 8, at *11-16. For this independent reason, the challenged claims are PGR-eligible.

B. Ground 1: Claims 1-6 of the '335 patent lack enablement and should be cancelled

The '335 patent fails to enable a POSA to make the full scope of the claimed invention without undue experimentation. *Wyeth*, 720 F.3d at 1384; *MagSil*, 687 F.3d at 1380-81. As discussed above, the challenged claims cover a broad genus of ruxolitinib analogs (and mixtures of those analogs), each of which has deuterium incorporated at one or more positions on ruxolitinib. CON1001, 366:14-34; CON1002, ¶¶75-79, 82-84, 150. Neither the '335 patent specification, which shares the same specification as the earlier-filed parent applications, nor its provisional applications, provides a POSA with guidance for replacing one or more hydrogen atoms with a deuterium atom on ruxolitinib. *Genentech*, 108 F.3d 1361; *see* CON1001, 69:7-366:6; CON1002, ¶¶15, 81-147, 164-165, 177-178; CON1006, 7-

12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111.

As supported by Dr. Crimmins, an analysis of the *Wands* factors demonstrates that it would have required undue experimentation to make the full scope of the claimed invention. *Wands*, 858 F.2d at 737. Neither the '335 patent specification, nor any of the identical earlier-filed parent applications, describe a single embodiment within the scope of the claims. Nor do the provisional applications to which the '335 patent purports to claim priority benefit. When coupled with the absence of teachings in the specification and the dearth of prior art regarding incorporation of deuterium into compounds like ruxolitinib, it is clear that a POSA would not have been led to make the claimed deuterated ruxolitinib analogs and would have needed to engage in undue experimentation. *Storer*, 2017 WL 2661863 *9; *ALZA*, 603 F.3d at 939, 941; CON1002, ¶¶15, 38-74, 94-140, 154-156, 164-166, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-

86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

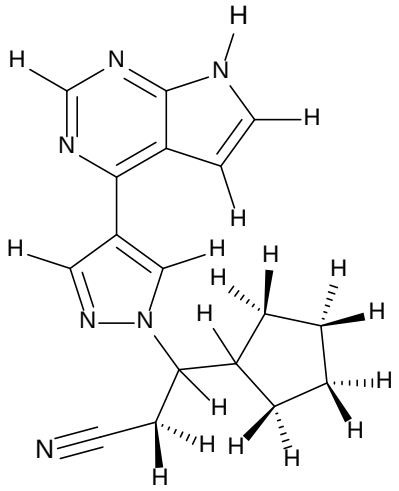
Whether experimentation is undue is determined by analysis of the eight *Wands* factors: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Wands*, 858 F.2d at 737. Analysis of each of these factors, described in detail below, shows that a POSA could not make at least 95% of the claimed compounds without undue experimentation.

The evidence, supported by Dr. Crimmins' Declaration, demonstrates by a

preponderance of the evidence that claims 1-6 of the '335 patent are unpatentable under 35 U.S.C. §112(a) and should be cancelled.

1. The challenged claims have a broad scope

Claims 1-6 encompass a vast genus of more than 250,000 individual ruxolitinib analogs (and more than 500,000 analogs in claims 1 and 2) in which one or more hydrogen atoms have been replaced by a deuterium atom, as well as mixtures of such analogs. CON1001, 366:14-34; CON1002, ¶¶75-80, 82-84, 91, 150. The genus is vast because the claims do not specify substitution of any particular hydrogen atom (hydrogen atoms are shown in the Figure below), but instead, include *every possible combination* of one to 18 deuterium replacements, as well as mixtures of those substituted analogs.



See CON1001, 109:1-110:38, 366:14-34; CON1002, ¶¶75-79, 82-84, 91, 150.

Properly viewed in the context of the plain language of the '335 patent claims and specification, there is no reason to limit the claim scope to anything less

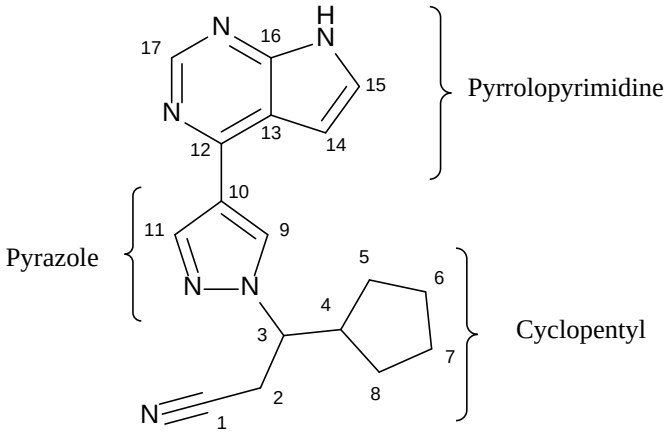
than a genus of compounds having every possible pattern of deuterium substitution. CON1001, 366:14-34; CON1002, ¶¶75-79, 82-84, 91, 150.

There are more than 250,000 possible deuterated analogs of the (3R)-ruxolitinib stereoisomer (2^{18}-1 = 262,143). CON1001, 366:14-34; CON1002, ¶83. Similarly, there are more than 250,000 possible deuterated analogs of the (3S)-ruxolitinib stereoisomer. *Id*. Because claim 1 is silent as to the stereochemistry, it encompasses *each* of the (3R) and (3S)-ruxolitinib stereoisomers, and thus claim 1 and dependent claim 2 each encompass more than 500,000 possible deuterated ruxolitinib analogs. *Id*. Claims 3-6, on the other hand, encompass *either* the (3R) or the (3S)-ruxolitinib stereoisomers. *Id*. Thus, each of claims 3-6 encompasses more than 250,000 possible deuterated ruxolitinib analogs. *Id*. Challenged claims 1-6 encompass a vast array of deuterated ruxolitinib analogs, as well as mixtures of each analog. CON1001, 366:14-34; CON1002, ¶¶75-79, 82-84, 91, 150.

2. The nature of the invention is complex

With so many combinations of hydrogen atoms that may be replaced, the possible deuterium substitution patterns are numerous and exceedingly complex. CON1001, 366:14-34; CON1002, ¶¶18-23, 75-79, 82-84, 91, 150. A large majority of these substitution patterns require synthetic approaches and/or separation techniques that were not available even as of June 3, 2016. Much of the complexity derives from the myriad stereochemical outcomes that are possible, especially

when multiple carbon positions on the cyclopentyl ring of ruxolitinib are each substituted with only one deuterium atom. CON1002, ¶¶91-122, Appendices 1-2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-178, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1030, 1624-1646; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1048, 523-524, 541-564, 593-615, 629-645; CON1049, 288-289; CON1054, 1183-1185. Shown below is the structure of ruxolitinib with the carbon atoms numbered.



The cyclopentyl ring contains 9 of the 18 hydrogen atoms on ruxolitinib, and thus has one-half of all the hydrogen atoms on ruxolitinib. CON1001, 109:1-110:38; CON1002, ¶¶99. Therefore, the number of possible deuterium substitution patterns on the cyclopentyl ring alone is 2^9 or 512. *Id.*

As described in more detail below in §§V.4.a.-b, the combination of the various stereochemical possibilities on the cyclopentyl ring with the possible positions of hydrogen replacement on other parts of ruxolitinib (the pyrazole or pyrrolopyrimidine rings, for example) provides for a complex assortment of possible deuterium substitutions. As a consequence, obtaining a majority of the claimed compounds is exceedingly difficult, if not impossible. The '335 patent is silent as to how to address this complexity, and there is nothing in the prior art that would teach the POSA how to overcome the complexity in the synthesis of these analogs. CON1002, ¶¶15, 38-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1030, 1624-1646; CON1033, 34:35-40; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1054, 1183-1185.

While attempts to prepare deuterated ruxolitinib analogs might have resulted in specific mixtures of the claimed compounds, including mixtures of stereoisomers, separating individual deuterated analogs from such a mixture would have been very difficult, if not impossible, using known techniques. This is

especially so where the difference between the analogs is no more than a few deuterium atoms. CON1002, ¶¶15, 38-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1030, 1624-1646; CON1033, 34:35-40; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1054, 1183-1185. The '335 patent is also silent as to how to separate such analogs and the knowledge in the art fails to address this challenge as well. *See id.*

3. Level of ordinary skill in the art

Because the '335 patent and its challenged claims relate to a genus of chemical compounds, a POSA would have a Master's degree or a Ph.D. in chemistry, biochemistry, physical organic chemistry, or a related discipline. CON1002, ¶¶28-30, 88-90. Alternatively, the POSA may have had a Bachelor's degree in one of those fields, but accompanied by more experience. *Id.*

A POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team. *Id.* However, before the earliest effective filing date of

June 3, 2016, the art would not have provided a solution on how to selectively replace one or more hydrogen atoms with one or more deuterium atoms on compounds such as ruxolitinib, e.g., on positions of the ruxolitinib cyclopentyl ring or at one of the carbon positions 9 or 11. *Id.*

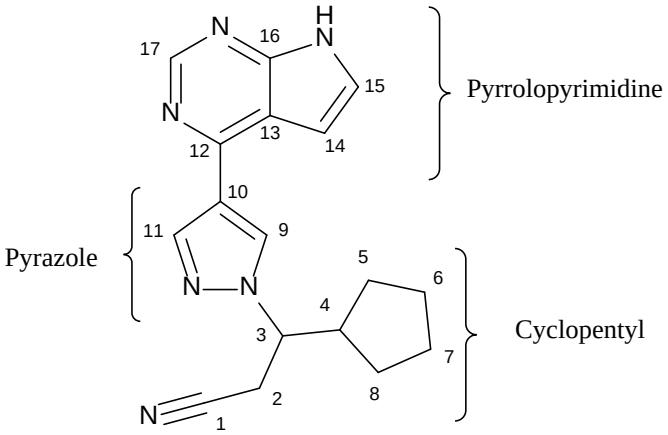
4. Unpredictability in the art: a POSA would have been unable to make and/or isolate at least 95% of the claimed genus

Dr. Crimmins confirms that, as of June 3, 2016, a POSA would not have been able to make and/or isolate at least 95% of the claimed deuterated analogs. CON1002, ¶¶15, 38-140, 154-156, 177, Appendices 1-3. As explained below, the replacement of hydrogen atoms by deuterium atoms on ruxolitinib is synthetically difficult for the vast majority of the deuterated ruxolitinib analogs. *Id*. Most of the hydrogen atom replacements, or combinations thereof, cannot be made by known synthetic methods without also introducing deuterium in undesired locations. *Id*. Such non-specific replacement of hydrogen means that the desired deuterated ruxolitinib analog would be part of a mixture with other deuterated ruxolitinib analogs. *Id*. Deuterated ruxolitinib analogs in such mixtures that differ from each other by no more than a few deuterium atoms would have nearly identical physical properties, and are consequently extremely difficult, if not impossible, in almost all instances to separate from each other. *Id.* Because the individual ruxolitinib analogs cannot be separated from each other, most mixtures of those analogs

cannot be made. This is because a POSA would need the individual analogs in order to adjust the relative amounts for the various mixtures. *Id*. The '335 patent is silent on how to address any of these synthesis and separation challenges. *See* CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

a) The vast majority of the deuterium substitution patterns on the cyclopentyl ring would have been impossible to make and/or isolate

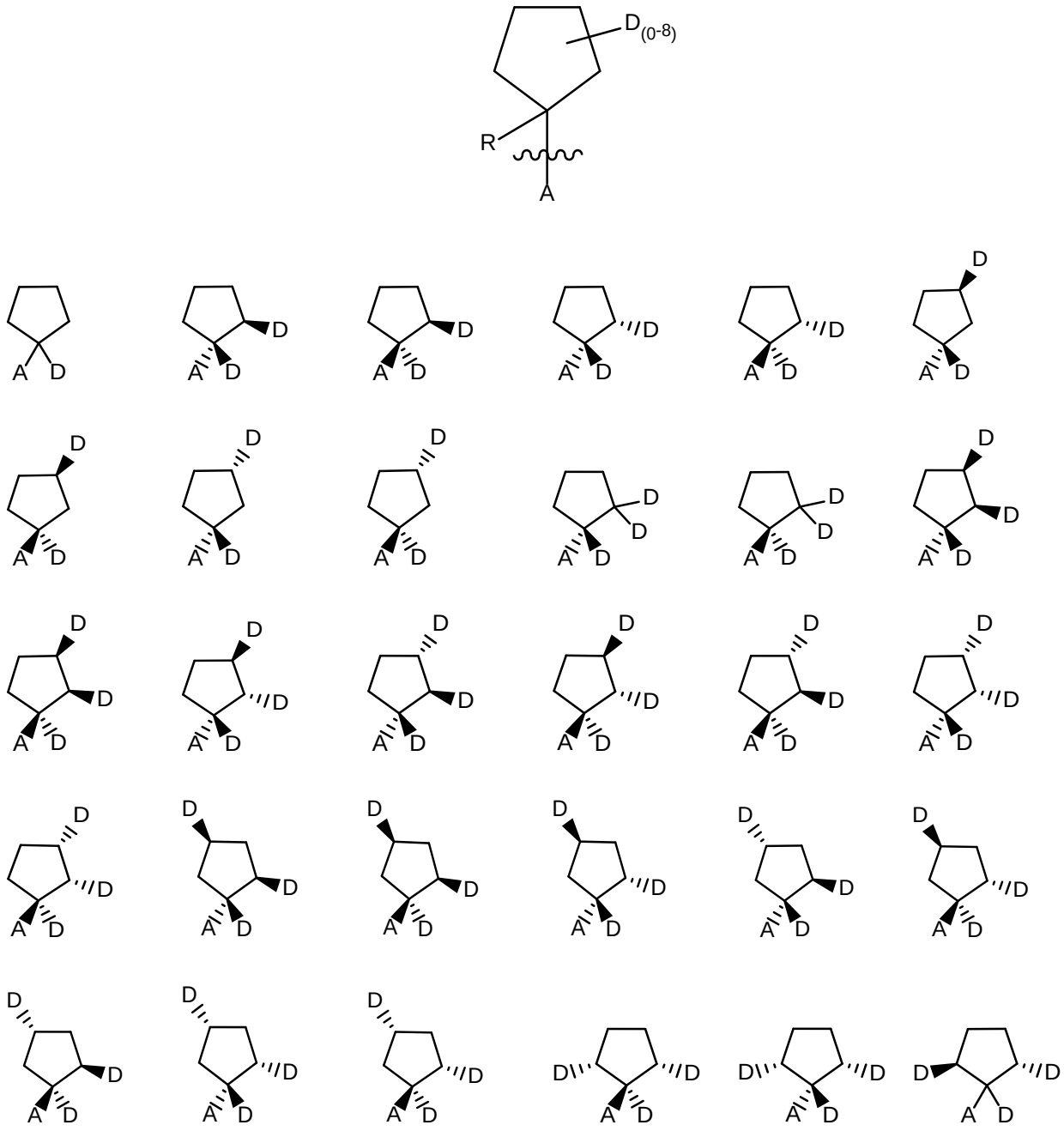
The vast majority of the claimed compounds of the '335 patent have one or more deuterium substitution patterns on the cyclopentyl ring (shown below) that cannot be made and/or isolated by synthetic methods available to a POSA as of June 3, 2016.

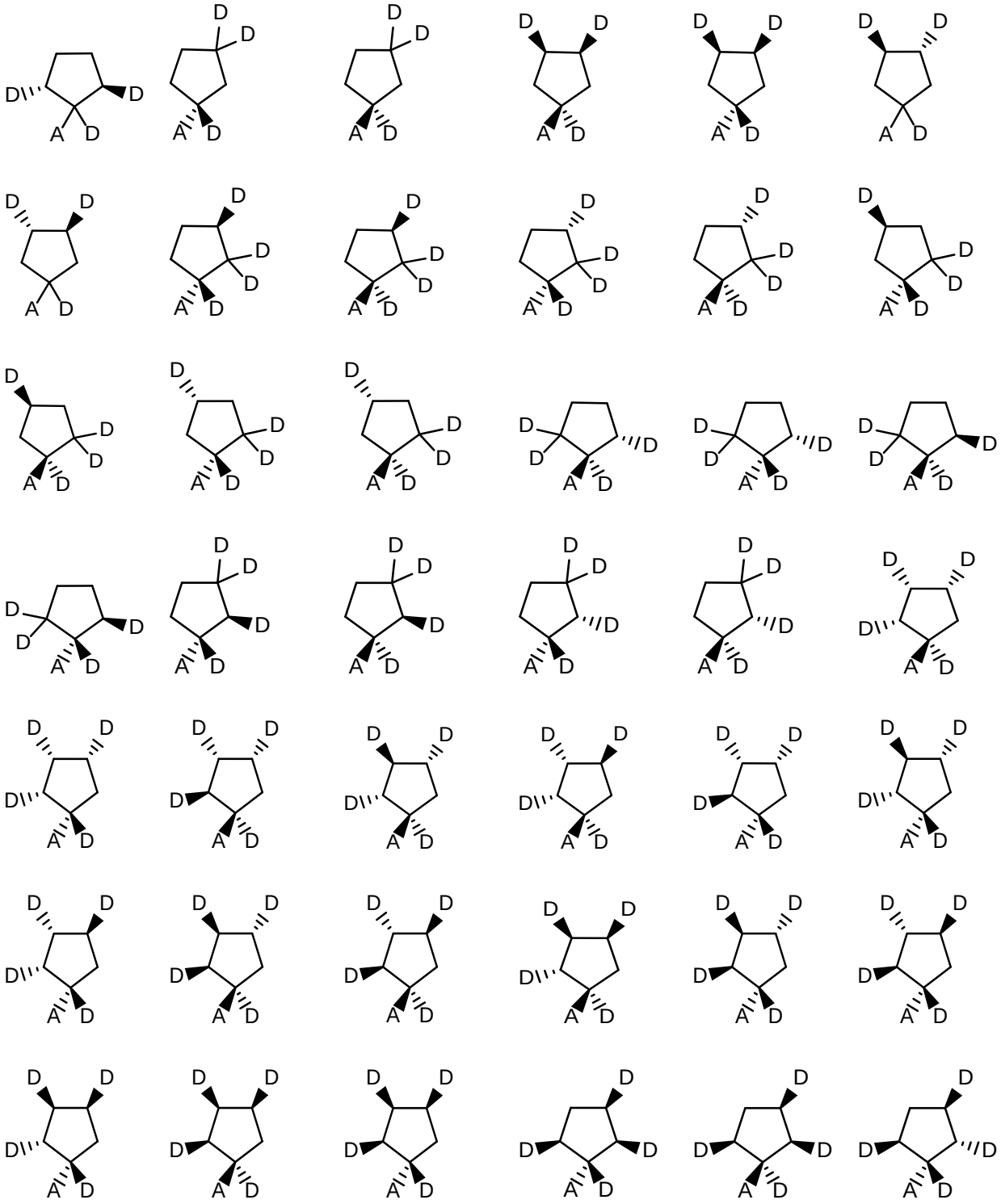


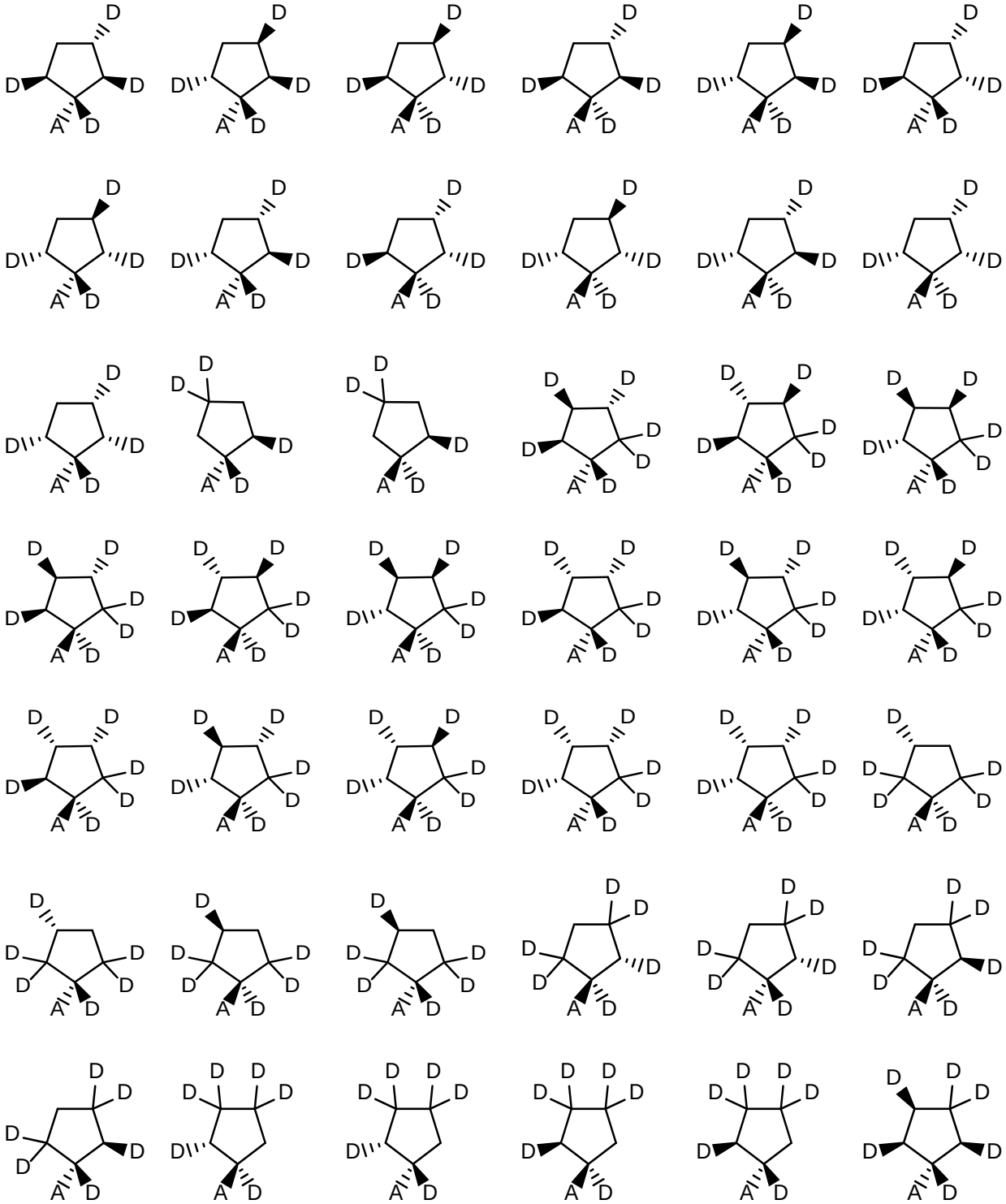
As explained above in §V.2, the number of possible deuterium substitution patterns on the cyclopentyl ring alone is 2^9 or 512. CON1002, ¶99; *see* CON1001, 109:1-110:38, 366:14-34. Each of the more than 500,000 deuterated ruxolitinib analogs of claims 1 and 2 (and the more than 250,000 deuterated ruxolitinib analogs of each of claims 3-6) has one of the 512 possible cyclopentyl substitution patterns. CON1002, ¶¶99-101.

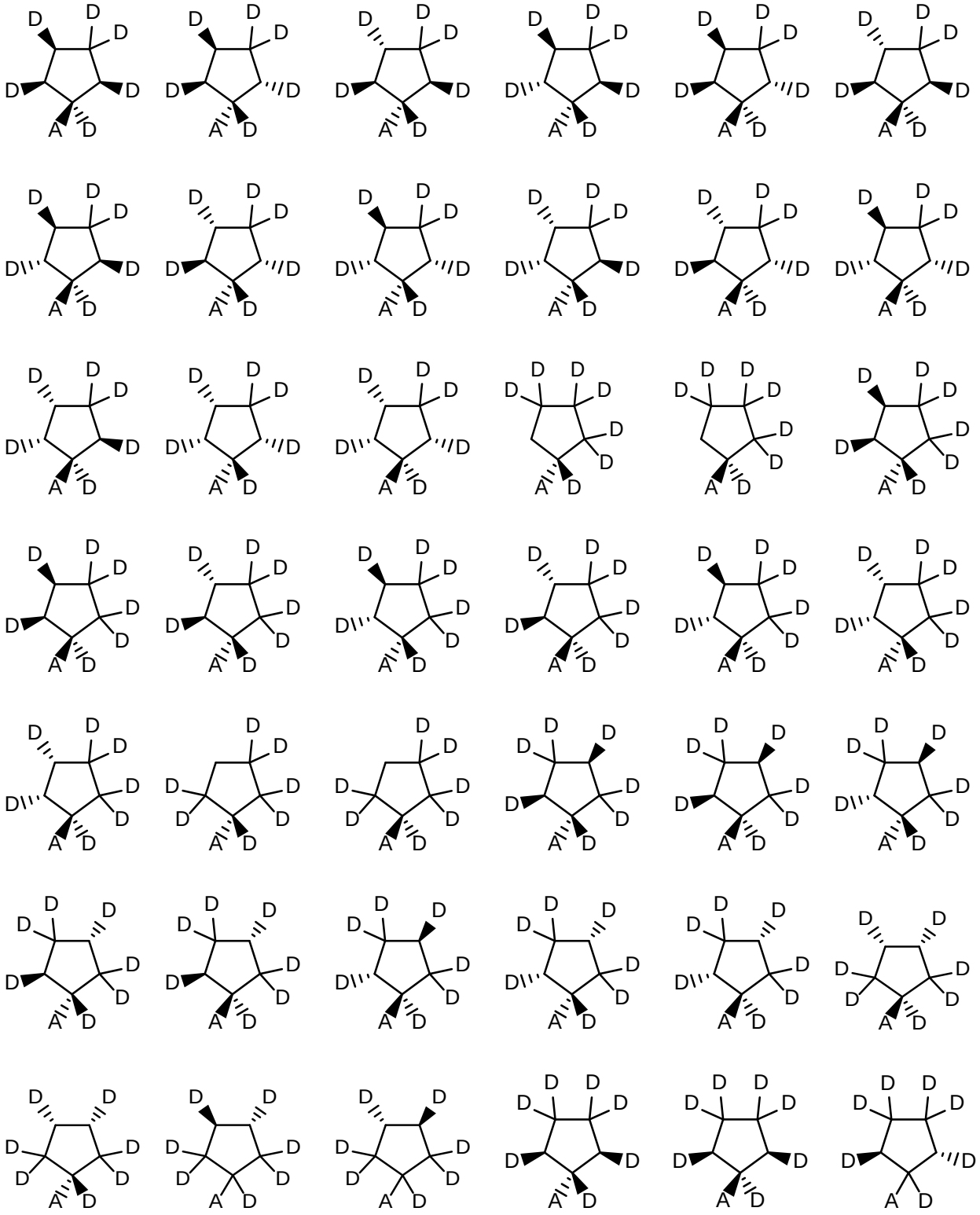
One-half of the claimed analogs contain one of the 256 cyclopentyl substitution patterns shown below in Table 1 (Appendix 1 of Dr. Crimmins' declaration). *Id.* The other half of the claimed analogs is an identical set *except* that at the carbon position where the "A" substituent attaches there is a hydrogen atom rather than a deuterium atom. *See* CON1002, ¶101, Appendix 2

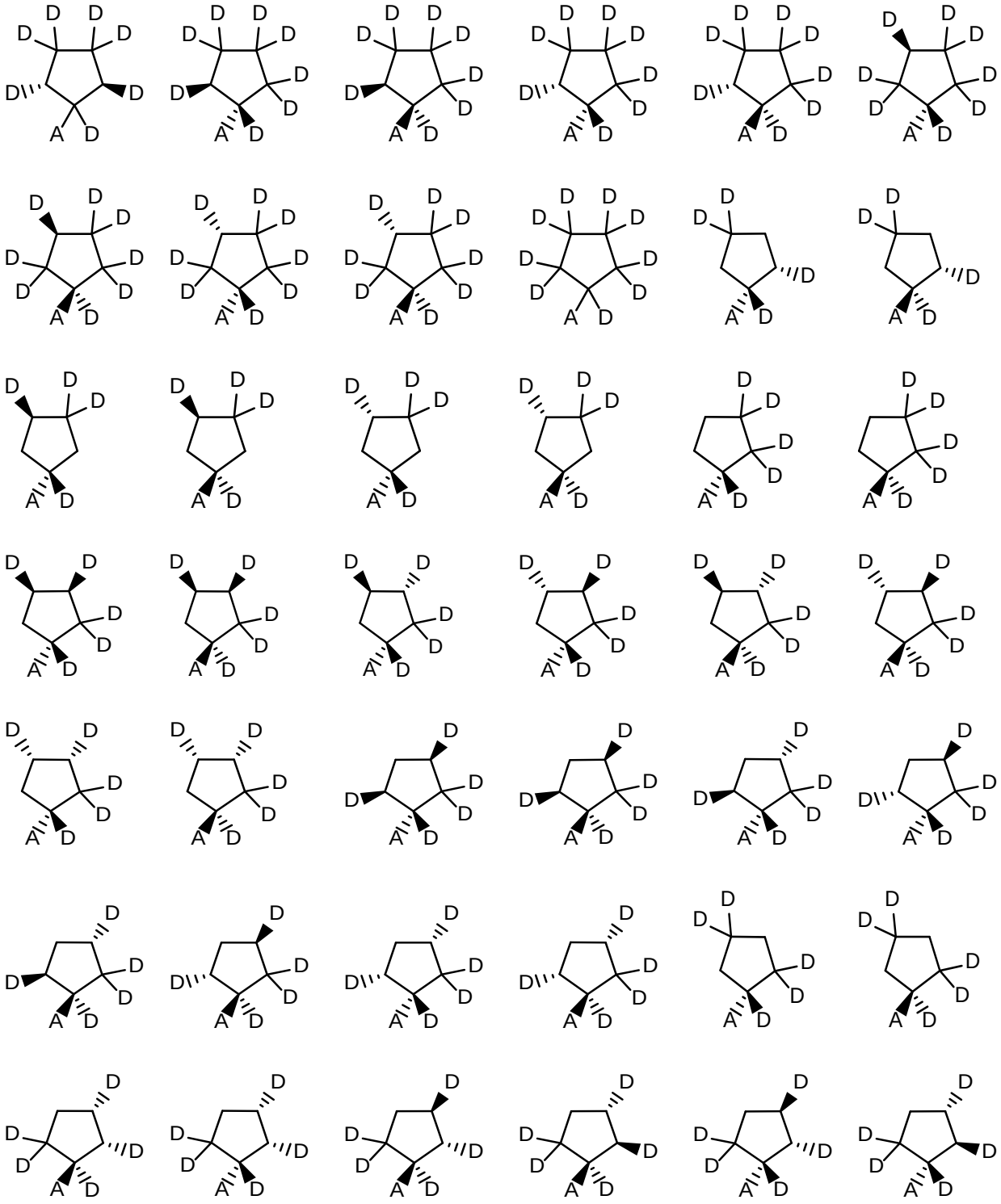
Table 1. Deuterated Cyclopentyl Rings in the Claimed Compounds (R =D; A is the remainder of the ruxolitinib molecule)

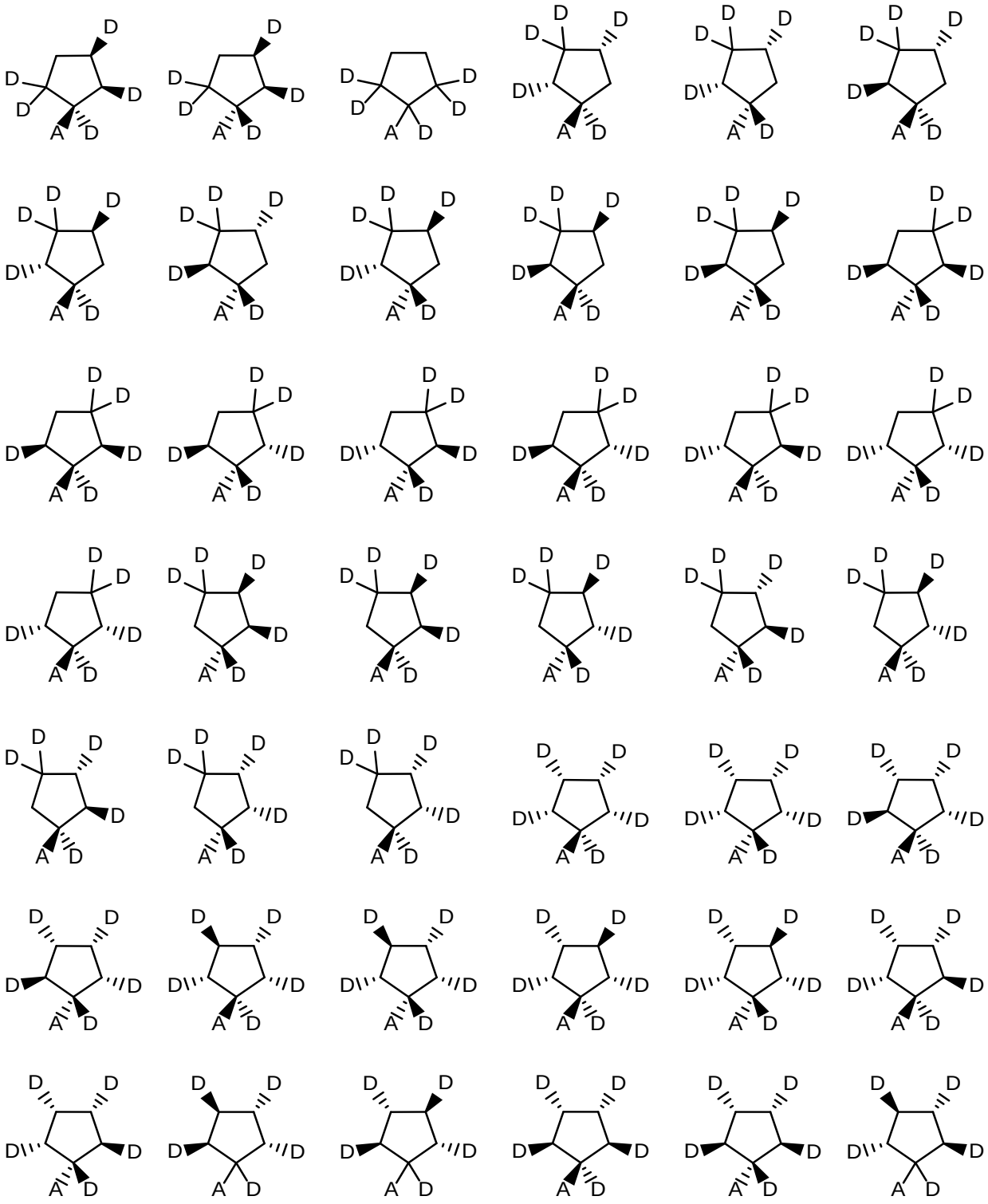


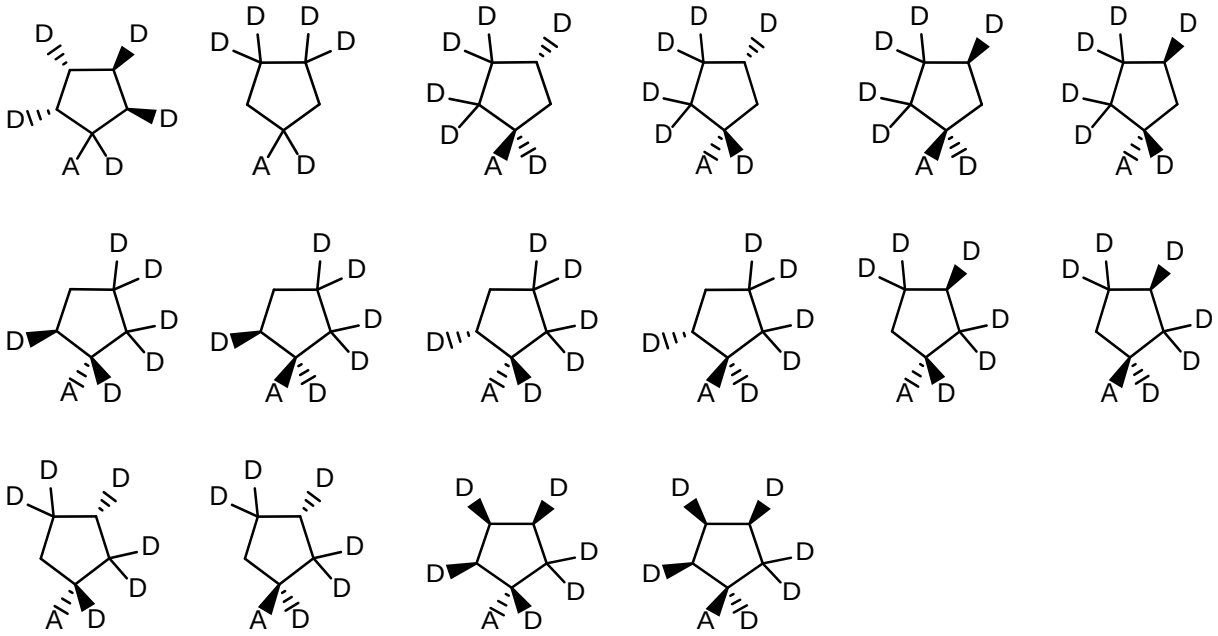










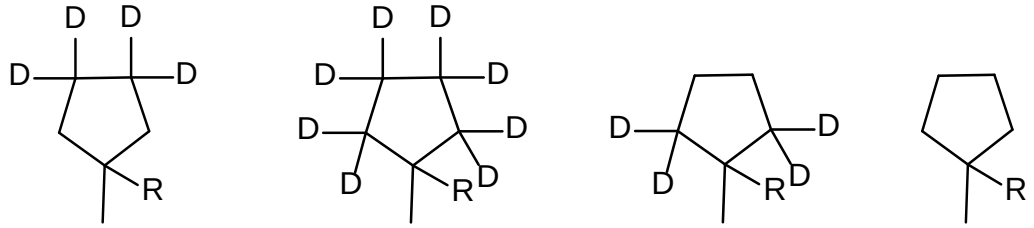


CON1002, ¶¶100-102; Appendix 1.

Table 1 illustrates the structural complexity underlying the synthetic challenge for making the full scope of claims 1-6. Only a handful of deuterium substitution patterns for the cyclopentyl ring of ruxolitinib (carbon positions 4-8 of the cyclopentyl ring) can be made and/or isolated using known techniques. CON1002, ¶¶97-122; Appendices 1-2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3598-3599; CON1020, 169, 176-178, 187; CON1025, 7745-7746, 7750, 7753-7755, 7757-7759; CON1026, 748; CON1027, 5234; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1046, 1351-1352; CON1049, 288; CON1054, 1183-1185. The ruxolitinib analogs that may be made using known techniques are those that, in most cases,

have a *symmetric* substitution of deuterium on the cyclopentyl ring. *Id.* Examples are shown in Table 2 below, and Silverman (CON1004) describes and enables these deuterium substitution patterns. *Id.*

Table 2. Symmetric Deuterium-Substitution of the Cyclopentyl Ring (R = H or D; where D not specified an H is present)



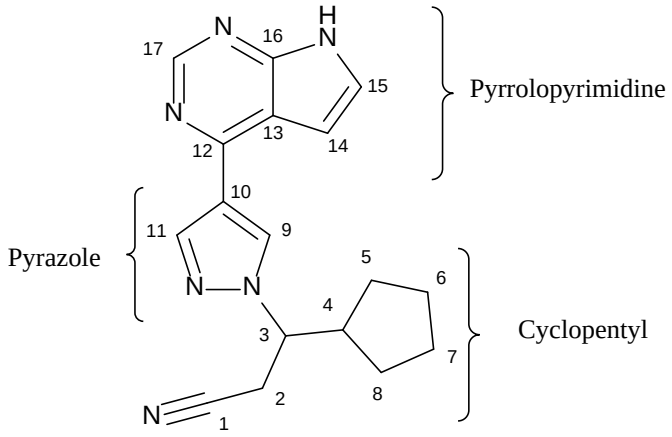
CON1002, ¶¶102-106; *see* CON1001, 109:1-110:38, 366:14-34; CON1004, 30-38.

However, deuterated ruxolitinib analogs having a substitution pattern shown in Table 2 represent a small percentage of the genus of claimed deuterated ruxolitinib analogs. CON1002, ¶¶99-108. Because R can be H or D, Table 2 represents eight symmetric deuterium substitution patterns. *Id.* These eight symmetric deuterium substitution patterns account for about 1.5% of the 512 total cyclopentyl substitution patterns illustrated in Table 2. *Id.*

Moreover, even though about 1.5% of the 512 total cyclopentyl substitution patterns could be made (as demonstrated in Silverman), not all of the claimed deuterated ruxolitinib analogs that have such symmetric cyclopentyl rings can be synthesized. For example, a compound having a symmetric deuterium-substitution pattern but also exhibiting a single deuterium atom substitution at either the 9 or 11

position on ruxolitinib would be challenging for the reasons discussed below. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

Dr. Crimmins explains that deuterated ruxolitinib analogs having cyclopentyl ring substitution patterns other than the symmetric ones discussed above are considerably more difficult to synthesize and/or isolate using known techniques. CON1002, ¶¶97-122. The synthetic challenges stem from the absence of reliable methods to introduce deuterium non-symmetrically at the methylene positions of the cyclopentyl ring of ruxolitinib (positions 5-8 below).

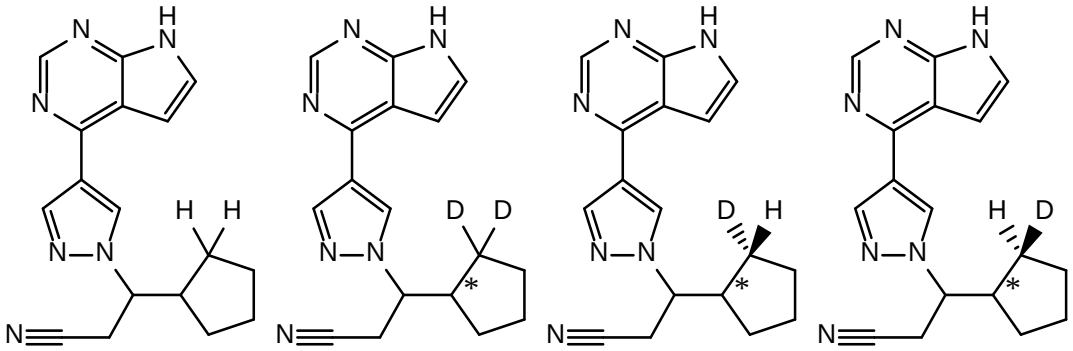


CON1002, ¶¶97-122; Appendices 1-2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3598-3599; CON1020, 169, 176-178, 187; CON1025, 7745-7746, 7750, 7753-7755, 7757-7759; CON1026, 748; CON1027, 5234; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1046, 1351-1352; CON1049, 288; CON1054, 1183-1185.

The '335 patent is silent on how to introduce deuterium at the methylene positions of the cyclopentyl ring. In the absence of guidance from the patent, a POSA attempting non-symmetric replacement on the cyclopentyl ring would have considered using either deuterium exchange reactions or reductive reactions, based on what was known in the art. But, as illustrated below, these reactions often give inseparable mixtures of stereoisomers. The limitations of these reactions are attributable, in part, to the similar steric environments and electronic properties of carbon positions 5-8 of the cyclopentyl ring. CON1002, ¶¶97-122; Appendices 1-

2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3598-3599; CON1020, 169, 176-178, 187; CON1025, 7745-7746, 7750, 7753-7755, 7757-7759; CON1026, 748; CON1027, 5234; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1046, 1351-1352; CON1049, 288; CON1054, 1183-1185.

To illustrate, the potential replacement of hydrogen with deuterium at carbon position 5 provides the four possibilities shown below:

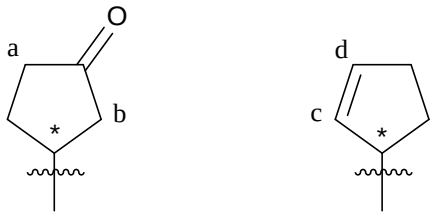


Group 1 Group 2 Group 3 Group 4

CON1002, ¶109; CON1001, 109:1-110:38, 366:14-34. The compounds in Groups 3 and 4 contain a single deuterium in carbon position 5, in either the "up" position (Group 3) or "down" position (Group 4). CON1002, ¶109. The asterisk (*) denotes a chiral center that is not present in Group 1, which, as described by Dr. Crimmins, presents an additional synthetic challenge for Groups 2-4 because a new chiral

center is formed, yielding different stereoisomers that are difficult, if not impossible, to separate. *Id*.

To make the deuterated analogs of Groups 3 or 4, a POSA may have considered, for example, utilizing an intermediate cyclopentanone (i) or cyclopentene ring (ii) for introducing deuterium:



(i) (ii)

CON1002, ¶¶111, 117-120; CON1019, 3598-3599; CON1020, 169, 187; CON1025, 7745-7746, 7750, 7754-7755, 7757-7759; CON1030, 1626, 1628; CON1036, 5469-5472; CON1037, 2778-2779; CON1035, 298-300; CON1046, 1351-1352. Hydrogen-deuterium exchange reactions could introduce deuterium on the cyclopentanone in positions "a" and "b" adjacent to the carbonyl (*see* (i)). CON1002, ¶111; CON1025, 7745-7746; CON1046, 1351-1352. However, it would be difficult to replace hydrogen only at position "a" or only at position "b" (*see* (i)) while controlling the stereochemistry of the addition. *Id.* The replacement is likely to produce a mixture of mono-deuterated analogs along with multiply-deuterated analogs. *Id.* A POSA would also recognize that reduction of the cyclopentene at positions "c" and "d" also suffers from a lack of selectivity (*see*

(ii)), as it would be difficult to: (a) control the direction of deuterium addition from one face of the ring; and (b) incorporate deuterium at one position and not the other. CON1002, ¶¶117-120; CON1025, 7745-7746, 7750, 7754-7755, 7757-7759; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779. It was not routine to add deuterium at both "c" and "d," so that one deuterium is in the "up" position and the other is in the "down" position (i.e., trans to one another). *Id*. Furthermore, when adding deuterium to the same face of the cyclopentyl ring, a POSA would not be able to predict the degree to which both deuterium atoms would be added in the "up" or "down" positions. *Id.*

When more than one of carbon positions 5-8 of the cyclopentyl ring are substituted with deuterium, and at least one of them is singly-deuterated, the synthetic challenge is especially daunting. CON1002, ¶¶38-74, 94-122, Appendices 1-2. Dr. Crimmins describes research involving deuterium exchange and reductive methods on aromatic and non-aromatic saturated carbons, like those in the cyclopentyl ring of ruxolitinib. *Id*. The researchers report high unpredictability regarding positional selectivity and degree of incorporation. *Id.* Dr. Crimmins further explains that these methods would result in mixtures of deuterated compounds that would be difficult, if not impossible, to separate and isolate using known separation techniques. CON1002, ¶¶38-74, 94-122; Appendices 1-2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3598-

3599; CON1020, 169, 176-178, 187; CON1025, 7745-7746, 7750, 7753-7755, 7757-7759; CON1026, 748; CON1027, 5234; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1046, 1351-1352; CON1049, 288; CON1054, 1183-1185.

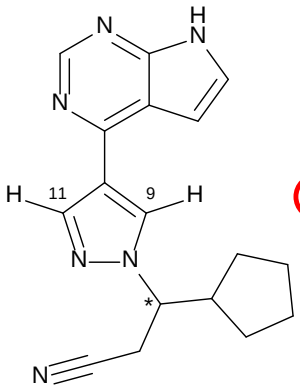
These challenges for deuteration at any one of carbon positions 5-8 alone extend to at least 50% of the compounds encompassed by the claims. CON1002, ¶109. Consequently, considering all possible replacements on the cyclopentyl ring, Dr. Crimmins concludes that it would be unfeasible to make about 90% of the claimed deuterated ruxolitinib analogs based on the challenges of the cyclopentyl ring alone. CON1002, ¶¶38-74, 94-122; Appendices 1-2; CON1001, 109:1-110:38, CON1004, 30-38; CON1019, 3598-3599; CON1020, 169, 176-178, 187; CON1025, 7745-7746, 7750, 7753-7755, 7757-7759; CON1026, 748; CON1027, 5234; CON1030, 1626, 1628; CON1035, 298-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1039, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1044, 183; CON1046, 1351-1352; CON1049, 288; CON1054, 1183-1185.

b) Other hydrogen replacements with deuterium would also have been difficult, if not impossible, for a POSA to make and/or isolate

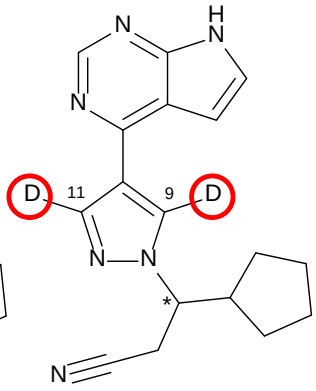
Replacing the other nine of the 18 hydrogen atoms of ruxolitinib (those not on the cyclopentyl ring) with deuterium also presents serious synthetic and/or isolation challenges. CON1002, ¶¶123-140; CON1001, 109:1-110:38; CON1004, 30-37; CON1019, 3597-3600; CON1020, 169, 187; CON1025, 7753-7755, 7757-7759; CON1026, 747-749; CON1033, 34:35-40; CON1035, 300; CON1043, 29:30-30:16, 43:5-47:3; CON1048, 522-532, 541-564, 593-615, 640-645. Many deuterium substitution patterns for these other nine hydrogen positions, including the selective incorporation of deuterium in only one of positions 9 or 11, cannot be made. *Id*. The difficulties in replacing a hydrogen atom with a deuterium atom on the pyrazole ring of ruxolitinib (i.e., positions 9 and 11) extend to 50% of ***all*** the claimed compounds. CON1002, ¶¶124-125. Combining the synthetic challenges of the pyrazole ring with those of the cyclopentyl ring further reduces (by one-half) the number of claimed compounds that can be made using techniques known in the art. CON1002, ¶¶123, 135-136. Taking together the challenges of these two parts of ruxolitinib, with only routine experimentation a POSA could not have made about 95% of the claimed genus. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-

749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

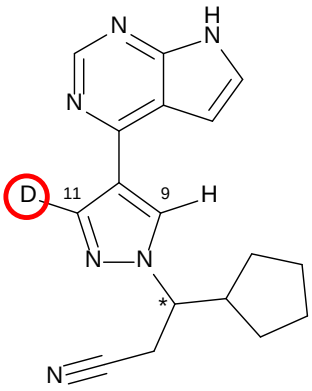
To illustrate the challenges of the pyrazole ring, the claimed deuterated analogs will have one of the substitution patterns shown below in Groups 5-8, with about equal frequency. CON1002, ¶¶124-125.



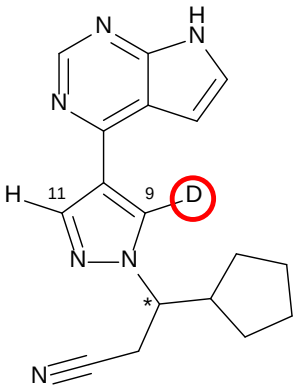
Group 5



Group 6



Group 7



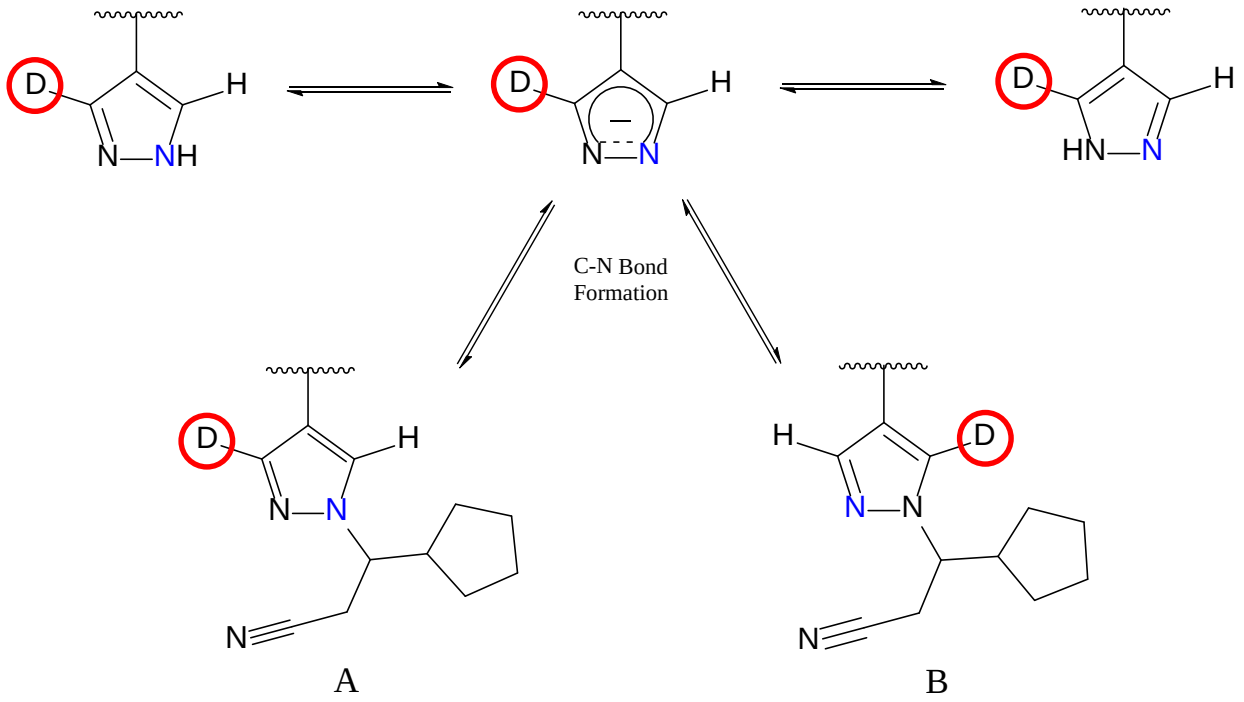
Group 8

Compounds from Group 7 and Group 8 represent 50% of all claimed compounds. *Id*. However, as Dr. Crimmins explains, a POSA would not have been able to make and/or isolate a compound that is in Group 7 and not Group 8, or vice versa. This is

because, by a variety of synthetic methods, positions 9 and 11 cannot be distinguished. Furthermore, a POSA would have been unable to separate a Group 7 compound from one in Group 8. CON1002, ¶¶123-136; CON1001, 109:1-110:38; CON1004, 30-37; CON1019, 3597-3600; CON1020, 169, 187; CON1025, 7753-7759; CON1026, 747-749; CON1033, 34:35-40; CON1035, 300: CON1043, 29:30-30:16, 43:5-47:3; CON1048, 522-532, 541-564, 593-615, 640-645.

One difficulty with positions 9 and 11 is illustrated in Scheme 15 of Dr. Crimmins' Declaration:

Scheme 15



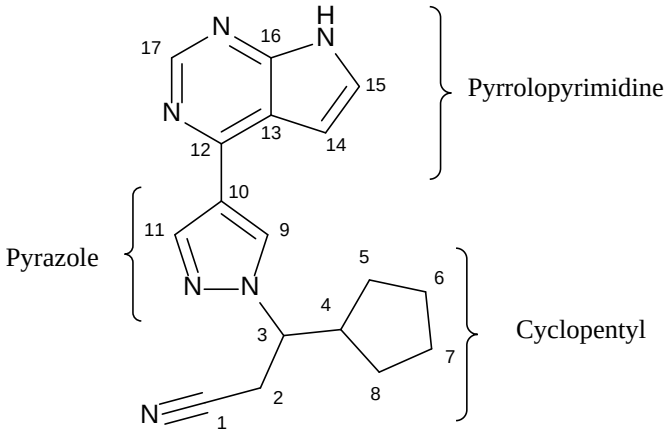
CON1002, ¶131. Dr. Crimmins explains that even if a POSA were able to replace hydrogen with deuterium at only one of positions 9 or 11, and conduct the

subsequent coupling reaction (carbon-nitrogen bond formation reaction), two inseparable positional isomers (Compound A and Compound B) would be formed in about equal amounts. *Id.* As shown above in Scheme 15, the nitrogen atoms of the pyrazole ring are equivalent due to tautomerization (i.e., where two or more isomers are in equilibrium and are readily converted from one isomeric form to another, as shown in the top structures in Scheme 15). CON1002, ¶131; CON1033, 34:35-40. The tautomerization results in about equal amounts of the two positional isomers A and B following the subsequent coupling reaction. *Id*. Dr. Crimmins notes that the positional isomers A and B would be highly difficult, if not impossible, to separate using known techniques. *Id.; see* CON1019, 3597-3600; CON1020, 169, 187.

Dr. Crimmins also considered alternative synthetic strategies for introducing deuterium after the coupling reaction to avoid the problem resulting from tautomerization. CON1002, ¶¶123-136. After considering these alternative strategies, Dr. Crimmins concludes that in view of the lack of techniques available to incorporate deuterium at only one of positions 9 or 11, as well as the lack of techniques available to separate the distinct deuterated ruxolitinib analogs, a POSA would have been unable to make and/or isolate the compounds with deuterium replacement at carbon position 9 only or 11 only. *Id*. Thus, in addition to the challenges facing a POSA to make and/or isolate the claimed analogs having

deuterium substitution on the cyclopentyl ring, it would be unworkable to make and/or isolate deuterated ruxolitinib analogs having a deuterium at carbon position 9 only or 11 only. CON1002, ¶¶123-136; CON1001, 109:1-110:38; CON1004, 30-37; CON1019, 3597-3600; CON1020, 169, 187; CON1025, 7753-7759; CON1026, 747-749; CON1033, 34:35-40; CON1035, 300; CON1043, 29:30-30:16, 43:5-47:3: CON1048, 522-532, 541-564, 593-615, 640-645.

In addition to the difficulties described above, a POSA would also face challenges with replacing a hydrogen atom with a deuterium atom on other portions of ruxolitinib, such as on the pyrrolopyrimidine ring (i.e., carbon positions 14, 15, and 17, and the NH on the figure below).



CON1002, ¶¶137-140; *see* CON1001, 109:1-110:38, 366:14-34; CON1025, 7753-7755, 7757-7758; CON1026, 748-749.

As Dr. Crimmins explains, each position on the pyrrolopyrimidine ring would require a different synthetic approach, thereby magnifying the complexity

involved for preparing the full scope of the claims. CON1002, ¶138. Thus, in addition to the challenges facing a POSA to make and/or isolate the claimed analogs having a hydrogen replaced by a deuterium atom on the cyclopentyl and pyrazole rings, a POSA would be unable to make and/or isolate the claimed genus of deuterated ruxolitinib analogs having one or more deuterium atoms on other portions of ruxolitinib, including the pyrrolopyrimidine ring. CON1002, ¶¶137-140; *see* CON1025, 7753-7755, 7757-7758; CON1026, 748-749. When considering the difficulties to make and/or isolate deuterated ruxolitinib analogs having non-symmetric deuterium substitution patterns on the cyclopentyl ring or deuterium substitution at only one of carbon positions 9 or 11 on the pyrazole ring or at carbon positions 14, 15, 17, or the NH on pyrrolopyrimidine ring, a POSA would have been unable to make at least 95% of the claimed deuterated ruxolitinib analogs. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38;

CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

c) Deuterated ruxolitinib analogs are nearly identical with respect to physical properties, making them difficult to separate

Dr. Crimmins explains that most deuterated ruxolitinib analogs are expected to be nearly identical to each other with respect to their physical properties. CON1002, ¶¶32-34; *see* CON1018, 368, 385; CON1019, 3595-3600; CON1020, 169, 186; CON1022, 2:31-34; CON1053, 1154; CON1054, 1183-1185. This is because replacing a single hydrogen atom with a single deuterium atom only increases the molecular weight by one atomic mass unit. *Id.* Consequently, deuterated ruxolitinib analogs that differ from each other only in the position of deuterium atoms are likely to be nearly identical to each other with respect their size, polarity, vapor pressure, and solubility. CON1002, ¶¶32-34, 62-74; CON1018, 368,385; CON1019, 3595-3600; CON1020, 169, 186; CON1022, 2:31-34; CON1045, 34-38; CON1053, 1154; CON1054, 1183-1185. Similarly, if two analogs differ by no more than a few deuterium atoms (e.g., four hydrogen atoms replaced by deuterium versus six), they would also share nearly identical physical properties. *Id.*

Without a difference in these physical properties, one deuterated ruxolitinib analog most likely could not have been isolated or purified from another by separation techniques available on or before June 3, 2016. CON1002, ¶¶62-74, 112-116, 119, 128-134, 138. This is because the commonly-available separation techniques, which included chromatography, extraction, distillation, sublimation, and recrystallization, rely on some difference in physical properties. *Id*. For example, available chromatography techniques require a difference in size or polarity; available distillation or sublimation techniques require a difference in vapor pressure; available extraction techniques require a difference in partition coefficients; and available recrystallization techniques require a difference in solubility. *Id.*

Because deuterated ruxolitinib analogs are expected to be nearly identical to each other with respect to their physical properties, known separation techniques that rely on differences in the physical properties described above would likely fail to achieve any separation. *Id.*

d) As of June 3, 2016, a POSA would have been unable to make most mixtures of the deuterated ruxolitinib analogs

The vast majority of mixtures that arise from all of the possible combinations cannot be made unless the POSA can also make the individual analogs. Without the ability to isolate the vast majority of deuterated ruxolitinib

analogs from other deuterated analogs, even the mixtures of compounds that could have been (or still can be) obtained by available methods are very limited. As Dr. Crimmins explains, the chemistry available to a POSA as of June 3, 2016, would have yielded only a tiny fraction of the nearly infinite number of mixtures that the '335 patent claims encompass. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185. Thus, because the vast majority of the claimed compounds cannot be made and/or isolated, the vast majority of the mixtures of the claimed compounds cannot be made either. *Id*.

5. The '335 patent specification provides no working examples or direction for replacing hydrogen atoms on ruxolitinib

The '335 patent discloses ***no*** examples within the vast genus of deuterated ruxolitinib analogs encompassed by the challenged claims. CON1002, ¶¶141-144, 157-163. In fact, the '335 patent discloses no examples of any deuterated compound and does not describe how to synthesize and/or isolate even one of the more than 500,000 deuterated ruxolitinib analogs. *Id*.

In connection with "radio-isotopes," the '335 patent does state that "[s]ynthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an [sic] ordinary skill in the art will readily recognize the methods applicable for the compounds of the invention" (CON1001, 68:23-28); but deuterium is not a radioisotope. CON1002, ¶¶27, 34, 92, 141-143, 158, 160; CON1018, 368, 385; CON1019, 3595, 3599, 3608; CON1022, 2:3-34. In any event, as discussed above, there were no known deuterium-incorporation and/or separation techniques available to a POSA sufficient to make the vast majority of the claimed analogs. CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4;

CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185. As confirmed by Dr. Crimmins, the '335 patent (and each of its identical parent applications) provides no direction or working examples to enable a POSA to make the full scope of claimed deuterated ruxolitinib analogs. CON1002, ¶¶15, 38-74, 94-140, 154-156, 165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-

564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185. Neither does any provisional application to which the '335 patent claims priority. CON1002, ¶¶15, 38-74, 94-140, 154-156, 164, 166, 177, Appendices 1-3; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111.

6. The quantity of experimentation needed to make the genus of claimed deuterated ruxolitinib analogs is excessive

As discussed above in §V.B.4 and as explained by Dr. Crimmins, as of June 3, 2016, replacing hydrogen with deuterium at one or more of the hydrogen atoms on carbon positions 5-8 of the cyclopentyl ring or carbon positions 9 and 11 of the pyrazole ring, as well as other locations on ruxolitinib, such as the pyrrolopyrimidine ring, was (and still is) complex, difficult, and often largely unpredictable. CON1002, ¶¶154, 167-78. The '335 patent does nothing to address this complexity. It provides no examples of any deuterated compounds. As discussed above in §V.B.5, the generic reference to "[s]ynthetic methods for incorporating radio-isotopes into organic compounds" in the '335 patent (CON1001, 68:23-28), fails to compensate for the scarcity of deuterium-incorporation techniques available to a POSA to successfully make the full scope of the genus of deuterated ruxolitinib analogs. CON1002, ¶¶15, 38-74, 94-140,

154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

In view of the absence of any teaching in the '335 patent disclosure of synthetic and/or separation methods for making the claimed deuterated ruxolitnib analogs, coupled with the complexity of making a vast majority of the analogs encompassed by the challenged claims, a POSA would not have been led to make the claimed analogs, and could not have done so without engaging in excessive, non-routine experimentation. *Storer*, 2017 WL 2661863 *9; *see also ALZA*, 603 F.3d at 941 (finding that because "the field of ascending release dosage forms was not mature at the time the [asserted] patent was filed," "the preparation of such

dosage forms was not routine"). Thus, the quantity of experimentation needed to make the full scope of the challenged claims as of June 3, 2016, was excessive.

7. Weighing the Wands factors shows no enablement of claims 1-6 of the '335 patent

The amount of testing and experimentation required to enable a skilled artisan to practice the full scope of the claimed genus of deuterated ruxolitinib analogs would have been far more than routine—it would have been undue. *Wands*, 858 F.2d at 737. Weighing the *Wands* factors supports finding lack of enablement for the full scope of the challenged claims. *See* CON1002, ¶¶15, 38-74, 94-140, 154-156, 164-166, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407;

CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

The breadth of the challenged claims include deuterated ruxolitinib analogs that represent every possible combination of one to 18 deuterium replacements for hydrogen on ruxolitinib. CON1001, 366:14-34; CON1002, ¶¶77-79, 82-84. Thus, the claims encompass a vast genus of deuterated ruxolitinib analogs: more than 500,000 possible deuterated ruxolitinib analogs for claims 1 and 2 and more than 250,000 possible deuterated ruxolitinib analogs for each of claims 3-6. CON1001, 366:14-34; CON1002, ¶¶75-80, 82-84, 91-92. The claims also encompass mixtures of these deuterated ruxolitinib analogs. CON1001, 109:1-110:38, 366:14-34; CON1002, ¶¶75-80, 82-84, 91, 99, 150.

To determine if the full scope of the claimed deuterated ruxolitinib analogs is enabled, the skilled artisan would look to the direction provided by the inventors in the patent's specification. *Storer*, 2017 WL 2661863 *6 ("[F]or new chemical compounds *the specification must provide sufficient guidance* that undue experimentation is not required to obtain the new compounds." (emphasis added)); *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 1000 (Fed. Cir. 2008) ("An enablement analysis begins with the disclosure in the specification."); *U.S. Endodontics*,

PGR2015-00019, Paper 17, at *20. Here, the '335 patent specification provides *no guidance* for synthesizing and/or isolating any deuterated ruxolitinib analog. There are no working examples for a deuterated ruxolitinib analog or indeed for deuterating any of the trillions of potential compounds in the '335 patent. *Id.* That leaves the skilled artisan to search beyond the '335 patent's disclosure for teachings in the art as of June 3, 2016. *Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75, at*10 (P.T.A.B. June 14, 2014) ("The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art."); *see Wyeth*, 720 F.3d at 1386 (practicing full scope of claims requires undue experimentation where, *inter alia*, "[s]ynthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry").

As explained by Dr. Crimmins, the synthesis methods and separation technologies disclosed in the prior art and available to a POSA on or before June 3, 2016, would not have provided guidance to make at least 95% of the claimed genus, including the examples provided in Appendix 3 of Dr. Crimmins' declaration. This is because existing methods could not make and/or isolate ruxolitinib analogs having non-symmetric deuterium substitution patterns at carbon positions 5-8 of the cyclopentyl ring or a single deuterium at carbon positions 9 or

11 of the pyrazole ring, as well as other locations on ruxolitinib such as the pyrrolopyrimidine ring, as explained above in §V.B.4. *Id.* Also, because the methods and technologies available to a POSA to make at least 95% of the claimed genus of deuterated ruxolitinib analogs, and mixtures of those analogs, were complex and unpredictable, the quantity of experimentation needed to make the full scope of the claimed genus would have been undue. *Storer*, 2017 WL 2661863 *9; *ALZA*, 603 F.3d at 939-941; *see also Atlas Powder Co. v. E.I. Du Pont de Nemours*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) ("[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid.").[5] As such, each of the *Wands* factors weighs toward

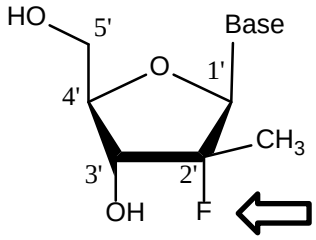
[5] To the extent Incyte relies on *Atlas Powder*, in which the Federal Circuit found enablement despite a large number of inoperative combinations, *Atlas Powder* is distinguishable. In *Atlas Powder*, not only did the art provide teachings on how to make the claimed emulsion blasting agent, but the asserted patent contained prophetic examples describing the claimed agent. *Atlas Powder*, 750 F.2d at 1576-77. As discussed above, neither the art nor the '335 patent provides any teachings on how to make more than a small fraction of claimed compounds. CON1002, ¶¶94-144.

finding lack of enablement for the challenged claims of the '335 patent. *See* CON1002, ¶¶15, 38-74, 94-140, 154-156, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

8. Controlling precedent compels a finding of no enablement of claims 1-6 of the '335 patent

Analysis of each of the *Wands* factors compels a finding of no enablement for challenged claims 1-6. Holding otherwise would contravene Federal Circuit precedent in *Storer* and *ALZA*, the facts and holding of which compel a finding of no enablement for the claimed genus. *Storer*, 2017 WL 2661863 at *9; *ALZA*, 603 F.3d at 943.

In *Storer*, the Federal Circuit affirmed the Board's interference decision that found Storer's provisional patent application was not enabled. *Storer*, 2017 WL 2661863 at *9. The interference involved methods of treating hepatitis C by administering novel compounds with a five-membered ring having a particular stereochemistry, i.e., a fluorine substituent in the "2' (down)" position (shown with an arrow below):



Id. at *2.

After weighing the *Wands* factors, the Board determined that Storer's provisional application, which did not "identify any specific structure having the 2'F (down) substituent," did not enable the nucleosides having a 2'F (down) substituent because their synthesis would require undue experimentation. *Id.* at *5. Notably, the Board found that despite the availability of fluoridation techniques in the art, fluoridation "to produce a 2' "down" tertiary fluorine was not taught or suggested by the prior art." *Id.* at *4. The Board also found that "fluoridation of tertiary alcohols to produce a tertiary fluorine in the 2' "down" position, was highly unpredictable." *Id.* at *5.

The Federal Circuit credited the Board for correctly recognizing that "for

new chemical compounds the specification must provide sufficient guidance that undue experimentation is not required to obtain the new compounds." *Id.* at *6. The court also pointed to *Genentech*, 108 F.3d at 1366, for the proposition that "the specification, not the knowledge of one skilled in the art, . . . must supply the novel aspects of an invention in order to constitute adequate enablement." *Id.* at *7.

On appeal, Storer argued that the prior art provided "a well-known precursor compound that is only one step away from the target compound." *Id.* at *5. Though the provisional application did not disclose the precursor itself (Matsuda Compound 17), Storer argued that its synthetic schemes taught how Matsuda Compound 17 could be made. *Id.* at *6. Storer further argued that a skilled artisan would know how to convert this precursor to the five-membered ring having a tertiary 2' F in the down position using standard fluorinating reagents in the prior art. *Id.*

The Federal Circuit first looked to the guidance in the specification, but found the disclosure in the provisional application inadequate because none of the synthetic schemes proceeded through Matsuda Compound 17. *Id.* at *7. Furthermore, the court found that even accepting Storer's position that the skilled artisan would have started with Matsuda Compound 17, Storer failed to show that fluorination reactions using that compound would predictably provide the required five-membered ring with fluorine in the correct stereochemistry. *Id.* at *8. Instead,

the record demonstrated evidence of Storer's repeated failures to synthesize the desired compound. *Id.* Among other things, the evidence showed that "attempted fluorination reactions . . . could fail, resulting in unfluorinated elimination and/or rearrangement products, or products with incorrect stereochemistry," as well as side reactions. *Id.* at *7-8. Because the evidence of record demonstrated sufficient variability and unpredictability, the amount of experimentation to synthesize the claimed compound with the correct stereochemistry was deemed high. *Id.* at *9. In view of the inadequacy of the disclosure and the unpredictability of the fluorination reactions that were in the prior art, Storer's provisional application failed to enable the claimed subject matter. *Id.*

As in *Storer*, Incyte's '335 patent and earlier-filed applications have inadequate disclosures. They do not describe any deuterated ruxolitinib analogs or any deuterium-containing building blocks, reagents, or reactions for making the analogs. Although the '335 patent provides a synthesis of ruxolitinib, none of Incyte's synthetic schemes teach or suggest how to make a *deuterated* ruxolitinib analog. Thus, the '335 patent and earlier filed applications "do not supply the novel aspects of the invention." *Id.* at *7; *see* CON1002, ¶¶15, 38-74, 94-140, 154-156, 164-165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12,

34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

Also like *Storer*, the prior art available to a POSA attempting to make deuterated ruxolitinib analogs does not overcome the inadequacy of Incyte's disclosures. Except for the small fraction of symmetrically-substituted analogs on the cyclopentyl ring successfully made by Silverman (CON1004), which published in 2013, the prior art does not teach how to make the vast majority of claimed compounds. *Id*. In *Storer*, based on the state of the art for fluorination chemistry, the Federal Circuit found that the critical stereochemical result would not predictably ensue for the tertiary fluorine in the 2' down position on the five-

membered ring. *Storer*, 2017 WL 2661863 at *8. Similarly, as Dr. Crimmins has noted throughout his Declaration, the stereochemical outcomes needed to make the vast majority of the claimed deuterated ruxolitinib analogs for the five-membered cyclopentyl ring in ruxolitinib—which has one-half of all the hydrogen atoms on ruxolitinib—would not predictably ensue based on the deuterium chemistry prior art available to a POSA as of June 3, 2016. *See* CON1002, ¶¶15, 38-74, 94-140, 154-156, 164-165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-

564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185.

Furthermore, the vast number of deuterium substitution patterns, especially on the cyclopentyl ring, compound significantly the challenges for a POSA to make deuterated ruxolitinib analogs. Whereas *Storer* addressed one position and one substituent on a five-membered ring, the five-membered cyclopentyl ring in the challenged claims has five positions (carbon positions 4-8) and any combination of up to nine deuterium atoms for a total of 512 deuterium substitution patterns. In addition, a POSA would face additional challenges making the deuterated ruxolitinib analogs having a single deuterium at carbon positions 9 or 11 of the pyrazole ring and other locations on ruxolitinib, such as the pyrrolopyrimidine ring. *Id*.

Incyte failed to supply an enabling disclosure of the "novel aspects" of replacing one or more hydrogen atoms on ruxolitinib with deuterium. *Genentech*, 108 F.3d at 1366. The '335 patent is devoid of any isotopically substituted compounds and failed to "provide sufficient guidance [such] that undue experimentation is not required to obtain" the deuterated ruxolitinib analogs. *Storer*, 2017 WL 2661863 at *6; CON1002, ¶¶15, 38-74, 94-140, 154-156, 165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267;

CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60; CON1054, 1183-1185. As in *Storer*, the Board should find Incyte's claimed deuterated ruxolitinib analogs are not enabled.

ALZA warrants a similar finding of non-enablement. In *ALZA*, the claims recited methods for treating Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD) with a dosage form comprising methylphenidate and that had an ascending release rate. *ALZA*, 603 F.3d at 936-37. After agreeing that the scope of the claims encompassed both osmotic and non-osmotic dosage forms, the parties disputed enablement of the encompassed non-osmotic dosage

forms (they agreed that osmotic dosage forms were enabled). *Id.* at 938-39. The court agreed that evidence with respect to three *Wands* factors in particular—guidance provided by the specification, presence or absence of working examples, and breadth of the claims—supported finding the asserted claims non-enabled. *Id.* at 939-40.

The patent specification at issue in *ALZA* contained only a generic disclosure of approaches for achieving sustained release dosage forms. *Id.* at 941. The Federal Circuit found that it failed to disclose "any specific starting material or of any of the condition[s] under which a process can be carried out." *Id.* Instead, the court found that the asserted patent provided "only a starting point, a direction for further research." *Id.* Based on the absence of direction or working examples, in addition to evidence demonstrating the unpredictability of making the claimed non-osmotic dosage forms, the court found that it would have required undue experimentation to practice the full scope of the asserted claims. *Id.* at 942-43.

As in *ALZA*, the '335 patent specification provides no guidance or working examples to support how to make and/or isolate the claimed deuterated ruxolitinib analogs. The disclosure fails to provide 1) guidance or working examples of deuterated starting materials; 2) conditions for preparing such starting materials; or 3) guidance or working examples showing how one would incorporate deuterium into any of the many trillions of potential compounds or any of the 600 compounds

in the Examples in the '335 patent. For the reasons addressed above, the mere disclosure of synthesizing non-deuterated ruxolitinib in the '335 patent does not enable a POSA to make, *inter alia*, most deuterated ruxolitinib analogs with a hydrogen atom replaced by a deuterium atom at carbon positions 5-8 of the cyclopentyl ring or carbon positions 9 and 11 of the pyrazole ring, or most mixtures having such substitution patterns. CON1002, ¶¶15, 38-74, 94-140, 154-156, 165, 177, Appendices 1-3; CON1001, 109:1-110:38; CON1004, 30-38; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016, 6-9, 16, 27-86, 88-111; CON1019, 3597-3600; CON1020, 169-172, 176-185, 187; CON1025, 7745-7761; CON1026, 747-749; CON1027, 5234; CON1028, 8134-8135; CON1029, 52-58; CON1030, 1624-1646; CON1031, 26:42-55, 30:1-67; CON1032, 16:44-17:53; CON1033, 34:35-40, 57:29-58:4; CON1034, 165-166; CON1035, 297-300; CON1036, 5469-5472; CON1037, 2778-2779; CON1038, 318; CON1039, 4275, 4277; CON1040, 2923-2944; CON1042, 4405-4407; CON1043, 29:30-30:16, 43:5-47:3; CON1044, 183; CON1045, 34-38; CON1046, 1351-1352; CON1047, 89, 102-119, 121-127, 135-139; CON1048, 522-532, 541-564, 593-615, 629-645; CON1049, 288-289; CON1050, 62-66; CON1051, 2611; CON1052, 19:46-60;

CON1054, 1183-1185.

The prior art and knowledge of a POSA fails to fill the void left by the lack of disclosure in the '335 patent specification. *See ALZA*, 603 F.3d at 941 ("ALZA was required to provide an adequate enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification."). Based on Silverman (CON1004), which published in 2013, a POSA could make some of the ruxolitinib analogs having symmetric deuterium substitution on the cyclopentyl ring (*see* §V.B.4.a above). The prior art, however, does not teach a POSA how to make and/or isolate deuterated ruxolitinib analogs with a hydrogen atom replaced by a deuterium atom non-symmetrically at carbon positions 5-8 of the cyclopentyl ring or a single deuterium atom at carbon positions 9 or 11 of the pyrazole ring. *Id*.

Thus, the '335 patent does not contain "such full, clear, concise, and exact terms as to enable any person skilled in the art" to make the full scope of claimed deuterated ruxolitinib analogs. 35 U.S.C. §112(a). As such, the '335 patent specification, which shares the same limited disclosure as the earlier-filed parent and provisional applications, fails to enable the full scope of claims 1-6. Therefore, the challenged claims are unpatentable.

C. Ground 2: Claims 1-6 of the '335 patent lack written description and should be cancelled

The written description requirement "plays a vital role in curtailing claims . . . that have not been invented, and thus cannot be described." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc). Here, the challenged claims encompass a broad genus of more than 250,000 deuterated ruxolitinib analogs that Incyte did not invent. This is because the '335 patent, which shares the same specification as its earlier-filed parent applications, fails to describe even *a single* compound with a hydrogen replaced by deuterium, let alone ruxolitinib with a hydrogen replaced by deuterium. CON1002, ¶¶16, 24-27, 141-143, 157-164, 166, 178. Moreover, there is a nearly infinite number of mixtures of analogs possible, none of which are described. The '335 patent provisional applications are equally lacking. *Id*. The evidence, supported by Dr. Crimmins' declaration, demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable under 35 U.S.C. §112(a). *Id.* Thus, claims 1-6 of the '335 patent should be cancelled.

When evaluating written description, the Federal Circuit and Board consider the factors described in *Capon v. Eshhar* and *Ariad*: the nature and scope of the claims, the complexity of the relevant technology, "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science

or technology, [and] the predictability of the aspect at issue." *Capon v. Eshhar*, 418 F.3d 1349, 1357–59 (Fed. Cir. 2005); *Ariad*, 598 F.3d at 1352; *see Fox Factory, Inc., v. SRAM, LLC*, PGR2016-00043, Paper 9, at *9-13 (P.T.A.B. Apr. 3, 2017) ("Whether the genus is supported vel non depends upon the state of the art and nature and breadth of the genus."); *Ossia, Inc., v. Energous Corp.*, PGR2016-00024, Paper 20, at 37-38 (P.T.A.B. Nov. 29, 2016) (pointing to *Ariad* as stating "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology"). This Petition addresses the evidence falling within these factors in §V.B above, in the context of the overlapping *Wands* factors. Applying the factors to this evidence demonstrates that the inventors did not "actually invent[] the invention claimed." *Ariad*, 598 F.3d at 1351.

1. The '335 patent fails to provide any blaze marks to the claimed subgenus of deuterated ruxolitinib analogs

Comparing the challenged patent claims to the '335 patent disclosure, it becomes readily apparent that upon filing the '057 application on June 3, 2016, Incyte pieced the claims together, picking and choosing from disparate bits of the broad disclosure. But a patent application's undifferentiated description cannot provide adequate written description support if it lacks "blaze marks" to guide a reader "through the forest of the specification." *Novozymes*, 723 F.3d at 1349

(quoting *In re Ruschig*, 379 F2d. 990, 994-95 (C.C.P.A. 1967)). Instead, to satisfy the written description requirement, the application must describe the claimed subject matter "as an integrated whole rather than as a collection of independent limitations." *Novozymes*, 723 F.3d at 1349. The '335 patent falls far short of meeting this requirement and therefore fails to adequately describe what is claimed.

The facts here are analogous to those in *Novozymes*, which turned on an applicant's failure to describe claim elements as an integrated whole. *Id.* In *Novozymes*, the claims-at-issue recited a subgenus of specific alpha-amylase variants comprising, *inter alia*, a single amino acid substitution in a sequence of about 500 amino acids for alpha-amylase. The specification disclosed as separate disclosures, *inter alia*, 1) the specific alpha-amylase as one of six others with a focus on another alpha-amylase, 2) the amino acid substitution as one of 33 others, and 3) the functional aspect of the claim. *Id.* at 1348. Critically, however, the application "never presented [those limitations] together in any particular embodiment." *Id.* at 1341-42. The Federal Circuit concluded that despite the "formal textual support for each individual limitation recited in the claims" a POSA would search the specification "in vain for the disclosure of even a single species that falls within the claims or for any 'blaze marks' that would lead an ordinarily skilled investigator toward such species among a slew of competing

possibilities." *Id.* at 1349.

Like *Novozymes*, the '335 patent provides at best "only generalized guidance listing several variables that might, in some combination, lead to a useful result." *Id.* at 1346. Here, Incyte chose a very specific compound, ruxolitinib, out of the many trillion potential heteroaryl substituted pyrrolo[2,3-b]pyridines and heteroaryl substituted pyrrolo[2,3-b]pyrimidines within the vast genus of Formula I, and out of approximately 600 disclosed compounds. CON1001, 7:1-27:50, 69:7-366:6; CON1002,¶¶24-27, 141-163. Incyte combined this generic disclosure with a very general disclosure of replacing or substituting one or more atoms in "a compound of the invention" with an isotope. CON1001, 32:60-64; 67:56–68:16 (the specification recites "[a]n 'isotopically' or 'radio-labeled' compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring)"). CON1002, ¶¶24-27, 141-163. The generic disclosure goes on to recite a list of 21 isotopes and radionuclides that could be used to replace any atom on any of the disclosed compounds. CON1001, 67:56-68:16; CON1002, ¶¶24-27, 141-163.

Thus, even if the '335 patent on its face appears to provide "formal textual support," i.e., the actual words for the claim limitations, under *Novozymes* formal

textual support is not enough.[6] *Novozymes*, 723 F.3d at 1349; *see also Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011); *Enzo Biochem., Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002). Something more is needed, and here the '335 patent "never presented [the claim limitations] together in any particular embodiment." *Novozymes*, 723 F.3d at 1341-42. Specifically, the '335 patent specification lacks 1) even a single species of deuterated ruxolitinib, or even *any* isotopically-labeled compound and 2) any blaze marks pointing from the compounds disclosed in the '335 patent and list of isotopes to the claimed deuterated ruxolitinib analogs. CON1002, ¶¶16, 24-27, 141-143, 157-163, 178.

As confirmed by Dr. Crimmins, nothing in the generalized guidance of the '335 patent specification directs a skilled person to choose ruxolitinib out of the

[6] Incyte asserted to the Examiner that written support for the challenged claims is found in the boiler plate language that the "present invention further includes isotopically-labeled compounds." CON1017, 337 (citing specification as-filed, page 60, line 35 (CON1017, 78:35). However, *Novozymes* dismissed "formal textual support" as lacking where the disclosure fails to lead a POSA "toward such species among a slew of competing possibilities." 723 F.3d at 1349. The Board should do the same here.

trillions of potential compounds, or even the approximately 600 disclosed compounds, and to replace one or more of the ruxolitinib hydrogen atoms with deuterium, as opposed to any of the other recited isotopes. *Id.* Therefore, the '335 patent contains no disclosure within the four corners of the patent to demonstrate possession of the claimed genus of deuterated ruxolitinib analogs.

During prosecution of earlier-filed U.S. Appl. Nos. 13/076,220 (CON1009), 14/020,505 (CON1008), 14/274,948 (CON1007), 14/711,576 (CON1006), Incyte introduced claim sets by preliminary amendment on filing including ruxolitinib in specific compositions and methods of use. *See, e.g.*, CON1009 (sustained release compositions); CON1008 (sustained release compositions for treating a laundry list of diseases); CON1007 (methods related to inhibiting, blocking, or modulating various JAK1 or JAK2 activities); CON1006 (methods for treating skin disorders by topical administration). Yet, these claim sets would still not direct a POSA to the claimed subject matter because none of them point to a deuterated ruxolitinib analog from amongst the '335 patent's vast disclosure. CON1002, ¶¶16, 24-27, 141-143, 157-164, 166, 178; CON1006, 7-12, 34, 60-267; CON1007, 7-12, 34, 60-267; CON1008, 7-12, 34, 60-267; CON1009, 7-12, 34, 60-267; CON1010, 7-12, 34, 60-267; CON1011, 7-12, 34, 60-267. Thus, these claim sets do not provide a blaze mark to the challenged claims.

The provisional applications to which the '335 claims priority benefit

similarly also fail to provide any blaze marks to deuterated ruxolitinib. CON1002, ¶¶16, 24-27, 141-143, 157-164, 166, 178; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016,6-9, 16, 27-86, 88-111. Each of the provisional applications recites Formula I, and hundreds of compounds in the Examples (increasing from approximately 230 to 530 compounds from Appl. Nos. 60/749,905 to 60/859,404), one of which is ruxolitinib. *See* CON1002, ¶¶157-164, 166, 178; CON1012, 6-11, 29, 50-221; CON1013, 6-11, 29, 50-221; CON1014, 6-10, 27, 49-219; CON1015, 6-10, 21, 42-157; CON1016,6-9, 16, 27-86, 88-111. The provisional applications also mention deuterium only as a hydrogen isotope, and all but the first-filed provisional application, include it in a lengthy list of other potential isotopes. *Id*. Taken together, none of this disclosure blazes a path to the now-claimed deuterated ruxolitinib analogs.

Evaluation of written description should be forward-looking. *Novozymes*, 723 F.3d at 1349 (describing that "the proper vantage point [for viewing written description is] 'of one with no foreknowledge of the specific compound'"); *see also Biogen MA Inc. v. Forward Pharma A/S*, Interference No. 106,023, Doc. No. 813, at *21 (P.T.A.B. March 31, 2017) (citing to *Novozymes* for the proposition that "[t]he evaluation of written description is forward-looking, i.e., the evaluation is made from the perspective of a person skilled in the art with no foreknowledge of

the later-claimed invention"). Here, the '335 patent claims were first presented more than 10 years after Incyte filed its earliest priority application, almost 3 years after Concert filed the Silverman patent application disclosing several deuterated ruxolitinib analogs, and one month after Concert announced initiation of Phase 1 clinical testing of the deuterated ruxolitinib analog CTP-543 to treat alopecia areata. Piecing together unrelated disclosures from the innumerable competing possibilities mentioned in the '335 patent is only possible by "[w]orking backward from a knowledge of [Concert's claims and success], that is by hindsight." *Novozymes*, 723 F.3d at 1349. Claims 1-6 should be cancelled as unpatentable for lack of adequate written description.

2. The '335 patent fails to disclose any species within the claimed genus of more than 250,000 deuterated ruxolitinib analogs

For genus claims such as those challenged here, "an adequate written description . . . requires more than a generic statement of an invention's boundaries." *Ariad,* 598 F.3d at 1349. Instead, the written description requires a representative number of species that fall within the scope of the genus. *Id.* at 1350. Here, in addition to being unpatentable under the established *Novozymes* standard, the challenged claims are unpatentable because the '335 patent discloses absolutely no species of deuterated ruxolitinib analogs. CON1001, 69:7-366:6; CON1002, ¶¶16, 24-27, 141-143, 157-164, 178. As such, the '335 patent (together

with its identical parent applications and provisional applications) fails to describe any species within the scope of the claims, much less a representative number of deuterated ruxolitinib analogs within the scope of the claims. *Id.*

The facts here are analogous to those in the Federal Circuit's decision in *Billups-Rothenberg, Inc. v. Assoc. Regional Univ. Pathologists, Inc.*, 642 F.3d 1031 (Fed. Cir. 2011). In *Billups*, the court found description of the claimed genus deficient. *Id.* at 1037. There, the claims-at-issue encompassed methods of identifying "a genus of unknown genetic mutations." *Id.* Like the '335 patent specification here, the *Billups* patent "did not identify even *a single species* [of genetic mutation] that satisfies the claims." *Id.* (emphasis added). And despite the later discovery of a species (a specific genetic mutation) within the claimed genus, the court indicated that "Billups cannot satisfy the written description requirement merely through references to later-acquired knowledge." *Id.*

Much like *Billups*, Incyte cannot satisfy the written description requirement for the full scope of the challenged claims. As discussed above and confirmed by Dr. Crimmins, nowhere does the '335 patent specification describe how to synthesize and separate deuterated ruxolitinib analogs with deuterium replacement at, e.g., any of carbon positions 5-8 of the cyclopentyl ring or carbon positions 9 and 11 of the pyrazole ring, nor does it disclose a single embodiment of a deuterated analog of ruxolitinib. CON1001, 69:7-366:6; CON1002, ¶¶16, 24-27,

141-143, 157-164, 178. The prior art, including Silverman (CON1004), and the existing knowledge in the field as of June 3, 2016 or any earlier, do not fill the holes in the '335 patent's disclosure. *Ariad*, 598 F.3d at 1358 ("The state of the art at the time of filing was primitive and uncertain, leaving Ariad with an insufficient supply of prior art knowledge with which to fill the gaping holes in its disclosure."). Moreover, even if the species disclosed in Silverman (CON1004) were somehow applicable as relevant knowledge in the prior art to supplement the written description, that disclosure would anticipate at least claims 1-4 of the '335 patent (*see* §V.D below).

The '335 patent specification fails to disclose any, let alone a representative number of, species of deuterated ruxolitinib analogs within the scope of the claims. Moreover, there is a nearly infinite number of mixtures of analogs possible, none of which are described. Therefore, as in *Billups*, the challenged claims 1-6 lack sufficient written description in the patent. Thus, each of the challenged claims is unpatentable.

D. Ground 3: Claims 1-4 are anticipated by Silverman

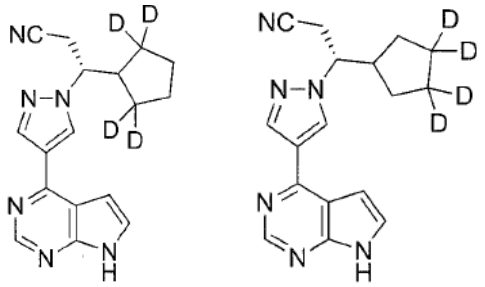
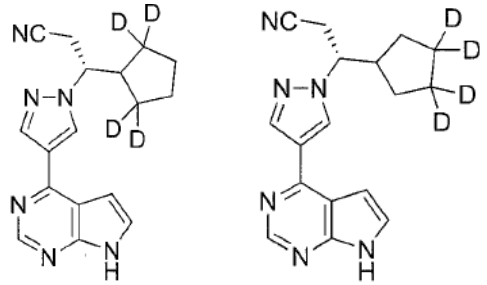
WO 2013/188783 ("Silverman" (CON1004)), published on December 19, 2013, anticipates claims 1-4 of the '335 patent. As discussed in §V.A.1-2, the challenged claims are not entitled to an effective filing date earlier than June 3, 2016, because the claims lack written description and are not enabled as of June 3,

2016 or, indeed, any date to which the '335 patent claims priority benefit. As such, Silverman is prior art under 35 U.S.C. §102(a)(1).

Silverman anticipates claims 1-4, because, as discussed below and supported by the declaration of Dr. Crimmins, Silverman discloses each and every element of claims 1-4, arranged as claimed. This is because Silverman describes at least one species within the genus of claims 1-4. CON1002, ¶¶17, 167-176, 179; CON1004, 8-13, 16-23, 26-34. Silverman does so in a manner enabling to a POSA as it teaches how to make specific symmetric deuterium substitution patterns on the cyclopentyl ring of ruxolitinib (*see* §V.B.4.a above). CON1002, ¶¶17, 167-176, 179; CON1004, 8-13, 16-23, 26-34.

Claims 1 and 3: As discussed above, claims 1 and 3 of the '335 patent encompass deuterated ruxolitinib analogs, including deuterated analogs of (3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile. CON1001, 366:14-34; CON1002, ¶¶82-84, 170. Silverman discloses multiple deuterated (3R)-ruxolitinib analogs, including, as shown in the chart below, compounds 107 and 103 in which hydrogen atoms are replaced by deuterium atoms on the cyclopentyl ring on the ruxolitinib. CON1004, 8-13, 26-34; CON1002, ¶¶170-172. Dr. Crimmins opines that each of compounds 107 and 103 of Silverman is 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-

pyrazol-1-yl]propanenitrile wherein one or more hydrogen atoms are replaced by deuterium. CON1004, 8-13, 26-34; CON1002, ¶¶170-172.

Claim 1 and 3 of the '335 patent	**Disclosure in Silverman**
1. A compound, which is 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1 H -pyrazol-1-yl]propanenitrile, wherein one or more hydrogen atoms are replaced by deuterium; or a pharmaceutically acceptable salt thereof.	 **Compound 107** **Compound 103** CON1004, 26-34.
3. A compound, which is (3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1 H -pyrazol-1-yl]propanenitrile, wherein one or more hydrogen atoms are replaced by deuterium; or a pharmaceutically acceptable salt thereof.	 **Compound 107** **Compound 103** CON1004, 26-34.

Additionally, Silverman provides detailed syntheses for each of these compounds. CON1004, 26-34, Examples 1-2; CON1002, ¶¶167-176. As Dr. Crimmins explains, the starting materials used in each synthesis was 98 atom %D. CON1004, 26-34, Examples 1-2; CON1002, ¶¶172. He further explains that based on the chemistry used to make Compounds 103 and 107, it is highly unlikely that

much of the deuterium on the cyclopentyl ring would be lost (i.e., replaced by hydrogen) during the synthesis of the compounds. CON1002, ¶172; *see* CON1004, 26-34, Examples 1-2. Therefore, Dr. Crimmins opines that each of Compounds 107 and 103 of Silverman would also contain a high degree of deuterium incorporation (>95%) at each deuterium on the compounds. CON1002, ¶172; *see* CON1004, 26-34, Examples 1-2. Thus, because Silverman discloses how to "make" a distinct deuterated ruxolitinib (Compounds 107 and 103), and demonstrates that one could indeed make the compounds, Silverman would have been enabling to a POSA prior to the '335 patent's earliest effective filing date to make the compounds. CON1004, 26-34, Examples 1-2; CON1002, ¶¶172-173; *see In re Gleave*, 560 F.3d 1331, 1335-36 (Fed. Cir. 2009) ("[A] reference satisfies the enablement requirement of [pre-AIA] § 102(b) by showing that one of skill in the art would know how to make the relevant sequences disclosed in [the prior art].").

Claims 2 and 4: These claims depend from claims 1 and 3, respectively, and encompass a pharmaceutical composition comprising a deuterated (3R)-ruxolitinib analog and a pharmaceutically acceptable carrier. CON1001, 366:14-34; CON1002, ¶¶82-84, 174. Silverman describes combining the disclosed deuterated (3R)-ruxolitinib analogs with a pharmaceutically acceptable carrier to make a pharmaceutical composition to be administered to patients. CON1004, 16-23; CON1002, ¶¶174-176.

Claim 2 and 4 of the '335 patent	**Disclosure in Silverman**
2. A pharmaceutical composition comprising a compound of claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.	"The invention also provides pyrogen-free **pharmaceutical compositions comprising** an effective amount of a **compound of Formula I or Formula A** (e.g., including any of the formulae herein), **or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier**." CON1004, 16.
4. A pharmaceutical composition comprising a compound of claim **3,** or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.	"The invention also provides pyrogen-free **pharmaceutical compositions comprising** an effective amount of a **compound of Formula I or Formula A** (e.g., including any of the formulae herein), **or a pharmaceutically acceptable salt of said compound; and a pharmaceutically acceptable carrier**." CON1004, 16.

Based on Silverman, a POSA would have known how to make a pharmaceutical composition containing one of its disclosed deuterated (3R)-ruxolitinib analogs (e.g., compound 107) with a pharmaceutically acceptable carrier. CON1004, 16-23, 26-34; CON1002, ¶¶167-176. Indeed, Silverman describes several types of pharmaceutical compositions (see, e.g., CON1004, 17) and pharmaceutically acceptable carriers (see, e.g., CON1004, 16-17) and directs a POSA to use formulating methods "well known in the art of pharmacy," citing to *Remington: The Science and Practice of Pharmacy*, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000). *See, e.g.*, CON1004, 17. To the extent

anything more is needed to formulate the claimed pharmaceutical compositions of claims 2 and 4, Incyte's '335 patent is silent. Thus, Silverman's disclosure would have been enabling to a POSA before June 3, 2016 to make pharmaceutical compositions comprising Silverman's disclosed deuterated (3R)-ruxolitinib analogs. CON1002, ¶¶17, 167-176, 179.

VI. CONCLUSION

This petition demonstrates by a preponderance of the evidence that every challenged claim has an effective filing date no earlier than June 3, 2016, making the '335 patent PGR-eligible. It established that every challenged claim is unpatentable under 35 U.S.C. §112(a) for lack of enablement and lack of written description. Additionally, Silverman anticipates claims 1-4 of the '335 patent under 35 U.S.C. §102(a)(1). Consequently, Petitioner requests that the Board institute trial and cancel claims 1-6.

VII. COMPLIANCE WITH REQUIREMENTS FOR PGR

- Petitioner certifies that (a) before the date on which this petition for review is being filed, neither the petitioner nor any real party-in-interest filed a civil action challenging the validity of a claim of the patent; (b) neither Petitioner nor any real party-in-interest or privy of Petitioner is estopped from challenging the claims on the grounds above.
- Petitioner certifies the '335 patent is available for PGR on the above grounds.

- The '335 patent issued on May 30, 2017, and this Petition is being filed within nine months of issuance.
- As shown in in §V.A above, the Challenged Claims have an effective filing date of no earlier than June 3, 2016, and are therefore eligible for PGR under AIA §3(n)(1).
- The real party-in-interest is Concert Pharmaceuticals, Inc.
- Petitioner is not aware of any judicial matter that would affect or be affected by a decision in this proceeding, but pending U.S. Patent Appl. Nos. 15/233,652; 15/356,957; and 15/606,634 claim priority to U.S. Patent Appl. No. 15/173,057, which issued as the '335 patent.
- A power of attorney is filed herewith according to 37 C.F.R. §42.10(b).
- Please charge the required fee to Deposit Acct. No. 19-0036 (Customer ID No. 45324).
- Petitioner certifies that this Petition is 15,773 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.
- Petitioner consents to service by email to the addresses below:

Lead Counsel: Deborah A. Sterling (Reg. No. 62,732)

Back-up Counsel: Robert C. Millonig (Reg. No. 34,395)

Marsha Rose Gillentine (Reg. No. 58,403)
Jeremiah B. Frueauf (Reg. No. 66,638)

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, NW
Washington, DC 20005
202.772.8679 (telephone)
202.371.2540 (facsimile)

dsterlin-PTAB@skgf.com
bobm-PTAB@skgf.com
mgillentine-PTAB@skgf.com
jfrueauf-PTAB@skgf.com

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Date: June 27, 2017
1100 New York Avenue, N.W.
Washington, DC 20005-3934
(202) 371-2600

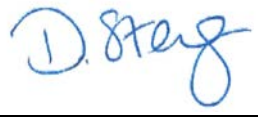
Deborah A. Sterling
Registration No. 62,732
Lead Attorney for Petitioner Concert Pharmaceuticals, Inc.

CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e), 42.205(b))

The undersigned hereby certifies that the above-captioned Concert Pharmaceutical, Inc.'s Petition for Post-Grant Review Under 35 U.S.C. §§ 321-328 and 37 C.F.R. § 42.200 et seq., was served in its entirety on June 27, 2017, upon the following parties via First Class Mail:

Fish & Richardson PC (INCYTE)
P.O. Box 1022
Minneapolis MN 55440

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Deborah A. Sterling, Ph.D.
Lead Counsel for Petitioner
Registration No. 62,732

Date: June 27, 2017

1100 New York Avenue, N.W.
Washington, D.C.20005-3934
(202) 371-2600