Filed: October 16, 2017

Filed on behalf of: Incyte Corporation

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CONCERT PHARMACEUTICALS, INC.,
Petitioner,

v.

INCYTE CORPORATION,
Patent Owner.

Case PGR2017-00034
Patent 9,662,335

PATENT OWNER'S PRELIMINARY RESPONSE

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EXHIBIT	DESCRIPTION
2001	*FDA Approves Incyte's Jakafi™ (ruxolitinib) for Patients with Myelofibrosis*, BUSINESS WIRE (Nov. 16, 2011) (http://www.businesswire.com/cgi-bin/mmg.cgi?eid=50075108&lang=en).
2002	*Understanding Myelofibrosis (MF) - A guide for patients and caregivers*, Incyte Corporation (May 2017).
2003	*FDA Approves Jakafi® (ruxolitinib) for the Treatment of Patients with Uncontrolled Polycythemia Vera*, BUSINESS WIRE (Dec. 4, 2014) (http://www.businesswire.com/multimedia/home/20141204005888/en/)
2004	Jana von Hehn et al, *Safety, Pharmacokinetic and Pharmacodynamic Evaluation of CTP-543 (Deuterated Ruxolitinib) in a Phase I Healthy Volunteer Study*, CoNCERT Pharmaceuticals Inc. (2014).
2005	B. Belleau et al, *Effect of Deuterium Substitution in Sympathomimetic* Amines *on Adrenergic Responses*, 133 SCIENCE 102 (Jan. 13, 1961).
2006	Allan B. Foster, *Deuterium isotope effects in studies of drug metabolism*, 5 TRENDS IN PHARMACOLOGICAL SCIENCES 524, 524-27 (1984).
2007	L. Shao & M.C. Hewitt, *The kinetic isotope effect in the search for deuterated drugs*, 23(6) DRUG NEWS & PERSPECTIVES 398, 398-404 (2010).
2008	Amanda *Yarnell, HEAVY HYDROGEN DRUGS TURN HEADS, AGAIN*, 87 Chemical & engineering news 36, 36-39 (2009).

EXHIBIT	DESCRIPTION
2009	File History for U.S. Patent Application No. 15/173,057, Preliminary Amendment (June 3, 2016).
2010	File History for U.S. Patent Application No. 15/173,057, Non-Final Office Action (Dec. 14, 2016).
2011	File History for U.S. Patent Application No. 15/173,057, Notice of Allowance and Fees (April 11, 2017).
2012	File History for U.S. Patent Application No. 14/570,954 Non-Final Office Action (July 26, 2017).
2013	Roger Tung, *The Development of Deuterium-Containing Drugs*, INNOVATIONS IN PHARMACEUTICAL TECHNOLOGY, No. 32, pp. 24-28 (2010).
2014	U.S. Patent Application Pub. No. 2007/0066657 (filed Sept. 14, 2006).
2015	U.S. Patent No. 7,863,274 (filed Feb. 8, 2007).
2016	U.S. Patent No. 7,528,131 (filed Apr. 18, 2008).
2017	*CoNCERT Pharmaceuticals, Inc. - Precision Deuterium Chemistry Backgrounder*, CoNCERT Pharmaceuticals, Inc. (2007).
2018	*Concert Pharmaceuticals Unveils CTP-543 for Treatment of Alopecia Areata*, BUSINESS WIRE (May 4, 2016).
2019	U.S. Patent No. 8,796,267 (filed June 17, 2008).
2020	Jakafi® Label (March 2016).

I. Introduction

Petitioner has challenged claims 1-6 of U.S. Patent No. 9,662,335 ("the '335 patent," Ex. 1001), which cover the compound ruxolitinib[1] having one or more hydrogens replaced by deuterium. (Ex. 1001 at claim 1.) Petitioner does not dispute that ruxolitinib was specifically exemplified and deuteration expressly described in priority applications dating back to at least 2006. Yet, Petitioner asserts that the patent is based on a PGR-eligible transitional application due to an alleged lack of enablement and written description, and an alleged June 3, 2016, effective filing date.

Petitioner's assertions are premised upon irrelevant evidence and erroneous legal standards and, consequently, fail as a matter of law. For those reasons, the '335 patent is not PGR eligible, and the Silverman[2] document undergirding Petitioner's anticipation assertions is not prior art.

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[1] For simplicity, this Response uses "ruxolitinib" in the same manner as the Petition, *i.e.*, "ruxolitinib" refers to the named compound of claim 1 (3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile), which includes the (*3R*)- and (*3S*)- enantiomers. (*See* Pet. at 7, n.3; Ex. 1001 at claim 1.)

[2] WO 2013/188783 ("Silverman," Ex. 1004.)

In particular, Petitioner's written description challenge rests on misrepresentations and misapplications of the law and ignores the '335 patent's express disclosure. Petitioner asserts that under *Ariad*[3] "written description *requires* a representative number of species that fall within the scope of the genus."[4] (Pet. at 80.) But the en banc *Ariad* Court specifically held that written description can be *fully satisfied* by describing "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350. Petitioner's own claim construction and supporting declaration demonstrate why it would have been futile for Petitioner to argue that one could not "visualize or recognize" the members of the claimed genus from the ruxolitinib chemical structure expressly disclosed in the '355 patent.

And contrary to Petitioner's misapplication of the Federal Circuit's "blaze mark" jurisprudence, the claims are not based on picking and choosing among a menu of unconnected features in the specification. Nor is functional claiming used to define deuterated ruxolitinib. Rather, the '335 patent describes ruxolitinib as a

[3] *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) ("*Ariad*").

[4] Unless indicated otherwise, all emphases are added.

compound of the invention in a working example that includes its synthesis, and specifically discloses deuterium substitution for ***all*** "compounds of the invention." (Ex. 1001 at 109:1-110:38; 32:60-64, 67:65-68:6.) Petitioner does not dispute that ruxolitinib is a "compound of the invention" to which deuterium substitution expressly applies. It simply ignores these facts and fails to carry its burden to establish a lack of written description.

Petitioner also asserts that the '335 patent claims are not-enabled in priority documents before March 16, 2013 and thus the '335 patent is PGR eligible, and in addition that the claims are unpatentable as non-enabled. Petitioner's evidence, however, does not purport to demonstrate that undue experimentation would have been required to *make* the claimed deuterated ruxolitinib analogs. Just the opposite. Its declarant concedes and demonstrates that "***deuterated ruxolitinib analogs could be synthesized using different [known prior art] strategies***." (Ex. 1002 at ¶ 126.)

What Petitioner argues is that it would have been at least difficult to make and then *isolate* each of the deuterated compounds. But isolation is not a claim requirement, even as construed by Petitioner (*see* Pet. at 11-12). *SmithKline Beecham Corp v. Apotex Corp*, 403 F.3d 1331, 1339-40, 1346 (Fed. Cir. 2005) (claim to chemical compound "covers any amount of [the compound] without further limitation"). Nor is isolation required for their enablement. *In re Breslow,*

616 F.2d 516, 517-19, 522 (C.C.P.A. 1980) (reversing non-enablement rejection, holding that isolation of the claimed compounds was not required). Consequently, Petitioner's argument based on "isolation" is founded on a non-claim limitation and irrelevant to the issue of enablement.

For these reasons, the Petition lacks any basis to negate the '335 patent claims' written description or enablement support in the '335 patent or any of the priority documents dating back to at least December 6, 2006, all of which Petitioner admits "share[] an identical specification" with the '335 patent (Pet. at 3). The '335 patent claims have effective filing dates much earlier than the March 16, 2013 date on which the AIA became effective. Consequently, the effective filing date of the '335 patent claims is far too early for the '335 patent to be PGR eligible.

The Petition should be denied.

II. Background

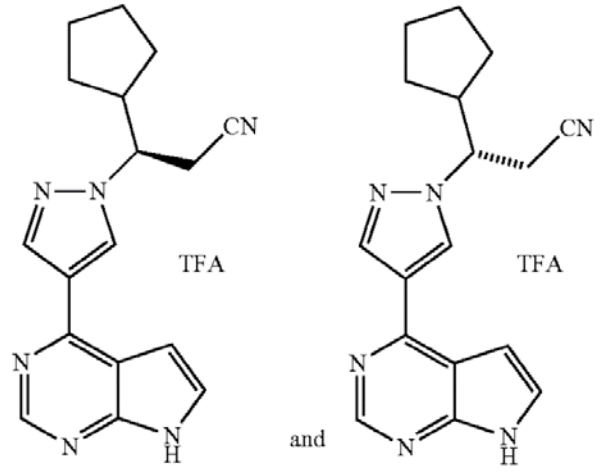
A. The '335 Patent and Prosecution History

The '335 patent[5] discloses inventive compounds, including ruxolitinib, that modulate the activity of Janus kinases—biologically important enzymes involved

[5] As noted in the text above, Petitioner admits that the '335 patent "shares an identical specification with each of the parent applications beginning with U.S.

in, among other things, immune-related diseases, skin disorders, myeloid proliferative disorders, and cancer. (*E.g.*, Ex. 1001 at 1:25-35.) Ruxolitinib's IUPAC name, chemical structure, exemplary synthesis, chiral separation, and biological activity are all expressly described in the specification. (*E.g.*, *id*. at Example 67 (109:1–111:46).) Indeed, its chemical structure is specifically illustrated:

Example 67: (3R)- and (3S)-3-Cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl] propanenitrile



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Appln. No. 11/637,545," filed on December 12, 2006. (Pet. at 3.) Thus, for simplicity, Patent Owner refers herein to the '335 patent specification with the understanding that the referenced passages apply equally to the pre-March 16, 2013, parent applications, going all the way back to at least the December 12, 2006 '545 application.

(*Id.* at 109:1-20.)

The specification's exemplary synthesis and ruxolitinib working example (Example 67) discloses forming ruxolitinib by the synthetic coupling of three main components: (i) the cyclopentyl ring, (ii) the pyrazole ring, and (iii) the pyrrolopyrimidine ring. (*E.g.*, *id.* at 108:9-38 (coupling pyrrolopyrimidine ring to pyrazole ring), 109:23-110:38 (synthesis of 3-cyclopentylacrylonitrile and coupling to the assembled pyrrolopyrimidine and pyrazole structure to form, after deprotection, ruxolitinib); *see also, e.g.*, Ex. 1002 at ¶ 126 (citing the '335 patent specification and showing coupling of pyrrolopyrimidine ring to pyrazole ring followed by coupling of 3-cyclopentylacrylonitrile to the assembled pyrrolopyrimidine and pyrazole structure).) The '335 patent working example further discloses preparing separated ruxolitinib enantiomers and explains that they "were found to be active JAK inhibitors." (Ex. 1001 at 109:66-110:4.)

The specification teaches that the "[c]ompounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds." (*Id.* at 32:60-61.) In this regard, the specification identifies "[i]sotopes of hydrogen includ[ing] tritium and deuterium." (*Id.* at 32:62-64.) The specification further states that the invention includes "isotopically-labeled compounds," defined as "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)." (*Id.* at 67:65–68:4.) Deuterium (^{2}H) is the first isotope identified. (*Id.* at 68:4-6.)

On June 3, 2016, Patent Owner Incyte filed the patent application (No. 15/173,057) that matured into the '335 patent. The specification was substantively "identical" to its priority application, U.S. Ser. No. 11/637,545, filed Dec. 12, 2006. (Pet. at 3.) Patent Owner concurrently submitted a preliminary amendment adding claims 89-94, which later issued, without change, as claims 1-6 of the '335 patent. (Ex. 2009.) In the preliminary amendment, Incyte referenced the above-identified disclosures as supporting claims 89-94. (*Id.* at 3.)

Consistent with Incyte's patent application and pre-March 16, 2013, priority documents describing and enabling these claims, the PTO examined and allowed claims 89-94 under the *pre-AIA first to invent* provisions. (Ex. 2010 at 3 of 18 ("The present application is being examined under the pre-AIA first to invent provisions."); Ex. 2011 at 5 of 5 (indicating allowance under first-to-invent standard).) Similarly, in rejecting one of ***Concert's*** pending patent applications to a deuterated ruxolitinib, the very same Examiner reconfirmed that "a POSA would have understood that [Incyte's specification] disclose[s] a genus of deuterated ruxolitinib molecules." (Ex. 2012 at 7 of 10.)

B. (*3R*)-Ruxolitinib (Jakafi®)

Patent Owner Incyte developed and markets (*3R*)-ruxolitinib under the trade name Jakafi® to treat certain cancers by inhibiting cytokines and growth factor receptors that use JAK1/2 for signaling. (Ex. 2001; Ex. 2002; Ex. 2020.) In 2011, Jakafi® became the first, and to date still the only, FDA-approved treatment for intermediate and high-risk myelofibrosis, a debilitating bone marrow cancer. (*Id.*)[6]

Petitioner is attempting to copy Jakafi® using a deuterated analog. (Ex. 2004 ("CTP-543 is a deuterium-modified analog of ruxolitinib").) Copying FDA-approved drugs with deuterated analogs is, in fact, the premise of Concert's business. (*See* Ex. 2017 at 3 ("CoNCERT compounds are based on drugs with known efficacy and safety that address clinically validated targets," which "substantially reduce[s] R&D risk, time and expense.").) Indeed, it was only after FDA approval and Incyte's commercial launch of Jakafi® that Concert filed any patent applications or initiated any clinical trials relating to deuterated ruxolitinib. (*See* Ex. 1004 at 1 (earliest priority claim is June 15, 2012); Ex. 2018 at 1 (Concert announced pursuit of deuterated ruxolitinib in May 2016).)

[6] In 2014, it also became the first, and still the only, FDA-approved treatment for patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. (Ex. 2003; Ex. 2020.)

C. Deuterium Substitution

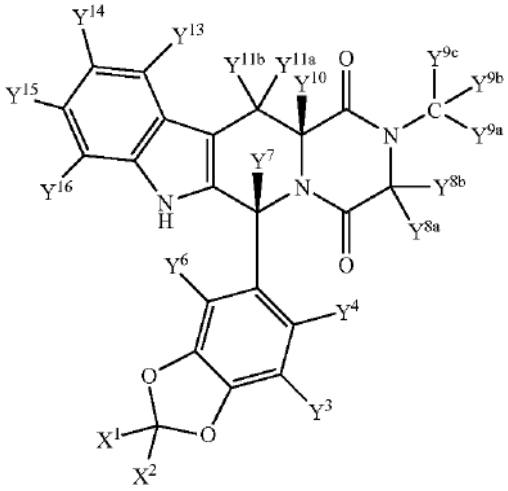
Deuterium (^{2}H) substitution of protium (^{1}H) has been practiced in the field of medicinal chemistry for over 50 years. (*See* Ex. 2005 (published in 1961); Ex. 2007 at 398.) It is commonly used for isotopic labeling, such as in routine metabolic studies, and for delaying metabolism to, for example, extend a biological half-life. (Ex. 2006 at 524-25; Ex. 2007 at 398-99.) As described by Petitioner, deuterium substitution is a "subtle" tool that Concert has never seen change the "potency or selectivity to relevant pharmacological targets." (Ex. 2013 at 24, 28; *see also* Ex. 2008 at 39 ("At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it[.]'").)

Petitioner alleges in its enablement arguments here that there is a "dearth of prior art" in the field of deuteration. (Pet. at 21.) Yet, for over a decade, Petitioner has represented in its patent applications that methods of incorporating deuterium in target compounds are "extensively documented," that "deuterium-labeled reagents" are commercially available, and that substituting one or more hydrogen atoms with deuterium is well within the skill of a person of ordinary skill in the art ("POSA"), especially when the targeted parent molecule's synthesis is known.

(*See* Ex. 2019 at 9:46-58[7]; *see also* Ex. 2016 at 6:29-38 (stating that deuteration "can be readily achieved by synthetic chemists of ordinary skill [by] utilizing corresponding deuterated . . . reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure").)

In fact, in patent documents claiming priority to 2005, Petitioner disclosed the following molecules having more hydrogen atoms than ruxolitinib and represented they "may be synthesized by *well-known techniques*" where "*each hydrogen is optionally and independently substituted with deuterium*":

[7] Citing exemplary literature from *The Journal of Labelled Compounds and Radiopharmaceuticals* ("most issues"), from *Current Organic Chemistry* (1998), and from the Central Institute of Isotope and Radiation Research (1989) for methods of incorporating deuterium "into bioactive small organic molecules," and listing known commercial suppliers of deuterium-labeled reagents, "among others" known in the art.



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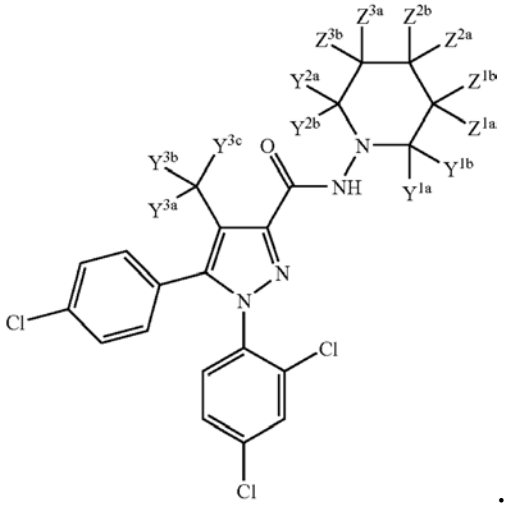

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(Ex. 2015 at 6:10-40, 7:27-53, 15:39-44; Ex. 2014 at ¶¶ 32-37, 96.)

Petitioner's Silverman application, relied on in the Petition as anticipatory prior art, without purporting to identify any new deuteration synthetic techniques or separation methods, discloses certain deuterated ruxolitinib analogs and states that they can be prepared by following the synthesis in a priority document of ***the '335 patent***:

> Compounds of Formula I or Formula A may be prepared in a manner analogous to those ***syntheses presented in US Patent 7,598,257*** [*i.e.*, a parent of the '335 patent] and in Organic Letters, 2009, 11(9): 1999-2009 using appropriately deuterated starting materials.

(Ex. 1004 at 14 (stamped page).) This is yet another gross inconsistency with Petitioner's assertions.

Accordingly, Petitioner's representations in the Petition that "knowledge in the field was not sufficient" (Pet. at 3) and deuterium substitution patterns "are numerous and exceedingly complex" (Pet. at 24) are irreconcilable with and undermined by its prior admissions to the effect that ruxolitinib deuteration requires no more than "standard synthetic protocols." *See, e.g.*, *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Paper 16 at 14, 16-17 (a petitioner's enablement challenge to a three-drug combination was undermined by its admissions elsewhere that "multi-drug combinations of chemotherapy agents were routinely used to treat breast cancer").

III. Claim Construction

Petitioner construes "one or more hydrogen atoms" of ruxolitinib in the claims to mean that "any one or any combination of the 18 hydrogen atoms of ruxolitinib may be replaced with deuterium." (Pet. at 11.) At this stage, Incyte does not dispute Petitioner's construction.

However, *inconsistent* with its own construction and *irrelevant* to enablement, Petitioner's PGR eligibility argument includes Petitioner's fabricated requirement that each individual deuterated species within the scope of the claims be "isolated." (Pet. at 26-27 ("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.").) Petitioner cites no basis in the claims, specification, or prosecution history for reading this "isolation" requirement into the claimed compounds. Indeed, doing so would be legal error, and the Board should simply bat down Petitioner's desperate Hail Mary pass. *SmithKline*, 403 F.3d at 1339-40, 1346 (claim to "[c]rystalline paroxetine hydrochloride [("PHC")] hemihydrate" "covers any amount of crystalline [PHC] hemihydrate without further limitation"; reversing claim construction requiring the non-claimed limitation "commercially significant amounts of PHC hemihydrate").

Petitioner also argues that the claims cover "a nearly infinite number of mixtures" of deuterated ruxolitinib analogs. (Pet. at 12; *see also id.* at 28-29 ("a POSA would need the individual analogs in order to adjust the relative amounts for the various mixtures").) But Petitioner's argument is nothing more than misdirection. The claims recite novel chemical compounds, *i.e.*, new molecules. Contrary to the premise of Petitioner's argument, the claims do not require mixtures. Mixtures are relevant only to the extent they contain a claimed deuterated ruxolitinib molecule. Nothing more is required for the deuterated ruxolitinib claimed beyond the existence, wherever found and in "any amount," of one or more deuterated ruxolitinib molecules. *SmithKline*, 403 F.3d at 1339-40, 1346.

IV. Petitioner Failed to Establish PGR Eligibility

To establish PGR eligibility here, Petitioner bears the burden of demonstrating by a preponderance of the evidence that the patent contains a claim not described or enabled by any pre-March 16, 2013, priority application. *See, e.g.*, *Wombat Security Techs. v. PhishMe, Inc.*, PGR2017-00009, Paper 7, at 7-8 (P.T.A.B. June 8, 2017); *Fox Factory, Inc. v. SRAM, LLC*, PGR2016-00043, Paper 9, at 7 (P.T.A.B. Apr. 3, 2017). The Petition fails to carry this burden and should be denied.[8]

A. Petitioner Misrepresents and Misapplies the Written Description Requirement

Petitioner seeks to apply an artificially heightened written description standard under which the '335 patent inventors were obligated to (1) identify ruxolitinib as "superior" or as a "lead compound" (Pet. at 8); (2) direct a POSA to "choose" deuterated ruxolitinib (*id*. at 77); and (3) describe particular species of deuterated ruxolitinib (*id*. at 80). Simply not so. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003) (written description "does not require a particular form of disclosure").

[8] The Petition rises and falls on its challenge to claim 1, as Petitioner does not purport to identify any independent basis to challenge any other claim.

The ’335 patent specification (1) discloses the (*3R*)- and (*3S*)- structures of the claimed 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile (*i.e.*, ruxolitinib); (2) provides a working example describing an exemplary chemical synthesis; (3) demonstrates separation of the (*3R*)- and (*3S*)-isomers, (4) describes ruxolitinib’s biological activity, and (5) expressly teaches deuterium isotopes of the “compounds of the invention.” (Ex. 1001 at 32:60-64, 67:65-68:6, 109:1-111:46 (Example 67).) These expressly described structural features, including the chemical structure and chemical formula (*id.* at 109:1-110:38), allow a POSA to easily visualize or recognize the members of the claimed genus, a point Petitioner’s own declarant concedes in his claim construction analysis. (*See* Ex. 1002 at ¶ 77.) Nothing more is required to satisfy the written description requirement. *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc*., 744 F.3d 725, 730 (Fed. Cir. 2014) (“[T]his court has repeatedly explained that an adequate written description requires a precise definition, such as *by structure, formula, chemical name*, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials. Describing a complex of dutasteride and solvent molecules is an identification of structural features commonly possessed by members of the genus that distinguish them from others, allowing one of skill in the art *to visualize or recognize* the identity of the members of the genus.” (citations and quotations omitted)).

Petitioner's attempts, moreover, to characterize this as an *Ariad* functional claiming case and a *Novozymes*[9] "blaze mark" case are further misdirection. This will now be explained.

1. *Ariad*'s "Representative Number of Species" Is Inapplicable to Claims Defined by Structural Features

Citing *Ariad*, Petitioner contends that "written description ***requires*** a representative number of species that fall within the scope of the genus." (Pet. at 80; *see* Ex. 1002 at ¶ 163.) Petitioner misrepresents the Federal Circuit's en banc opinion, which summarized the law as follows:

> We held that a sufficient description of a genus instead requires the disclosure of ***either*** a representative number of species falling within the scope of the genus ***or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus***. We explained that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

Ariad, 598 F.3d at 1350 (internal citations omitted).

[9] *Novozymes A/S v. Dupont Nutrition Biosci. APS*, 723 F.3d 1336 (Fed. Cir. 2013) ("*Novozymes*").

Providing a representative number of species is ***one way*** of describing a genus. *Id.* It is not required where, as here, common "structural features" are described, as in, *e.g.*, "3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1yl]propanenitrile"—a "compound of the invention"—having one or more hydrogen atoms replaced by deuterium (Ex. 1001 at 109:1-111:46, 32:60-64, 67:65-68:6). *Ariad*, 598 F.3d at 1350; *see also In re Robins*, 429 F.2d 452, 456-57 (C.C.P.A. 1970) ("*Mention of representative compounds* encompassed by generic claim language clearly *is not required by § 112* or any other provision of the statute."). Written description can be fully satisfied if the disclosure includes "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350.

Petitioner never argues that the structure of the claimed genus is insufficiently described such that a POSA could not have "visualized or recognized" the deuterated ruxolitinib members of the genus. Nor could it make such an assertion because, given the '335 patent's express disclosure of the chemical name and structure of ruxolitinib (Ex. 1001 at 109:1-111:46), a POSA indisputably would have known the location of each hydrogen atom, which, as the specification explains, can be replaced by deuterium. Petitioner's declarant, Dr.

Crimmins, concedes the point in his claim construction analysis. (Ex. 1002 at ¶ 77 (depicting the hydrogen atoms in ruxolitinib's chemical structure).)

Petitioner also relies on *Billups-Rothenberg, Inc. v. Assoc. Regional Univ. Pathologists, Inc.* (Pet. at 81-82), but that case, much like *Ariad*, concerned functional claiming. 642 F.3d 1031, 1033 (Fed. Cir. 2011). Specifically, the claims required detecting a gene mutation indicative of hemochromatosis. *Id.* The patentee, however, "had not yet identified any disease-causing mutations." *Id.* Instead, the specification "contain[ed] *only functional*, not structural, characteristics of the predicted mutations." *Id.* at 1037. Although the Court noted that the patent failed to identify any species that satisfied the claims, it did so not because reciting individual species was required, but to reinforce that no adequate structural characteristics of the predicted mutations were described. *Id.*

The facts in *Billups* bear no analogy to the instant case. The '335 patent claims a genus of ruxolitinib compounds that are deuterated, the structural characteristics of which are undeniably disclosed in the specification. Nothing more is required to satisfy written description, and Petitioner's assertion that disclosure of individual representative species is required is erroneous.

2. Petitioner's "Blaze Marks" Argument Misses the Mark

Petitioner additionally contends, in arguing lack of written description, that "blaze marks" to the claimed deuterated ruxolitinib are missing and that Incyte

"pieced the claims together, picking and choosing from disparate bits of the broad disclosure." (Pet. at 74; *see also id.* at 2.) To the contrary, there was no "picking and choosing," and thus no missing "blaze marks," because the '335 patent's explicit disclosure of deuterium substitution applies to ***all of the*** "***compounds of the invention***," including ruxolitinib. (Ex. 1001 at 32:60-64, 67:65-68:6: 109:1-110:38.) Petitioner does not contend otherwise; it simply ignores this express disclosure. Nor can Petitioner dispute that ruxolitinib is a "compound of the invention."

More specifically, the '335 patent describes ruxolitinib as a compound of the invention with great particularity, including by name, chemical structure, and exemplary synthesis. (Ex. 1001 at Example 67 (109:1 – 111:46).) Notably, within the '335 patent's enumerated examples, the specification emphasizes the (*R*)- and (*S*)- enantiomers of ruxolitinib as having been "found to be active JAK inhibitors." (*Id.* at 110:2-4.)

Although not a prerequisite to written description, the fact that the ruxolitinib enantiomers are emphasized in this way—a point not addressed by Dr. Crimmins—evidences the baselessness of his assertion that "a POSA reading the '335 patent specification would not have thought the inventors considered ruxolitinib . . . to be a lead compound" (Ex. 1002 at ¶ 158). *See, e.g., Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.,* 532 F. Supp. 2d 666 (D.N.J.

2007), *aff'd*, 566 F.3d 999, 1008–09 (Fed. Cir. 2009) (holding that "compound 12" would have been a "lead compound" based on its reported high potency).

The specification further teaches that the "***[c]ompounds of the invention*** can also include all isotopes of atoms occurring in the intermediates or final compounds." (Ex. 1001 at 32:60-61.) Among the isotopes, the specification particularly and expressly identifies "[i]sotopes of hydrogen includ[ing] tritium and ***deuterium***." (*Id.* at 32:62-64.) Consistently, the specification elaborates that the invention "includes isotopically-labeled compounds," defined as "***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)." (*Id.* at 67:65–68:4.) Deuterium (^{2}H) is the first isotope identified. (*Id.* at 68:4-6.)

Ruxolitinib, a compound whose structure and synthesis are expressly disclosed, is undeniably a "compound of the invention" to which the disclosed deuterium substitution applies. Thus, ruxolitinib and its deuteration are not "disparate" disclosures; they are ***directly related***. *See, e.g.*, *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1358-59 (Fed. Cir. 2016) (finding in the context of anticipation that alleged disparate disclosures were in fact "'directly related' and thus there is no impermissible picking and choosing").

That a POSA would have understood the '335 patent specification to describe deuterated ruxolitinib has been independently confirmed during prosecution of one of *Petitioner's* patent applications. In rejecting a currently pending Concert patent application seeking to claim a deuterated ruxolitinib, the very same USPTO patent examiner specifically found that a person of ordinary skill in the art would have understood the '335 patent to describe ruxolitinib that has been deuterated:

> Rodgers *[i.e., the '257 patent, which has the same specification as the '335 patent]* discloses 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-yl-1-yl]propanenitrile or a pharmaceutically acceptable salt thereof, and specific enantiomers of 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-yl-1-yl]propanenitrile. See, e.g., Rodgers, Claims 1-3. ***One of these specifically-recited enantiomers is ruxolitinib***. ***Rodgers explains that deuterated forms of the disclosed compounds are within the disclosure***, column 32, lines 13-17 [*i.e.*, Ex. 1001 at 32:60-64]. ***A person of ordinary skill in the art (POSA) reading Rodgers would have understood compounds of the disclosed invention (ruxolitinib) included compounds where deuterium isotopes replaced the hydrogen moieties of ruxolitinib. From these teachings, a POSA would have understood that Rodgers disclosed a genus of deuterated ruxolitinib molecules.***

(Ex. 2012 at 6-7 of 10.)

Even Petitioner's declarant, Dr. Crimmins, explains that the '335 patent provides "generic teachings that the compounds can contain isotopes, like deuterium[.]" (Ex. 1002 at ¶ 146.) That the specification describes, by Petitioner's count, "approximately 600" compounds in the Examples does not detract in any way from the patent's disclosure. *See In re Barr*, 444 F.2d 588, 596-97 (C.C.P.A. 1971) ("Appellants have specifically disclosed how to make and use a large number of compounds and have asserted that other compounds, similar to the compounds specifically disclosed in certain stated respects, may be made and used in the same fashion. We see no reason, on the state of this record, to suspect that their assertion is not accurate or that appellants are not the pioneer inventors they claim to be. Appellants' application runs to 132 pages in the transcript of record, and we are not persuaded that any useful purpose would have been served by extending it with further working examples."). The disclosed deuteration clearly applies to each and every one of the exemplified compounds of the invention, including, as the Examiner found, ruxolitinib.

Petitioner's misapplication of *Novozymes* provides further basis for the Board to reject Petitioner's written description argument. The claims in *Novozymes* were directed to an alpha-amylase variant having a combination of three specific features: (1) at least 90% sequence identity to BSG alpha-amylase,

(2) an amino acid substitution at serine 239, and (3) a ***particular functionality*** of increased thermostability at 90 °C, pH 4.5, and 5 ppm calcium. *Novozymes*, 723 F.3d at 1348. The specification, however, "nowhere describe[d] the actual functioning, thermostable alpha-amylase variants that those limitations together define[d]." *Id.* at 1349. That is, the specification contained no "blaze marks" to the alpha-amylase variants that exhibit the ***particular functionality*** claimed. *Id.* In fact, the parties agreed that "the only specifically described substitution . . . *[did] not* confer increased thermostability . . . and thus would fall outside of the claims." *Id.* (emphasis in original).

In contrast, the claims of the '335 patent are defined by structure, not by function. (Ex. 1001 at 366:14-34; *see also* Ex. 1002 at ¶ 77 (expressly showing the hydrogen atoms in the ruxolitinib molecule).) And, unlike *Novozymes*, this is not a case where a disclosed feature (deuteration) applies to certain compounds of the invention ***at the exclusion of others***. *See Novozymes*, 723 F.3d at 1348. Rather, as explained above, the deuteration described in the '335 patent applies to each of the "compounds of the invention," including ruxolitinib. *Novozymes* simply does not apply here.

For all these reasons, Petitioner's lack of written description argument fails, as does its argument that the alleged lack of written description limits the '335 patent claims to a PGR-eligible June 3, 2016 filing date.

B. Petitioner's Non-Enablement Theory Fails as a Matter of Law

We now turn to Petitioner's failing non-enablement argument. The enablement requirement is directed to how to make and use the *claimed invention*. 35 U.S.C. §112. The requirement does not extend to unclaimed features. *See DeGeorge v. Bernier*, 768 F.2d 1318, 1324 (Fed. Cir. 1985) ("[T]he enablement requirement of § 112 was satisfied by disclosure of detailed, *claimed* TCCPI circuitry without requiring detailed disclosure of all related, *unclaimed* circuitry with which the TCCPI might be interfaced." (emphasis in original)); *see also Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) ("Although Clontech's validity argument might have force had Invitrogen limited its claims to modified RT by reference to point mutation, Clontech overlooks the fact that the claims *are not limited by the method of achieving the mutation*.").

Petitioner provides no *evidence* that undue experimentation would have been required to *make* the *claimed* deuterated ruxolitinib analogs.[10] In fact, as detailed below in Subsection 1.a, Petitioner's declarant, Dr. Crimmins, affirmatively demonstrates that making each of the deuterated analogs he discusses was within the skill of a POSA. No more is required to enable the claimed deuterated

[10] Petitioner does not contest the "use" aspect of enablement.

ruxolitinib. *See, e.g.*, *Invitrogen Corp.*, 429 F.3d at 1071 (enablement is satisfied by "any mode of making and using the invention").

The Petition's enablement challenge boils down to whether each of the compounds, *after being made*, could have been *isolated* as individually pure species. (*See, e.g.*, Pet. at 26-27 ("While attempts to prepare deuterated ruxolitinib analogs might have ***resulted in specific mixtures of the claimed compounds*** . . . ***separating individual deuterated analogs from such a mixture*** would have been very difficult, if not impossible, using known techniques."); *id.* at 10 ("***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.").) However, as explained above under "Claim Construction" (Sec. III) and as detailed further below in Subsection 1.b, "isolation" is not a requirement of the claims, even as construed by Petitioner.

Petitioner cannot carry its burden by resting its enablement argument on an unclaimed and irrelevant "isolation" requirement—especially after its declarant affirmatively depicted how the claimed compounds could have been made using known techniques. *See, e.g.*, *Ossia, Inc. v. Energous Corp.*, PGR2016-00024, Paper 20 at 22-23 (P.T.A.B. Nov. 29, 2016) (rejecting non-enablement premised on an unclaimed feature where the petitioner argued "it is not possible to collect or gather *power*," but the claims were directed to "accumulat[ing] pockets of

energy"); *Inguran, LLC v. Premium Genetics (UK) Ltd.*, PGR2015-00017, Paper 8 at 18-19 (P.T.A.B. Dec. 22, 2015) (rejecting non-enablement premised on a non-limitation where the petitioner argued the patent "lacks any example showing a *single output channel*," but the claims recited "at least one channel" without an output designation).

Petitioner's further arguments are equally unavailing. As explained in Subsection 2 below, Petitioner's claim "breadth" and lack of "guidance" assertions ignore both the '335 patent's working example of ruxolitinib and Petitioner's own evidence that making the deuterated compounds was within the skill of a POSA. And its attempted case law analogies fall flat, as the declaration evidence offered by Petitioner demonstrates enablement, as explained in Subsection 3 below.

1. Petitioner's Evidence Demonstrates That "Making" Is Enabled and Challenges Only "Isolating"

The Petition *asserts* that a POSA "would have been unable to make and/or isolate" the claimed deuterated analogs without undue experimentation. (*See* Pet. at 28.) Its "make and/or isolate" and "synthesizing and/or isolating" mantra is repeated approximately 20 times in the Petition and approximately 27 times in the accompanying declaration. (*See, e.g.*, Pet. at 50; Ex. 1002 at ¶ 136.)

Apart from using the conjunction "and/or," however, the Petition cannot be read to separately contest "making." Its ***evidence*** demonstrates that the

compounds could have been made by standard techniques and, at best, challenges ***only*** whether the claimed compounds, once made, could have been ***isolated***. *See Midwest Indus. Supply, Inc. v. Soilworks, LLC*, PGR2016-00014, Paper 6 at 15 (P.T.A.B. Sept. 7, 2016) (denying institution, explaining, *inter alia*, that "the Petition directs us to no evidence—nothing beyond the *ipse dixit* attorney argument in the Petition itself—to support Petitioner's contention that a [POSA] would have been unable, without undue experimentation, to determine whether a particular mixture 'has methyl, dimethyl, and trimethyl-branched alkanes'").

Indeed, the Petition fails to identify ***even one*** deuterated ruxolitinib that would have required undue experimentation to make. Instead, after recognizing the '355 patent discloses synthesis of ruxolitinib using three component building blocks, Dr. Crimmins demonstrates in detail, as will be explained below, how to make, at least in mixtures, ***all*** the deuterium-substituted building blocks he considers. (Ex. 1002 at ¶¶ 97-140 (demonstrating, in turn, enablement for deuterium substitution on each of the cyclopentyl ring, pyrazole ring, and pyrrolopyrimidine ring); *see also, e.g.*, Pet. at 28 (citing, *inter alia*, these same paragraphs in the Crimmins declaration (¶¶ 97-140) and conceding that "*the desired deuterated ruxolitinib analog would be [made] as part of a mixture* with other deuterated ruxolitinib analogs").)

Nothing more is required for enablement, which is satisfied by "*any mode* of making and using the invention." *Invitrogen*, 429 F.3d at 1071 (rejecting non-enablement argument premised on an unclaimed "point mutation" method because a known "deletion mutation" technique could have been used to make the claimed genetically modified enzyme); *Midwest Indus.*, PGR2016-00014, Paper 6 at 14-15 (petitioner failed to show non-enablement starting from non-pure components and thus "enablement for making the claimed mixtures from pure components *[was] not necessary*").

And, as will be explained, because Petitioner's only actual contention that a POSA would have been unable to *isolate* certain deuterated analogs from reaction mixtures is irrelevant, "this evidence, even if unrebutted, would be insufficient to meet Petitioner's burden." *Fox Factory*, PGR2016-00043, Paper 9, at 14-15.

a. Petitioner's Declarant Demonstrates Enablement of Each Deuterated Building Block and Challenges Only Their "Isolation"

Petitioner's declarant addresses deuterium substitution of the three ruxolitinib synthetic building blocks taught in the '355 patent: (i) the cyclopentyl ring (Ex. 1002 at ¶¶ 97-122), (ii) the pyrazole ring (Ex. 1002 at ¶¶ 123-136), and (iii) the pyrrolopyrimidine ring (Ex. 1002 at ¶¶ 137-140). (*See also* § II.A. above.) Petitioner summarizes its enablement challenge as directed to "non-symmetric deuterium substitution patterns *at carbon positions 5-8 of the cyclopentyl ring* or a

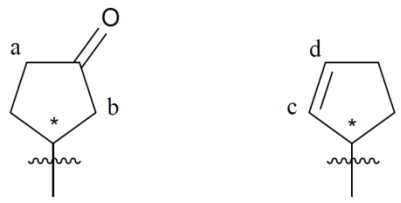
single deuterium *at carbon positions 9 and 11 of the pyrazole ring*, as well as other locations on ruxolitinib such as *the pyrrolopyrimidine ring*." (Pet. at 60-61; *see also id.* at 71, 72.) Yet, as shown below, for each of these three building blocks, Petitioner's evidence fails to identify even a single deuterated ruxolitinib that would have required undue experimentation to make.

Far from carrying Petitioner's burden on non-enablement, Petitioner's declarant, Dr. Crimmins, demonstrates that deuterating ruxolitinib's cyclopentyl, pyrazole, and pyrrolopyrimidine rings would *not* have required undue experimentation. To be sure, Dr. Crimmins argues that separation issues could have been difficult or even impossible. But, as explained below in Subsection b, separation is irrelevant to enablement of the claimed compounds.

i. Cyclopentyl Deuteration

Petitioner's declarant, Dr. Crimmins, divides deuteration of the cyclopentyl ring into symmetric and asymmetric substitution patterns. (*See* Ex. 1002 at ¶ 102.) Contrary to Petitioner's assertion that a "vast majority of the claimed compounds of the '335 patent have one or more deuterium substitution patterns on the cyclopentyl ring . . . that cannot be made and/or isolated by synthetic methods available to a POSA as of June 3, 2016" (Pet. at 29), Dr. Crimmins does not contend that ***making*** any such substitution patterns would have required undue experimentation.

Instead, Dr. Crimmins concedes that a POSA could have used standard techniques to make "'symmetric' deuterium substitution patterns" and identifies exemplary starting materials and schemes. (Ex. 1002 at ¶¶ 102-106 (see Figures 10-12, Schemes 7, 8).) For "asymmetric" substitution patterns "to replace a hydrogen atom with a deuterium atom at methylene positions of the cyclopentyl ring (*i.e.*, carbon positions 5, 6, 7, 8)" (*id.* at ¶¶ 109-110), Dr. Crimmins similarly provides known intermediates and means (deuterium exchange reaction) from which a POSA "would have likely obtained a complex mixture" of the asymmetrically deuterated cyclopentyl starting materials:

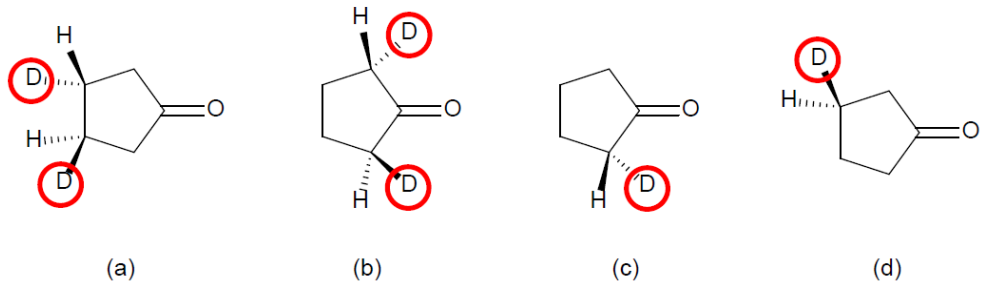
> 111. A POSA may have considered installing a single deuterium atom ***at any of positions 5-8*** on the cyclopentyl ring of ruxolitinib by utilizing a cyclopentyl intermediate containing a carbonyl or a cyclopentene intermediate, such as intermediates (i) and (ii) in Figure 14 below:
>
> Figure 14
>
> 
>
>
> (i) (ii)
>
> A POSA may have considered using an exchange reaction on a carbonyl intermediate (i) of Figure 14 by exposing it to acid or base to form the enol or enolate, respectively, which

> then reacts with a deuterium source to install the deuterium(s) at position "a" and/or "b". *See* CON1025, 7745-7746. . . . [A] POSA ***would have likely obtained a complex mixture*** of up to 16 compounds made up of positional isomers as well as diastereomers (4 positions with a binary choice of hydrogen or deuterium at each position). *See* CON1025, 7745-7746; CON1046, 1351-1352.

(*Id.* at ¶ 111.) Petitioner has not shown that a POSA "more likely than not" would have required undue experimentation to make deuterium substitutions in the cyclopentyl ring at least because its own declarant testified that a POSA could have "likely obtained" such substitutions by known techniques. (*See id.*)

Dr. Crimmins even identifies multiple *additional* routes a POSA could have followed to make the cyclopentyl ring asymmetric substitution patterns. (*See. e.g.*, *id.* at ¶¶ 117-118 ("reductive reaction"), ¶¶ 120-121 (using intermediates previously disclosed by Djerassi et al. and Dauphin et al. in the 1980s).) For example, he shows how a POSA could have prepared the chiral deuterated cyclopentanone intermediates in his Figure 16 using techniques known for over thirty years:

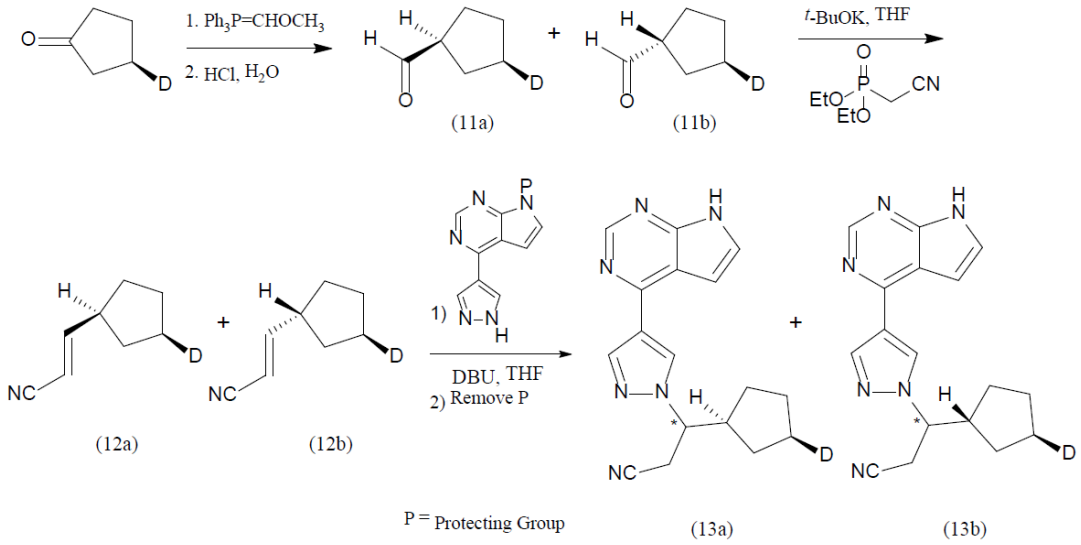
Figure 16



(*Id.* at ¶ 120.)

Using intermediate (d) as an example, Dr. Crimmins further shows in his Scheme 11 that it would have been routine for a POSA to incorporate these deuterated intermediates into the *same synthesis* described in the '335 patent specification for making ruxolitinib, with the result being deuterated ruxolitinib (13a, 13b):

Scheme 11



(*Id.* at ¶ 121 (citing "CON1001, 109:1-110:38," *i.e.*, Incyte's '335 patent specification).) Dr. Crimmins then expressly confirms that a POSA could have

used the "same synthetic strategy" not just for intermediate (d), but for "*all four cyclopentanone derivatives*" presented in his Figure 16 above. (*Id.* at n. 2.)

Dr. Crimmins' contention is that, after making these deuterated analogs in a mixture by the routes above, "a POSA would not have been able ***to routinely separate*** [them] using any standard separation techniques." (*Id*. at ¶ 116; *see also id*. at ¶ 119 ("A POSA would have likely obtained mixtures of deuterated compounds that, as discussed above in ¶¶112-116, would be difficult, if not impossible, ***to isolate*** using standard separation techniques."), ¶ 121 ("For the reasons discussed above in ¶¶112-116, the similarities between deuterated stereoisomers would make it difficult, if not impossible, to isolate the individual compounds using standard separation techniques.").) However, "isolating" or "separating" the deuterated analogs is irrelevant to enablement, as explained in Subsection b below.

ii. Pyrazole Deuteration

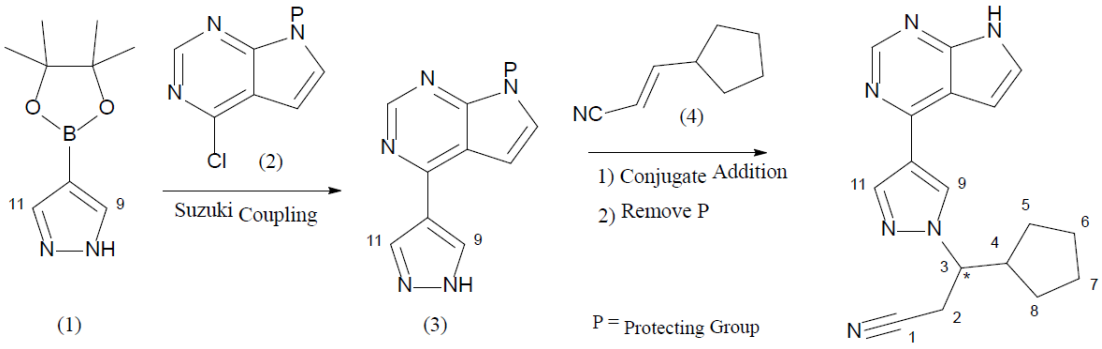
Petitioner *asserts* that "[t]he difficulties in replacing a hydrogen atom with a deuterium atom on the pyrazole ring of ruxolitinib (i.e., positions 9 and 11) extend to 50% of all the claimed compounds." (Pet. at 45.) However, Petitioner's evidence does not show that a POSA would have required undue experimentation to ***make*** the deuterated pyrazole ring analogs. As with the cyclopentyl ring, Dr.

Crimmins' identification of multiple standard synthetic routes demonstrates just the opposite.

Dr. Crimmins first demonstrates that a POSA could have prepared deuterated ruxolitinib analogs with deuterium at *both* positions 9 and 11 (*i.e.*, on the pyrazole ring) by following the same synthetic procedure described in the '335 patent (which Dr. Crimmins exemplifies in his Scheme 12 below) and simply changing the pyrazolo-boronate starting material (1) to a *di-deuterated* pyrazolo-boronate starting material (shown in his Scheme 13 below):

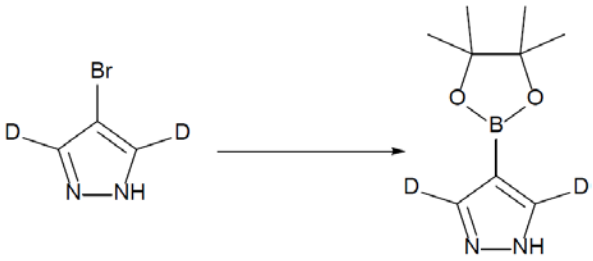
> ***[D]euterated ruxolitinib analogs could be synthesized using different strategies***. One such strategy, shown in Scheme 12 below, would involve a Suzuki coupling with a ***pyrazolo-boronate compound (1***) and a chloro-pyrrolopyrimidine compound (2) in the presence of a catalyst (*i.e.*, a palladium catalyst) to obtain a 4-pyrazolo-pyrrolopyrimidinyl compound (3), which is coupled to a cyclopentyl acrylonitrile compound (4) through a conjugate addition to obtain the desired ruxolitinib analog.

Scheme 12



(Ex. 1002 at ¶ 126 (citing "CON1001, 109:1-110:38," *i.e.*, the '335 patent specification).)

Scheme 13



> ***This dideuterated boronate*** compound could then be used in a Suzuki coupling and subsequent conjugate addition, as depicted above in Scheme 12, ***to obtain the desired derivatives of ruxolitinib having deuterium at both position 9 and 11***.

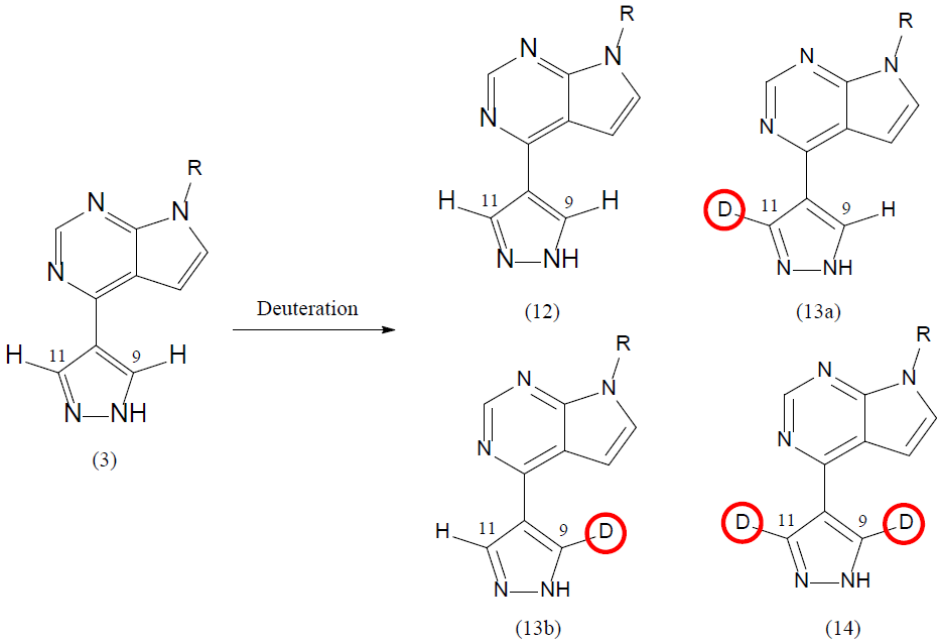
(*Id.* at ¶ 127.) As shown, this route provides deuterium substitution at *both* positions 9 and 11. (*Id.*)

Dr. Crimmins further demonstrates that a POSA could have made not just the di-deuterated pyrazole but *all* deuterated permutations at positions 9 and 11 by

following the same synthetic procedure described in the '335 patent (again, exemplified in his Scheme 12 above) and adding a standard deuterium exchange reaction to the pyrazole starting material (1) or (3). (*Id*. at ¶¶ 128-29 ("Hydrogen atoms on the pyrazole rings of compounds (1) and (3) of Scheme 12 may be replaced with a deuterium atom using a deuterium exchange reaction.").) Using pyrazole compound (3) as a model, Dr. Crimmins illustrates this standard deuteration technique in his Scheme 14 and expressly shows the resultant deuterated pyrazole analogs:

> Thus, as shown in Scheme 14 below, attempts to deuterate compound (3) ***would have likely resulted in mixtures of mono- and dideuterated pyrazole rings*** as well as additional deuterated analogs not shown.

Scheme 14



> *See* CON1025, 7756-7758; CON1026, 748-749. An analogous reaction of the pyrazole boronate compound (1) ***would have also likely resulted in mixtures of mono- and dideuterated pyrazole rings***.

(*Id.* at ¶ 129.)

Just as above for the cyclopentyl ring, Dr. Crimmins' contention is that, after preparing these deuterated analogs (13a, 13b, 14) in a mixture, their "physiochemical characteristics . . . would make them highly difficult, if not impossible, to separate using standard separation techniques." (*Id.* at ¶¶ 130-31.) Once again, as explained below in Subsection b, this alleged inability to "isolate" or "separate" is irrelevant to the '335 patent's compound claims.

iii. Pyrrolopyrimidine Deuteration

Petitioner *asserts* that 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." (Pet. at 49.) But it does not contend that substitution on this ring would require undue experimentation. Petitioner merely states that "different synthetic approache[s]" would be needed for each position (*id.*), an irrelevant and conclusory assertion. *See Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 707 F.3d 1330, 1336-40 (Fed. Cir. 2013) (reversing judgment that claims were invalid for lack of enablement because, even if

contended to be "complicated" and "difficult," "a reasonable amount of routine experimentation required to practice a claimed invention does not violate the enablement requirement").

Indeed, Petitioner offers *no evidence* that *making* the deuterated pyrrolopyrimidines would require undue experimentation. Rather, its declarant, Dr. Crimmins, points to Giles (Ex. 1026) and Atzrodt (Ex. 1025) to demonstrate how a POSA could have made *all* deuterated permutations of the ruxolitinib pyrazole ring in a mixture (*see* § ii above (*e.g.*, Scheme 14)) and concedes that the same "deuterium exchange reactions could be utilized . . . [for] ***the pyrrolopyrimidine ring system of ruxolitinib***" (Ex. 1002 at ¶ 46).

Dr. Crimmins is left to conclude:

> A POSA would have encountered the same problems discussed above, *i.e.*, ***the difficulty or inability to separate*** the deuterated ruxolitinib analog from its non-deuterated counterpart or other deuterated analogs that differ from each other by only a few deuterium atoms.

(*Id.* at ¶ 138.) "Separation" remains irrelevant, and notably absent from Petitioner's evidence is any "difficulty or inability" in ***making*** the claimed compounds.

b. "Isolating" Is Irrelevant to Enablement

Contrary to the premise of Petitioner's non-enablement argument, "isolation" or "separation" of any individual compounds is not required to enable "making" the claimed invention. And Petitioner nowhere contends that deuterated ruxolitinib analogs must be individually separated in order to be "used," *e.g.*, as JAK inhibitors as described in the '335 patent. Nor could Petitioner so contend given its prior representation that it has "never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'" (*See* Ex. 2008 at 39.)

Plain and simple, claim 1 of the '355 patent is directed to ruxolitinib where one or more of the hydrogen atoms are replaced with deuterium, and "covers any amount" thereof "without further limitation." *SmithKline*, 403 F.3d at 1339, 1346 (chemical compound claim "encompasse[d], without limitation, PHC hemihydrate," requiring no more than "one molecule of bound water for every two molecules of paroxetine hydrochloride in the crystal structure"); *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) (holding the district court did not err in finding that "product claims . . . are directed to a structural entity that is not defined or limited by how it is made."); (Pet. at 11 ("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.").) Even under Petitioner's construction (*see* Sec. III above), "isolation" is not a claim limitation and is not required for enablement.

Precedent, not cited by Petitioner, specifically considered and rejected the argument that isolation of a chemical species is required for enablement. *In re Breslow*, 616 F.2d 516, 517-18 (C.C.P.A. 1980). In *Breslow*, the claimed compounds were unstable, transient intermediates incapable of being isolated because they were "so reactive that they will react with each other if there is no other coreactant available." *Id*. The Examiner and the Board had rejected the claims, *inter alia*, under § 112 "for not disclosing how to prepare and isolate the compounds."[11] *Id.* at 516. The C.C.P.A. reversed, holding that the patentability of claims directed to novel chemical compounds requires that a POSA can "make," not isolate, them. *Id.* at 522 ("Surely, appellant has made his nitrile imines, used them, and taught others how to do so.").

[11] On appeal, the Commissioner conceded that if the claimed compounds satisfied § 101, nothing more would be required under § 112 because the appellant "at least taught how to make the unstable, non-isolatable, transitory compounds." *Breslow*, 616 F.3d at 519. Thus, the Commissioner agreed, even before the C.C.P.A. rendered its decision, that there is no additional "isolating" requirement to satisfy enablement.

Petitioner's argument that isolation is required for enablement because "a POSA would need the individual analogs in order to adjust the relative amounts for the various mixtures" (Pet. at 28-29) is merely an attempt to impose one more non-limitation (mixtures of isolated, individual analogs) on its original non-limitation (isolation). Nor is there any requirement for "selectively" synthesizing one deuterated compound at a time to make mixtures. (*See* Pet. at 28 (contending that a POSA could not have "selectively" synthesized one deuterated analog at a time, which "means that the desired deuterated ruxolitinib analog would be part of a mixture").) Such arguments fail in view of, *e.g.*, *SmithKline*, and *Breslow*, *supra*, which show that a compound can be present in any amount or form and even in inseparable mixtures. (*See also* § III above.)

2. *Wands* Factors Do Not Establish Non-Enablement

In addressing other *Wands*[12] factors, Petitioner describes the "breadth of the challenged claims [as] includ[ing] deuterated ruxolitinib analogs that represent every possible combination of one to 18 deuterium replacements for hydrogen on ruxolitinib." (Pet. at 58-59; *see also id.* at 23-24, 26.) But breadth alone is insufficient to establish that making compounds within the claim scope would require undue experimentation. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188-89 (Fed. Cir. 2014) (reversing judgment of non-enablement where the

[12] *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) ("*Wands*").

district court relied only on the large number of variables and parameters at issue and there was no evidence that "any experimentation, let alone undue experimentation" was required to practice the claimed invention). The *Wands* factors are not "a generalized *test* for deciding whether a patent disclosure is sufficiently detailed to support a broad claim" but rather "provide the *factual considerations* that a court may consider when determining whether the amount of that experimentation is either 'undue' or sufficiently routine such that an ordinarily skilled artisan would reasonably be expected to carry it out." *Id.*

As in *Alcon*, Petitioner here fails to establish, as explained in Sec. IV.B.1.a above, that it would have been beyond the skill of a POSA to make the compounds encompassed by the claims. To the contrary, Petitioner's declaration evidence establishing that deuterated ruxolitinib compounds could have been made by a POSA without undue experimentation belies any *Wands* argument based on the breadth of the claim or otherwise. (*See* § IV.B.1.a above.)

Moreover, the fact that Petitioner's declarant demonstrates that each of the three component building blocks described in the ***'335 patent's working example*** for synthesizing ruxolitinib (*see* Ex. 1001 at 109:1–111:46 (Example 67)) could have been deuterated by known techniques (*see* § IV.B.1.a. above) also disproves any assertion that the '335 patent specification provides "no guidance" or "working example" for preparing the claimed genus. (Pet. at 60.) Petitioner's alleged

absence of "guidance" is also irreconcilable with its representations elsewhere that substituting one or more hydrogen atoms with deuterium is within the skill of a POSA, particularly when the POSA has the synthesis of the target compound (*i.e.*, ruxolitinib) in hand. (*See, e.g.*, Ex. 2019 at 9:46-58 ("General methods of incorporating deuterium in similar compounds are extensively documented."); *supra* at § II.C.)

3. Petitioner's Cited Case Law In Fact Supports Denial

The case law alleged by Petitioner to "compel[]" a finding of non-enablement is readily distinguishable and instead supports denial of the Petition. (*See* Pet. at 62-72.)

Storer v. Clark (*see* Pet. at 62-68) involved method of treatment claims requiring administration of a compound having a specific stereochemistry—a 2'F (down) substituent. 860 F.3d 1340, 1344 (Fed. Cir. 2017). The evidence showed that, over a two-year interval after filing its provisional application, the patent owner "had difficulty and failures in synthesizing the target compound." *Id.* at 1351. Moreover, the schemes in the provisional application showed products "with the ***opposite*** stereochemistry" from that claimed. *Id.* at 1349.

The Board found that synthesizing the specific target compound would have required "at least two years of a high priority experimentation by persons skilled in the art, including multiple consultations with experts at the top of the fields and

additional formal training." *Id.* at 1351. That is, the Board determined a POSA could not have made the target compound by any method at the relevant time without undue experimentation. *Id.* The Federal Circuit affirmed, stating that "substantial evidence supports the Board's finding that 'a high amount of experimentation is necessary to ***synthesize***' the target compound." *Id.* at 1352.

In stark contrast, here, Petitioner's expert demonstrates that a POSA could have ***made***, *i.e.*, ***synthesized***, all of the deuterated ruxolitinib analogs discussed in his enablement analysis and contends only that ***isolating*** certain analogs from the product mixtures would have been difficult. (*See* § IV.B.1.a. above.) *Storer* reinforces that the relevant enablement question is whether the claimed compounds could have been ***made*** without undue experimentation. The answer here is "yes," according to Petitioner's own evidence.

Referencing *Storer*, Petitioner also argues that the '335 patent's specification does not "supply the novel aspects of the invention." (Pet. at 65.) But Petitioner ignores that ruxolitinib itself, deuterated or not, is a *novel chemical compound*. And ruxolitinib's chemical structure and synthesis are described in detail in the specification. (*E.g.*, Ex. 1001 at 109:1–111:46 (Example 67).)

No more is required because, as Petitioner previously admitted (*see* § II.C. above) and Petitioner's declarant demonstrates (§ IV.B.1.a. above), a POSA can use the '335 patent's disclosed synthesis and apply standard techniques to replace

one or more hydrogens with deuterium. *See, e.g.*, *Martin v. Johnson*, 454 F.2d 746, 751-52 (C.C.P.A. 1972) ("[E]very detail need not be set forth in the written specification if the skill in the art is such that the disclosure enables one to make the invention. . . . The recognition of the structure of a chemical compound ordinarily provides those skilled in the art with some information as to its synthesis. . . .").

Like *Storer*, *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935 (Fed. Cir. 2010), (Pet. at 69-72), is readily distinguishable. There, the issue was whether a POSA, absent undue experimentation, could have made non-osmotic oral dosage forms having a specific "ascending release" functionality. *ALZA*, 603 F.3d at 939-40. The outcome—undue experimentation—rested on ALZA having "tried and failed for a few months to produce non-osmotic ascending release dosage forms," and the weight of the evidence "dictate[d] that a person of ordinary skill in the art would have been required to engage in undue experimentation to develop non-osmotic oral dosage forms with ascending release rates." *Id.* at 942-43. In other words, the evidence established that a POSA could not have ***made*** the non-osmotic oral dosage forms having the specific functionality without undue experimentation.

In contrast, Petitioner's declarant, Dr. Crimmins, specifically demonstrates how a POSA could have used known techniques to synthesize, as individual compounds or as compounds in mixtures, all of the analogs discussed in his

analysis. (*See* § IV.B.1.a. above.) Evidence relating to an unclaimed "isolating" requirement is irrelevant. (*See* § IV.B.1.b. above.) Petitioner has failed to carry its burden to establish non-enablement, as well as to carry its burden that the alleged lack of enablement limits the '335 patent claims to a PGR eligible June 3, 2016 filing date.

V. Petitioner's Proposed Grounds 1, 2, and 3 All Fail for the Same Reasons It Failed to Establish Eligibility for PGR

For the same reasons discussed above, Petitioner's proposed Grounds 1, 2, and 3 all fail on their merits, as the Petition provides no basis to find the claims unpatentable under § 112. Because Petitioner fails to carry its burden to show lack of written description or non-enablement, there is also no basis to limit the claims of the '335 patent to a June 2016 date or any other date after March 15, 2013. Thus, the '335 patent is not PGR-eligible and Petitioner's Silverman is not prior art.

In reaching its decision, the Board should also disregard the Petition's bulk citations to Dr. Crimmins' declaration (*e.g.*, Pet. at 16 (citing over 88 paragraphs of Dr. Crimmins' declaration)), as well as the Petition's use of extensive and unexplained string citations to exhibits (*see, e.g.*, Pet. at 16 (string citation taking up over half a page and citing to 44 different exhibits with no parenthetical or analysis); *see also id*. at 10, 21-22, 25-27, 29, 39-40, 43-46, 50-51, 53, 55-59, 62,

65-67, 69, 71); 37 C.F.R. § 42.104(b)(5) ("The Board may exclude or give no weight to the evidence where a party has failed to state its relevance or to identify specific portions of the evidence that support the challenge"); *see also Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, IPR2015-00488, Paper 14 at 13-14 (P.T.A.B. July 24, 2015) (denying consideration of material "not presented and developed in the Petition" as violating "the particularity and specificity required of supporting evidence" and requiring the Board to "sift through" dozens of pages); *see also, e.g.*, *DIRECTV, LLC v. Qurio Holdings, Inc.*, IPR2015-02006, Paper 6 at 10 (P.T.A.B. April 4, 2016) ("[T]he Petition's consistent citations to large portions of the [Expert] Declaration runs afoul of the particularity and specificity required of supporting evidence under our governing statute and rules.").

VI. Conclusion[13]

For these reasons, Petitioner has not established eligibility for PGR or that it is reasonably likely to succeed on its challenge to any of claims 1-6 of the '335 patent. The Board should therefore deny the Petition and not institute post-grant review.

Respectfully submitted,

Dated: October 16, 2017

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[13] For issue preservation, Patent Owner notes the pending matter, *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S.). The filing of this preliminary response or any subsequent paper should not be regarded as a waiver into or consent to this proceeding should AIA post-grant proceedings be held unconstitutional by the Supreme Court.

CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 9,316 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: October 16, 2017

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and Exhibits 2001-2020 were served electronically via email on October 16, 2017, in their entirety, on the following:

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