UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INCYTE CORPORATION,
Petitioner

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner

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Case IPR2017-01256
Patent 9,249,149

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CONCERT PHARMACEUTICALS, INC.'S PATENT OWNER PRELIMINARY RESPONSE

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Patent Owner's Exhibit List

Exhibit	Description
Ex. 2001	Declaration of Scott L. Harbeson, Ph.D.
Ex. 2002	Declaration of Thomas B. Baillie, Ph.D., D.SC.
Ex. 2003	Thomas B. Baillie, Ph.D., D.SC., *curriculum vitae*
Ex. 2004	Thomas B. Baillie, Ph.D., D.SC., Materials Considered
Ex. 2005	K. Ghoreschi et al., *Janus kinases in immune cell signaling*, Immunol. Rev. 228:273–287 (March 2009)
Ex. 2006	*Physicians' Desk Reference* 1157-65 (70th ed. 2015)
Ex. 2007	S. T. Sawyer & K. Penta, *Association of JAK2 and STAT5 with Erythropoietin Receptors*, J. Biol. Chem. 271:32430-32437 (1996)
Ex. 2008	J. D. Clark et al., *Discovery and Development of Janus Kinase (JAK) Inhibitors for Inflammatory Diseases*, J. Med. Chem. 57:5023−5038 (2014)
Ex. 2009	J. Mackay-Wiggan et al., *Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata*, J. Clin. Invest. Insight, Sep. 22, 2016
Ex. 2010	L. Xing et al., *Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition,* Nature Med. 20:1043-49 (2014)
Ex. 2011	R. ter Heine et al., *Identification and Profiling of Circulating Metabolites of Atazanavir, a HIV Protease Inhibitor*, Drug Metab. Disp. 37:1826-40 (2009)
Ex. 2012	J.G. Shi et al., *The pharmacokinetics, pharmacodynamics and safety of orally dosed INCB018424 phosphate in healthy volunteers*, J. Clin. Pharmacol. 51:1644-165 (2011)
Ex. 2013	Rowland & Tozer, *Clinical Pharmacokinetics: Concepts and*

	Applications 1-65, 119-200, 220-29 (1995)
Ex. 2014	*Goodman & Gilman's The Pharmacological Basis of Therapeutics* 18-19 (Laurence L. Brunton ed., 11th ed. 2006)
Ex. 2015	A. Iurlo & D. Cattaneo, *Treatment of Myelofibrosis: Old and New Strategies*, *Clin. Med. Insights: Blood Disorders* 10:1 (2017)
Ex. 2016	M.F. McMullin et al., *Management of polycythaemia vera: a critical review of current data*, Br. J. Haematol. 172:337-349 (2016)
Ex. 2017	Press Release, Concert Pharmaceuticals Inc., Concert Pharmaceuticals Reports Year Ended 2016 Financial Results (Mar. 6, 2017)
Ex. 2018	R.S. Obach, *Prediction Of Human Clearance Of Twenty-Nine Drugs From Hepatic Microsomal Intrinsic Clearance Data: An Examination Of In Vitro Half-life Approach And Nonspecific Binding To Microsomes*, Drug Metab. & Disposition 27:1350-1359 (1999)
Ex. 2019	Appendices to the Declaration of Scott Harbeson
Ex. 2020	A.E. Mutlib & J.T. Klein, *Application of Liquid Chromatography/Mass Spectrometry in Accelerating the Identification of Human Liver Cytochrome P450 Isoforms Involved in the Metabolism of Iloperidone*, J. Pharmacol. Exp. Ther., 286:1285-93 (1998)
Ex. 2021	D.K. Walker et al., *Species Differences in the Disposition of the CCR5 Antagonist, UK-427,857, a New Potential Treatment For HIV*, Drug Metab. Dispos. 33:587-95 (2005)
Ex. 2022	November 16, 2010 Declaration of Vinita Uttamsingh, filed in U.S. Application Serial No. 11/941,925
Ex. 2023	G.T. Miwa & A.Y.H. Lu, *Kinetic Isotope Effects and 'Metabolic Switching' in Cytochrome P450-Catalyzed Reactions*, BioEssays 7:215-19 (1987)
Ex. 2024	February 3, 2012 Declaration of Vinita Uttamsingh, filed in U.S. Application Serial No. 12/102,164

Ex. 2025	L. Shao et al., *Derivatives of Tramadol for Increased Duration of Effect*, Bioorg. Med. Chem. Lett. 16:691–94 (2006)
Ex. 2026	WebCite® Query Page, http://webcitation.org/query (last visited July 18, 2017)
Ex. 2027	Basicmedical Key, Pharmacodynamics: Molecular Mechanisms of Drug Action, https://basicmedicalkey.com/pharmacodynamics-molecular-mechanisms-of-drug-action/ (last visited Jul. 18, 2017)
Ex. 2028	JAK-STAT Signaling, https://courses.washington.edu/conj /bess/jakstat/jakstat.htm (last visited Jul. 21, 2017)
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I. INTRODUCTION

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107, Patent Owner Concert Pharmaceuticals, Inc. ("Concert") submits this Preliminary Response to Incyte Corporation's ("Petitioner") Petition for *Inter Partes* Review of U.S. Patent No. 9,249,149 ("the '149 Patent"). The '149 Patent claims specific deuterated analogs of ruxolitinib, a drug approved for two types of cancer that affect red blood cell production. Petitioner argues that three of these octa- and tetra-deuterated analogs are obvious. These analogs, however, show significant pharmacokinetic differentiation compared to ruxolitinib. No prior art reference disclosed octa- or tetra-deuterated analogs of ruxolitinib. The octa-deuterated analog, also known as CTP-543, is Concert's Phase 2 clinical candidate for alopecia areata, a serious autoimmune disease for which there are no FDA-approved treatments. CTP-543 demonstrates unique clinical advantages that are not known in the prior art for deuterated compounds.

There are many reasons why the Board should deny institution. As a threshold issue, Petitioner has not demonstrated that its key obviousness references are "printed publications." Petitioner has not established that the Concert Backgrounder (Grounds 1 and 3) and Jakafi® label (Ground 1) would have been reasonably accessible to persons of ordinary skill in the art ("POSAs") as of the priority date, which is necessary to carry Petitioner's burden of proof.

On the merits, Petitioner fails to establish both a reason to select ruxolitinib for deuteration, and a persuasive motivation to modify ruxolitinib to make the claimed deuterated analogs. It also grossly oversimplifies the prior art, and in doing so, mischaracterizes the reasonable expectations of a POSA. In particular, Petitioner mischaracterizes the predictability of results by referencing an incomplete picture of the relevant metabolic process, and by making arguments that are contrary to their declarant's own publications. A more complete picture of metabolism, supported by many prior art examples, including those cited by Petitioner, shows that the metabolic effects of deuterium modification cannot be predicted *a priori*. The complexity involved in biological systems renders the effect of deuterated drugs in the body highly unpredictable. As a result, Petitioner has not demonstrated that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving a compound with any differentiated results compared to ruxolitinib.

Petitioner's arguments are also based on a mischaracterization of the *in vitro* data presented during prosecution of the '149 Patent and erroneous assumptions about the clinical profile of CTP-543. In fact, the *in vitro* results showed differentiation in metabolic stability, and CTP-543 has clinically meaningful advantages that were unexpected. Clinical data shows that CTP-543 has the potential for increased clinical response at a given dose and an increased

therapeutic window, unexpected advantages that are particularly relevant for the treatment of alopecia areata. With the increased clinical response at a given dose, patients are more likely to benefit from CTP-543 than from ruxolitinib. With an increased therapeutic window, a dose of CTP-543 that is effective for alopecia areata is likely to be safer than a similarly-effective dose of ruxolitinib. As confirmed by Dr. Thomas A. Baillie, Professor of Medicinal Chemistry and Dean Emeritus of the School of Pharmacy at the University of Washington, who is an expert in the synthesis and applications of deuterium-labeled compounds, nothing in the prior art predicted these surprising benefits. These benefits demonstrate patentability.

For at least the above reasons, the Board should deny institution.[1]

[1] In *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712, 2017 WL 2507340 (2017), the Supreme Court is considering whether IPR violates the Constitution by extinguishing private property rights through a non-Article III forum without a jury. While Concert is currently unable to bring that argument under binding Federal Circuit precedent, Concert reserves all rights pending the outcome of *Oil States*, including the right to object to this proceeding as unconstitutional.

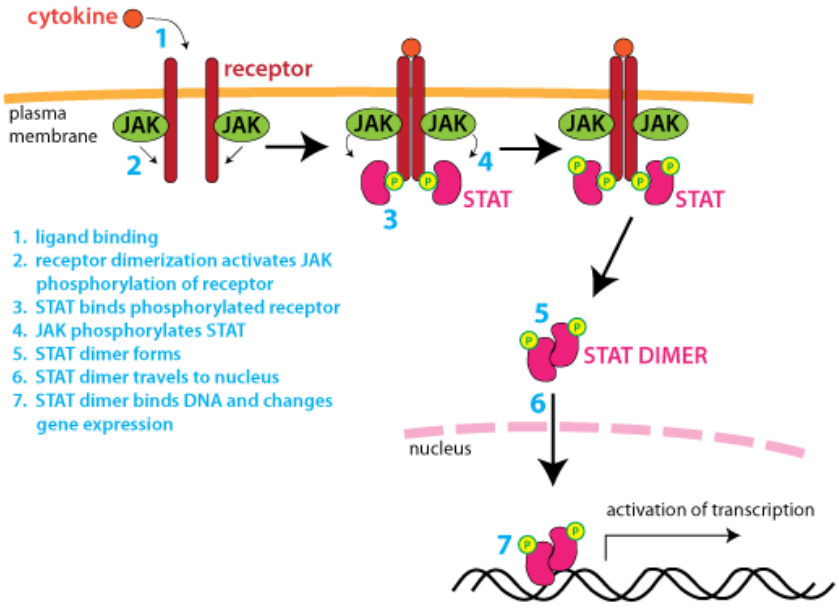
II. STATE OF THE ART

A. Ruxolitinib and Deuterated Ruxolitinib

Ruxolitinib is an inhibitor of Janus kinase 1 and 2 (JAK1/2). Ex. 1001 at 2:53-59. JAKs are a family of intracellular tyrosine kinases that play a central role in the signaling of many cytokine receptors. Ex. 1001 at 2:59-65.

The signaling pathway for JAKs is depicted in Figure 1 below. When a messenger protein known as a cytokine binds to its receptor, JAK proteins associated with the receptor dimerize and phosphorylate (activate) STAT proteins. The phosphorylated STAT (pSTAT) proteins then activate gene transcription, which then leads to further biological effects:

Figure 1: The JAK/STAT signaling pathway



Ex. 2028 at 1. A JAK inhibitor like ruxolitinib prevents the JAK protein from phosphorylating the STAT proteins, thereby preventing the downstream biological effects.

Interferon-gamma (IFN-γ) is a cytokine that regulates immune response through the JAK/STAT signaling pathway. In alopecia areata patients, levels of IFN-γ are elevated, resulting in hair loss. Ex. 2009 (Mackay-Wiggan), at 1. Another cytokine, erythropoietin (EPO), is essential for red blood cell production. After binding to its receptor, EPO also exerts its biological effects through the JAK/STAT signaling pathway. Thus, JAK inhibitors have the potential to inhibit the activities of both IFN-γ and EPO. JAK inhibitors therefore have the potential to treat alopecia areata, but also to suppress red blood cell production and cause anemia. Therefore, it is desirable to have a JAK inhibitor that controls aberrant IFN-γ activity for the treatment of alopecia areata while minimizing EPO inhibition to mitigate the risk of anemia.

Jakafi® (ruxolitinib) is approved for the treatment of two types of cancer that affect the production of red blood cells. Ex. 1001 at 2:66-3:6. Anemia is a common adverse effect in patients taking Jakafi®, occurring in more than 20% of patients. Ex. 2006 ("Jakafi® label"), at 7; *see also* 5 (disclosing dose modification instructions to help manage anemia).

B. Drug Metabolism and the Unpredictable Effect of Deuterium Substitution

Many drugs suffer from undesirable absorption, distribution, metabolism, and/or excretion (ADME), which can prevent or limit their use in certain indications. Ex. 1001, 1:20-23. Rapid metabolism, for example, can cause an otherwise effective drug to be cleared too rapidly. *Id.*, 1:28-31. Slower metabolism of a drug may worsen its side effects. Another ADME limitation is the formation of toxic or biologically reactive metabolites. *Id.*, 1:39-40. This may limit the safe dosing of a drug such that patients receive a suboptimal amount of the active agent. *Id.*, 1:40-43.

Oxidative metabolism by the cytochromes P450 (CYP450s) is the most common metabolic pathway of drug clearance. Ex. 1040-p.101. One strategy Concert uses to potentially alter CYP450 metabolism of a drug molecule is to replace one or more of its hydrogen atoms with deuterium atoms. Deuterium is a stable, non-radioactive isotope of hydrogen. *Id.*, Ex. 1001, 2:10-11. Compared to hydrogen, it forms stronger bonds with carbon. In select cases, this increased bond strength can positively impact the ADME properties of a drug, creating the

potential for improved drug efficacy, safety, and/or tolerability. This phenomenon is termed the kinetic isotope effect, or "KIE."[2] *Id.*, 2:12-15.

The effect of deuterium substitution on overall metabolic stability of a drug, however, is variable and unpredictable. *See, e.g.*, Ex. 1027-p.2 ("It is difficult to predict *a priori* which effect deuterium may have on a drug's metabolism."); Ex. 1006-p.3 (noting that the magnitude and nature of the deuterium benefit cannot be predicted *a priori*). The KIE is often masked by the complexity of the biological systems and a number of competing effects. Ex. 1008-p.49; *see also* Ex. 1027-p.3 ("The complexity of biological systems and the number of competing effects that can mask the DIE have made the application of deuterium to drug discovery highly unpredictable and challenging."); Ex. 1040-p.2. Two important reasons why a KIE can be masked in overall metabolism are: (1) the breaking of the carbon-hydrogen ("C-H") bond is not the rate-limiting step in the drug's metabolism; and (2) metabolic switching. These mechanisms are discussed further below.

[2] KIE is also sometimes termed "DIE," or deuterium isotope effect. These terms are used interchangeably herein. Additionally, Petitioner refers to "C-H" bond breaking when discussing KIE. This Response follows that convention, although it would be appropriate to refer to "C-D" bond breaking for a deuterated drug.

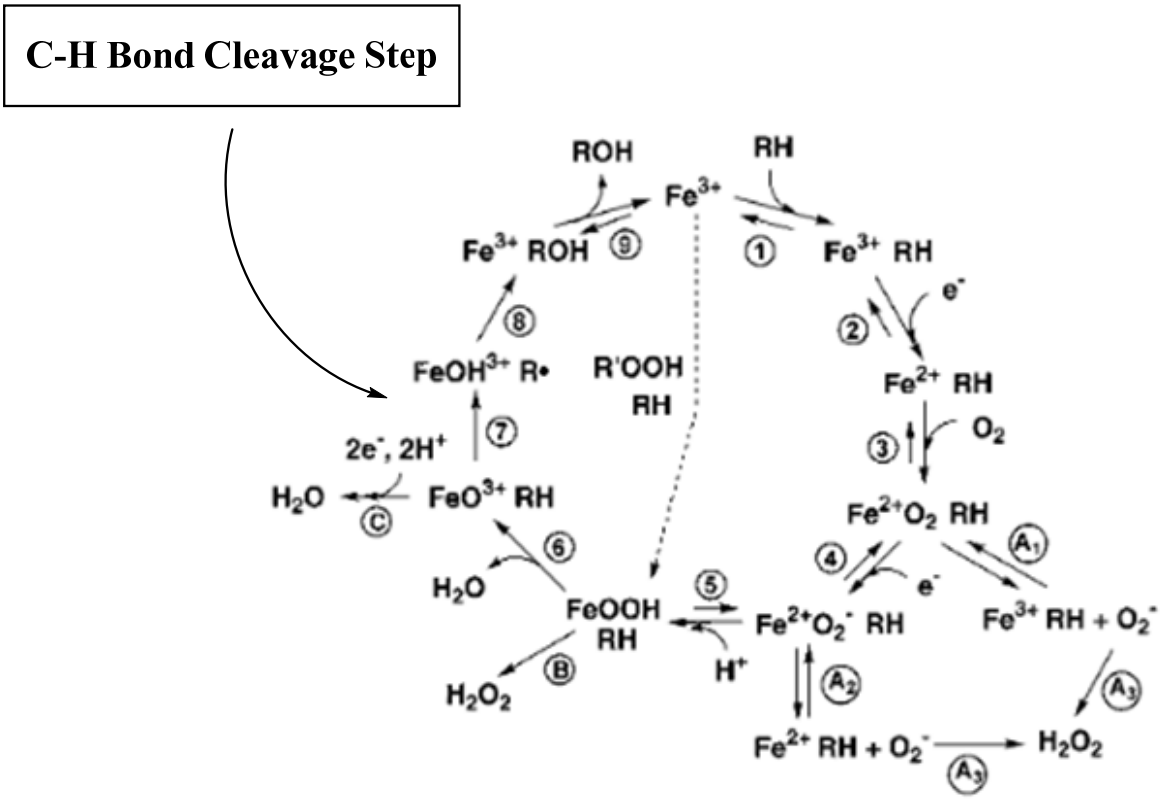
1. For Deuterium Modification to Affect Overall Metabolism, Breaking of the C-H Bond Must Be at Least Partially Rate-Limiting

As Petitioner acknowledges, to observe a KIE when hydrogen is replaced by deuterium, the C-H bond cleavage step in the molecule's metabolism must be at least partially rate-limiting.[3] *See* Ex. 1040-p.2; Ex. 1002, ¶ 52. One cannot predict whether C-H bond cleavage will be at least partially rate-limiting.

CYP450s (or P450s) are the major enzymes involved in the oxidation of drugs in humans. Ex. 1040-p.1; *see also* Ex. 1034-p.1. The CYP450 enzymatic process entails nine major steps.

[3] The rate-limiting step in a process is the slowest step, and therefore dictates the overall rate of the process. Consider a 3-step process. If Step 2 is the slowest step, then relatively small variations in the rates of Steps 1 or 3 will not impact the overall rate of the process.

C-H Bond Cleavage Is 1 of 9 Steps in Enzymatic Process



Ex. 1034-p.1. C-H bond cleavage occurs in step 7. Ex. 1012-p.1. Although Petitioner focuses on step 7, any of the steps in the metabolic process—substrate binding, reduction, oxygen binding to ferrous P450, addition of the second electron to the system, rearrangement to the final active oxygen species, C-H bond cleavage, product release, and any protein rearrangements—can be rate-limiting. Ex. 1034-p.1-2. As Petitioner's expert, Dr. Guengerich, has stated in his prior art publications, the identity of the rate-limiting step "can vary considerably depending on the particular P450 and the reaction involved." Ex. 1034-p.1 (citations omitted).

CYP450 3A4 (or CYP3A4) is the primary enzyme responsible for metabolizing ruxolitinib. Ex. 1002, ¶ 46. Contrary to the implications in his declaration, Dr. Guengerich stated in his prior publications that "[r]elatively little information is available regarding what step is rate-limiting in P450 3A4 reactions." Ex. 1035-p.1. He further stated: "[o]nly limited information has been obtained regarding steps 1 and 3–9 (Scheme 1) with P450 3A4 reactions. Without information on the extent to which chemical steps (*e.g.* substrate oxidation) limit catalysis, it will not be possible to understand or predict the behavior of this system." Ex. 1035-p.1.

Dr. Guengerich studied the kinetics of CYP450 3A4 metabolism of testosterone and found that although there was a high intrinsic KIE, it was strongly attenuated by metabolic switching. Ex. 1035. He concluded that C-H bond-breaking "is not rate-limiting," and that "other steps in the catalytic cycle make major rate-limiting contributions." Ex. 1035-p.9, 10. He also concluded that the C-H bond-breaking step "appears to be less rate-limiting in P450 3A4 reactions than with several reactions catalyzed by other mammalian P450s, *e.g.* P450s 1A2, 2A6, 2E1, and 2D6." Ex. 1035-p.10 (citations omitted); *see also* Ex. 1036-p.1 (C-H bond-breaking is not rate-limiting in P450 7A1 metabolism of cholesterol 7α-hydroxylation).

Thus, Petitioner's own expert has acknowledged that the relevant metabolic step in this case (the C-H bond breaking step in CYP450 3A4 reactions) is often less rate-limiting than is observed with the other CYP450s, which suggests that observing a significant KIE in a CYP450 3A4-mediated reaction is far from predictable.

2. Metabolic Switching Can Mask a Kinetic Isotope Effect

As noted above, metabolic switching—a change from one metabolic site on the molecule to a different site—can mask a KIE. Ex. 1008-p.50. If the KIE is masked, deuterium substitution will not affect the overall rate of metabolism of the drug molecule. Ex. 1008-p.50.

When metabolic switching occurs, there is a change in the ratio of metabolites formed, which can result in no observable change in the overall rate of drug metabolism. *Id.* Even if the rate of overall metabolism is altered, metabolic switching can nevertheless be problematic because it can potentially result in the increased formation of a metabolite that is more toxic. Ex. 1010-p.6. Metabolic switching is frequently observed in deuterium isotope studies. *See, e.g.*, Ex. 1033-p.4 (discussing different ratios of metabolites formed with deuteration and without); Ex. 1035 (Dr. Guengerich reports partial switching following deuteration of testosterone); Ex. 1039-p.3 (discussing examples of metabolic switching reported in the literature); Ex. 2023, at 3 (same).

With respect to metabolic switching, Petitioner acknowledges that switching can occur to a minor metabolite. *E.g.*, Ex. 1002, ¶ 106. However, Dr. Guengerich asserts that appreciable switching to a minor metabolite would not occur unless it is "generally present in a much larger amount than less than 5%." *Id.* This proposition is not supported by the reference on which Dr. Guengerich relies, Harada *et al.* (Ex. 1033). This reference reports that substitution of deuterium for hydrogen on the α-carbon of 7-ethoxycoumarin resulted in a "dramatic decrease" in the bond cleavage rate. Ex. 1033-p.1, 5. Nevertheless, Harada *et al.* found that the overall reaction rate was unchanged due to metabolic switching to the 6-hydroxy metabolite. *Id.*, p.1. Even though this metabolite represented only about 5% of the metabolite mixture before deuterium substitution, upon deuteration this metabolite increased about 5-fold. *Id.*, p.4. This large increase in the production of such a minor metabolite (what Harada characterizes as a "trace" metabolite), is contrary to Petitioner's assertion that such metabolic switching is not observed in these situations.

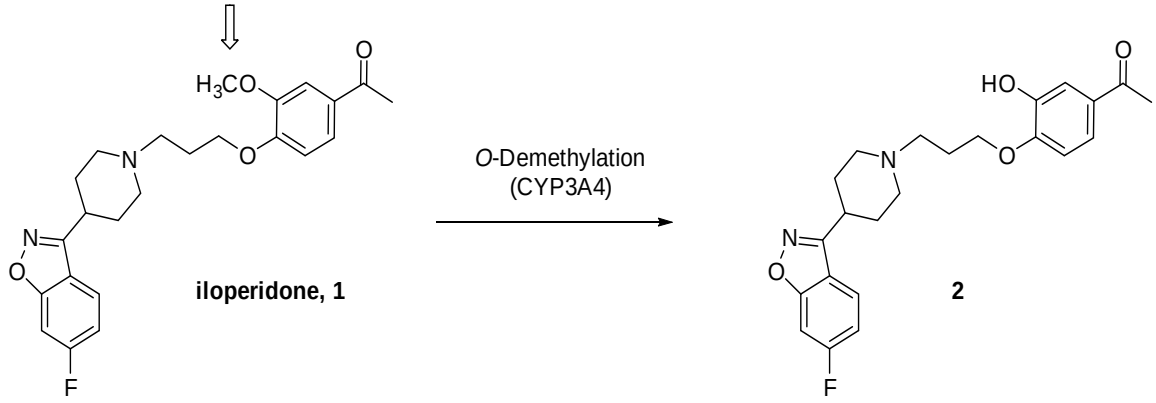
3. Examples of Unpredictable Results From Deuterated Drugs

As was known in the prior art, "the application of deuterium to drug discovery [was] highly unpredictable and challenging." Ex. 1008-p.50 (citation omitted). Below are just a few prior art examples showing that deuterium modification of drugs, even at "metabolic hotspots," does not improve

pharmacokinetic ("PK") properties in a predictable manner.[4] The first three examples show that deuterium modification can actually decrease metabolic stability, having an ***opposite*** effect to the desired improvement. The fourth example shows that *in vitro* results do not always translate to an *in vivo* setting.

a. **Deuterated Iloperidone**

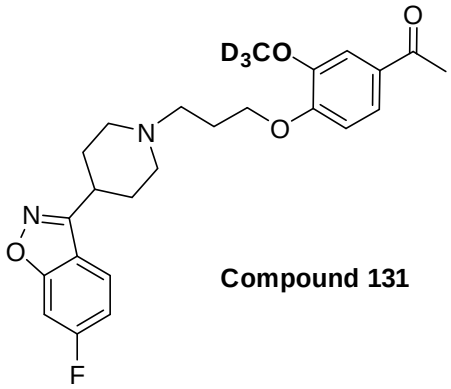
Fanapt® (iloperidone) is indicated for the treatment of schizophrenia. Ex. 2029. In human liver microsomes, CYP3A4 metabolizes iloperidone at the methoxy moiety of the phenyl ring, as indicated by the arrow below:



See Ex. 2020 (Mutlib), at Fig. 1.

Concert prepared a deuterated analog of iloperidone (Compound 131), which was deuterated at this "metabolic hotspot":

[4] Of course, failures in drug discovery tend to be under-reported.



Compound 131

Ex. 2024, February 3, 2012 Declaration of Vinita Uttamsingh, filed in U.S. Application Serial No. 12/102,164, at ¶ 5. Concert observed that deuteration at the known metabolic site resulted in *less* metabolic stability compared to iloperidone, *i.e.*, the deuterated analog showed a *shorter* half-life, not a longer half-life:

***In Vitro* $t_{1/2}$ in HLM**	
Compound	Average $t_{1/2}$ (min)
Iloperidone	59.0
Compound 131	35.4

Id. at Attachment B.

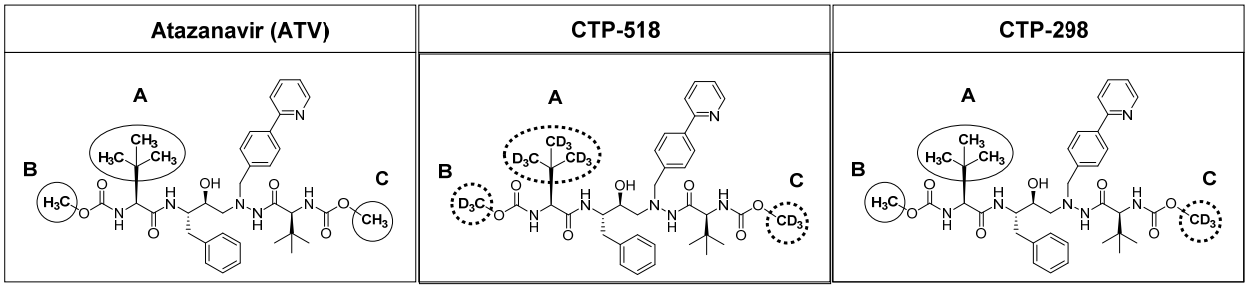
b. **Deuterated Atazanavir**

Petitioner touts deuterated Reyataz® (atazanavir) as a "success" in deuteration strategy in the years immediately preceding Concert's invention. Petition at 16. As will be discussed, however, Concert encountered unanticipated effects in humans as it moved forward with deuterated atazanavir. The atazanavir analog deuterated at three spots that, under Petitioner's theory, would have been

predicted to improve metabolic stability, actually demonstrated the ***opposite*** effect. Instead, enhanced metabolic stability was observed for a different analog that was deuterated at only one of the known "metabolic hotspots."

Bristol-Myers Squibb markets atazanavir as Reyataz®, for the treatment of human immunodeficiency virus ("HIV"). Ex. 1008-p.55. Reyataz® is dosed with the metabolic inhibitor ritonavir. *Id.*

Concert prepared deuterated analogs of atazanavir, including the clinical candidates CTP-518 and CTP-298, which were deuterated at known "metabolic hotspots." Ex. 2001 (Harbeson), ¶¶ 19-22. The structures of atazanavir ("ATV"), CTP-518, and CTP-298 are shown below:



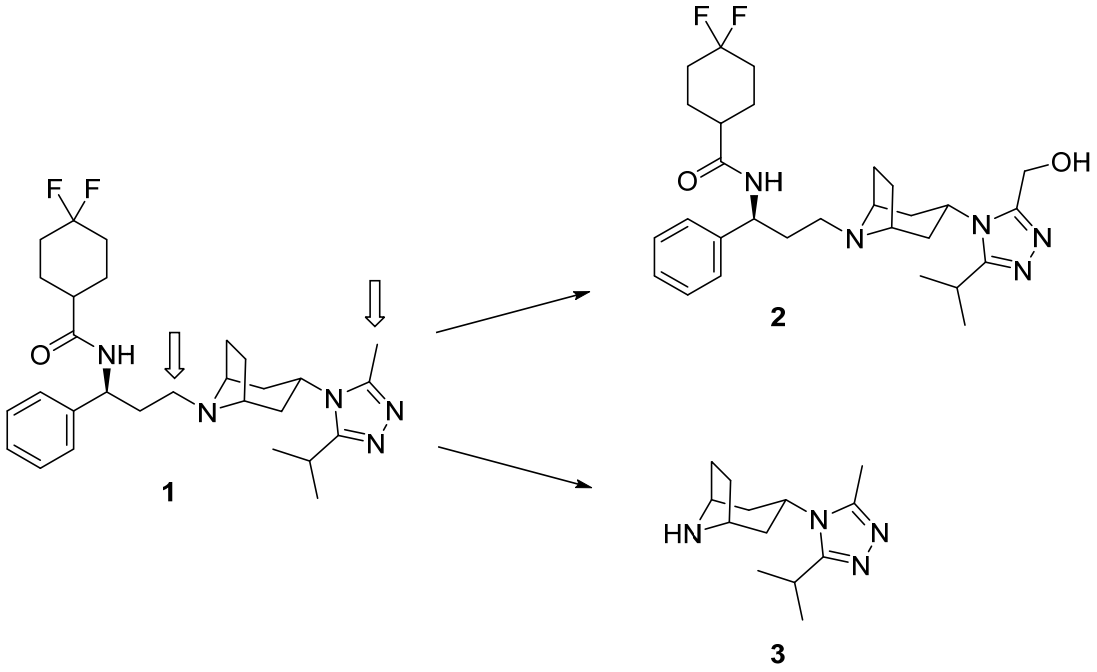
In Concert's human liver microsome ("HLM") studies, the half-life ("$t_{1/2}$") of CTP-518 compared to ATV was extended by 60%, while the $t_{1/2}$ of CTP-298 was extended by only 12%. *Id.*, ¶ 21.

Concert then compared CTP-518 and CTP-298 in two PK crossover studies in healthy human volunteers. *Id.*, ¶¶ 23-25. In these studies, CTP-298 surprisingly proved to be metabolically more stable in humans than either CTP-518 or ATV,

while CTP-518 was *considerably worse* than ATV in terms of plasma exposure. *Id*. Because CTP-518 has deuteration at the metabolic hotspots labeled as "A" and "B" in the above figure and CTP-298 does not, the clinical data for CTP-518 was thus the ***opposite*** of what Petitioner asserts would have been expected. Ex. 2002 (Baillie), ¶ 64. Accordingly, the atazanavir example cited in the Petition actually evidences that deuterium substitution at a drug's known "metabolic hotspots" is unpredictable.

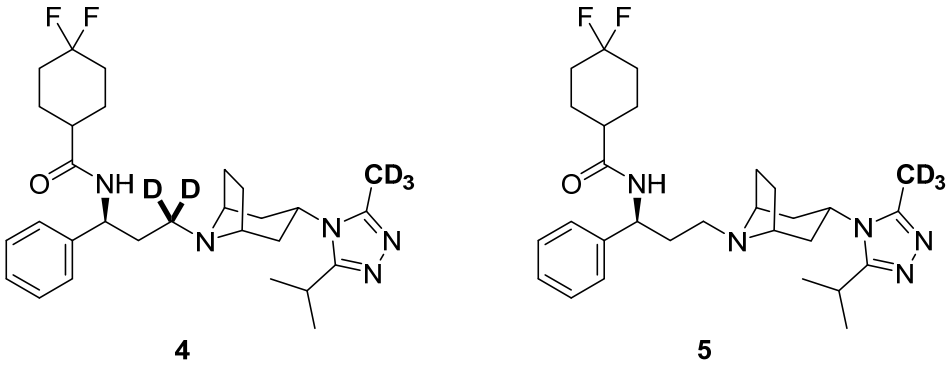
c. **Deuterated Maraviroc**

Another example of the unpredictable effect of deuteration is seen with deuterated maraviroc. Maraviroc (compound **1** below) is marketed as Selzentry® for the treatment of HIV infections. Ex. 2030. Two of the major metabolic pathways for maraviroc are: (1) oxidation of the methyl group to afford compound **2**; and (2) *N*-dealkylation of the tropane ring to afford compound **3** (arrows indicate metabolic sites):



Ex. 2021 (Walker), at Fig. 5.

Concert prepared deuterated analogs **4** and **5**:



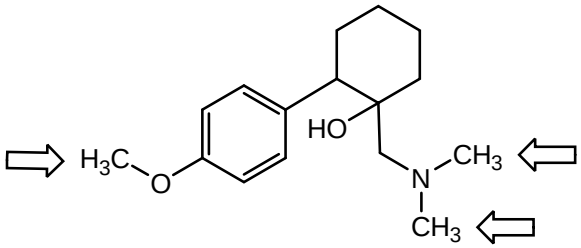
Ex. 2022, November 16, 2010 Declaration of Vinita Uttamsingh, filed in U.S. Application Serial No. 11/941,925, at Appendix B. In HLM studies, deuteration at both of the metabolic sites (compound 4) reduced *in vitro* microsomal clearance. Inexplicably, however, deuteration at only the methyl group (compound **5**) actually accelerated microsomal turnover compared with maraviroc:

***In Vitro* $t_{1/2}$ in HLM**	
Compound	Average $t_{1/2}$ (min)
Maraviroc	97.2
Compound 4	145.5
Compound 5	45.5

Id.; Ex. 2002 (Baillie), ¶ 70. Again, an analog deuterated at a "metabolic hotspot" actually demonstrated the ***opposite*** effect than that predicted by Petitioner.

d. **Deuterated Tramadol**

Even if deuteration slows the formation of metabolites, there may be no *in vivo* effect. For example, Shao attempted to slow CYP450-mediated metabolism of tramadol by replacing hydrogen with deuterium at metabolically active sites (at the O-methyl and N-methyl groups indicated below by the arrows):



Tramadol

See Exhibit 2025 (Shao), at 3. Although some of the deuterated analogs exhibited reduced *in vitro* metabolism, none of them were superior to tramadol in terms of potency, clearance was not reduced, and *in vivo* half-life was not increased. *Id.* at 3-4.

C. Deuterated Ruxolitinib Yielded Unexpected Results

In view of the state of the art, results of the claimed deuterated ruxolitinib analogs are unexpected, highlighted by the unique clinical advantages observed with CTP-543. Concert has conducted a human clinical study directly comparing the PK of CTP-543 and ruxolitinib. Ex. 2001 (Harbeson), ¶¶ 11-14. The results of this study, which are not discussed in the Petition,[5] revealed that CTP-543 has a number of unexpected, beneficial attributes compared to ruxolitinib. As will be discussed further in Section VII below, these attributes amount to unexpected results that favor patentability.

1. CTP-543 Has Superior PK Attributes Compared to Ruxolitinib

Concert's crossover clinical study indicated that while the dose-normalized C_{max} of both CTP-543 and ruxolitinib are not significantly different, there was a statistically significant improvement in several PK measures, such as $t_{1/2}$, clearance ("CL/F"), and AUC for CTP-543 compared to ruxolitinib:

[5] Concert announced the completion of this crossover study in a March 6, 2017 press release. *See* Ex. 2017.

Table 4: Comparison of CTP-543 and Ruxolitinib PK Parameters		
PK Parameter	**p-value**	**Statistically different ($p < 0.05$)**
C_{max}	0.0941	No
AUC_{inf}	0.0006	Yes
C_{12hr}	0.007	Yes
$t_{1/2}$	0.003	Yes
CL/F	0.0001	Yes

Ex. 2001 (Harbeson), ¶ 13.

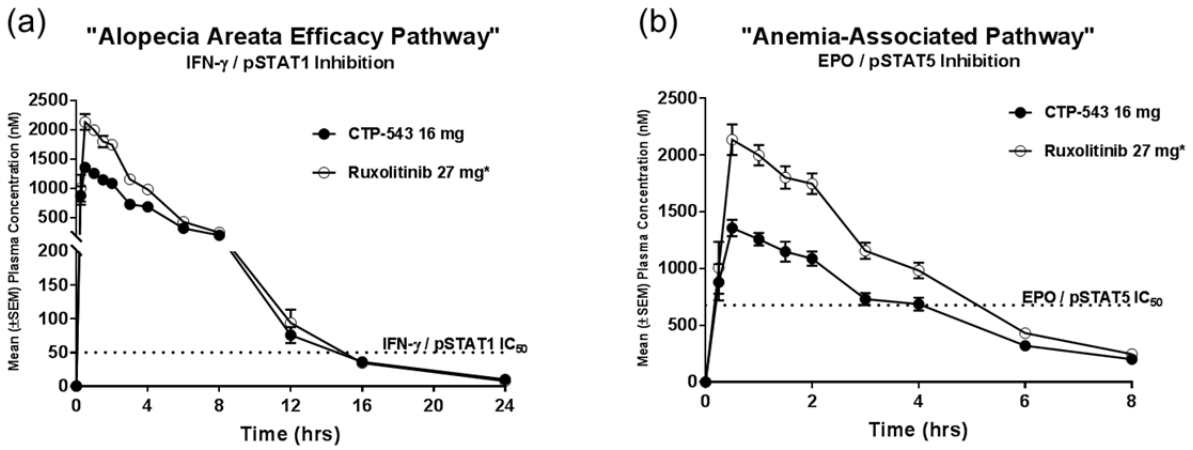
2. Increased Therapeutic Window

Both non-clinical and clinical studies show that, relative to ruxolitinib, doses of CTP-543 that are likely to be effective in the treatment of alopecia areata are less likely to cause anemia than similarly effective doses of ruxolitinib. Ex. 2001 (Harbeson), ¶¶ 16-17; Ex. 2002 (Baillie), ¶¶ 50-54.

As discussed above, JAK1/2 inhibitors have the potential to treat alopecia areata by suppression of IFN-γ stimulated pSTAT1 formation. *See supra* Section II.A. However, JAK2 inhibition also causes anemia via inhibition of the EPO/pSTAT5 pathway. *See id*. CTP-543 and ruxolitinib are each about 10-fold more potent against the IFN-γ pathway than the EPO/pSTAT5 pathway. Ex. 2001 (Harbeson), ¶ 10, Table 1. This difference, combined with the PK profiles of the drugs, will largely determine their therapeutic windows (for safety and efficacy) in treating alopecia areata. Ex. 2002 (Baillie), ¶¶ 41-48.

Based on its PK profile in humans, compared to ruxolitinib, CTP-543 will likely have an increased therapeutic window for treating alopecia areata. *Id*. Efficacy in alopecia areata requires a drug level in the body that is *high* enough to suppress IFN-γ/pSTAT1, while avoidance of anemia requires a drug level that is *low* enough to minimize inhibition of EPO/pSTAT5. *Id.*, ¶ 43. The therapeutic windows of the two drugs for alopecia areata are illustrated in Figure 3 from Dr. Baillie's Declaration (Ex. 2002):

Figure 3: Comparison of Single Doses of 16 mg CTP-543 and Simulated 27 mg Ruxolitinib PK Profiles for Time over IC_{50} of Relevant JAK/STAT Pathways



***Ruxolitinib 15 mg QD drug exposure data were dose normalized to 27 mg QD**

Ex. 2002, ¶ 43.

Figure 3(a) shows that a 16 mg dose of CTP-543 and a modeled 27 mg dose of ruxolitinib are estimated to provide similar inhibition of IFN-γ/pSTAT1 over time, as the curves are above the IC_{50} for the same amount of time. Ex. 2001 (Harbeson), ¶ 18; Ex. 2002 (Baillie), ¶¶ 43-46. Figure 3(b), on the other hand,

shows that these doses differ considerably with respect to the adverse, anemia-related EPO/pSTAT5 pathway. Baillie Dec., ¶¶ 43-46. Ruxolitinib undesirably inhibits EPO/pSTAT5 for a longer period of time. *Id.*, ¶ 45. Thus, CTP-543 has the potential to achieve similar efficacy as ruxolitinib in alopecia areata with less risk of anemia. *Id*. This difference between ruxolitinib and deuterated ruxolitinib in inhibiting the EPO signaling pathway while providing similar inhibition of the IFN-γ signaling pathway was entirely unexpected. *Id.*, ¶ 54.

3. Potential for Increased Clinical Response at a Given Dose

Another unexpected advantage of CTP-543 is the potential for patients to have an increased clinical response at a given dose for CTP-543 compared to ruxolitinib. Ex. 2001 (Harbeson), ¶ 14; Ex. 2002 (Baillie), ¶ 49. In Concert's human crossover study, individuals with the shortest ruxolitinib $t_{1/2}$ values had the greatest improvement in $t_{1/2}$ values when given CTP-543. Ex. 2002 (Baillie), ¶ 49. Thus, clinical data from Concert's human crossover study shows the potential for increased clinical response at a given dose, especially in individuals with the shortest ruxolitinib $t_{1/2}$ values. *Id.*

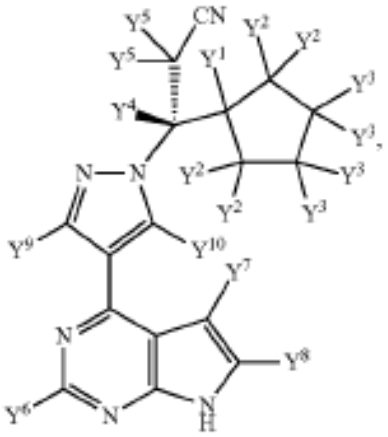
III. THE '149 PATENT

The '149 Patent issued on February 2, 2016, from an application filed on May 8, 2015. That application claims priority through a chain of applications to an

initial provisional application filed on June 15, 2012. The '149 Patent discloses specific deuterated analogs of ruxolitinib.

A. The Challenged Claims

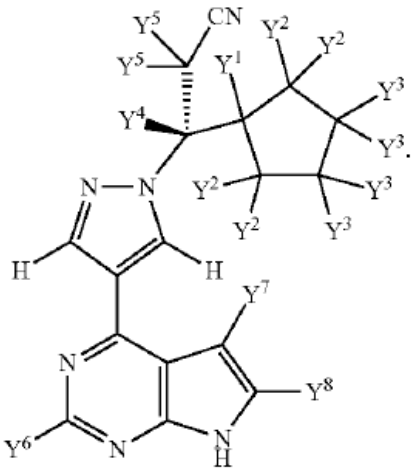
Claim 1 covers a genus of compounds depicted by Formula A, wherein Y^2 though Y^{10} comprise specific combinations of either hydrogen or deuterium, provided there is deuterium in each Y^2 and/or each Y^3:



Formula A

Independent claim 9 is similar, but specifies that Y^2 though Y^8 comprise specific combinations of either hydrogen or deuterium, provided there is deuterium in each Y^2 and/or each Y^3:

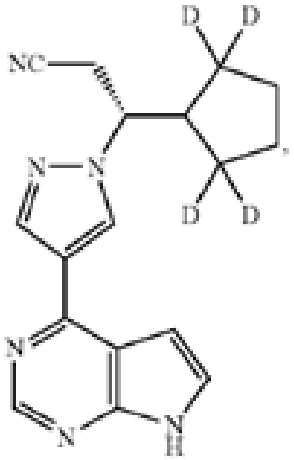
Formula I



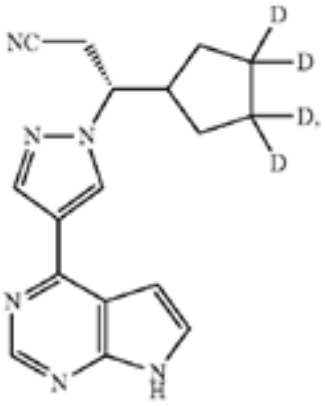
Dependent claims 2-6 and 10-14 narrow the claimed combinations of hydrogen and deuterium.

Claim 7 depends from claim 1 and narrows the claimed compounds to the three depicted below, or pharmaceutically acceptable salts thereof:

Compound 107

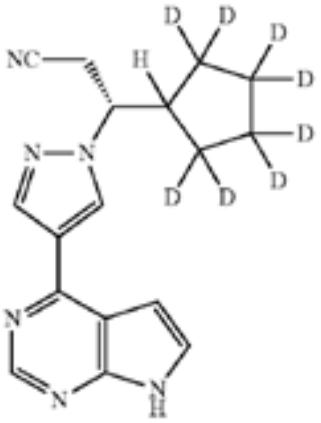


Compound 103



and

Compound 111



Claims 8 and 15 depend from claims 1 and 9, respectively, and are directed to pharmaceutical compositions comprising the claimed compounds.

Because Petitioner focuses only on octa-deuterated ruxolitinib, 3,3,4,4-tetra-deuterated ruxolitinib, and 2,2,5,5-tetra-deuterated ruxolitinib (Petition at 8-9)—the three analogs recited in claim 7—Concert does the same in this submission.

B. Summary of Relevant Prosecution History

As will be discussed further in section VII.A below, the obviousness arguments presented in the Petition are substantively the same as those already

considered and rejected during prosecution, and thus the Petition should be denied under 35 U.S.C. § 325(b).

As originally filed, the application that issued as the '149 Patent contained claims related to deuterated analogs of ruxolitinib, pharmaceutical compositions comprising the same, and methods of using the same. Ex. 1009 at 60-64. The Examiner rejected the claims as obvious over Rodgers (Ex. 1007) and other prior art that purportedly showed that "one is motivated to prepare deuterated versions of drugs to obtain a version with better pharmaceutical properties," and alternatively, that "one is motivated to prepare deuterated versions of drugs, which can be used to obtain valuable information about how the undeuterated drug or closely related drugs act in the body." *Id.* at 103, 105-08. The Examiner contended that "deuteration per se is a known improvement technique for getting a more useful version of the pharmaceutical, and that the improvement is of a predictable nature, as is seen by the success reported in the various secondary references." *Id.* at 111.

In response, the applicant argued that the claims were not unpatentable because, *inter alia*: (1) the claimed compounds demonstrated unexpectedly greater stability to metabolism than ruxolitinib in CYP3A4 Supersomes™ and HLMs; and (2) the effect of deuteration is not predictable, including because of metabolic switching, so any change in the overall metabolic stability of a drug is unexpected.

Id. at 253. The applicant supported point (1) with a declaration from Dr. Vinita Uttamsingh, which presented *in vitro* test results for three claimed compounds (Compounds 103, 107, and 111, the same three compounds addressed in the Petition). *Id.* at 285-88. The results showed that these compounds are substantially more metabolically stable than ruxolitinib. *Id.*; *see also* Ex. 1009 at 284.

The Examiner withdrew the obviousness rejection and ultimately allowed the claims. *Id.* at 310, 325-26, 330.

IV. PERSON OF ORDINARY SKILL AND CLAIM CONSTRUCTION

For purposes of this submission only, Patent Owner does not challenge Petitioner's POSA definition or proposed claim constructions. Patent Owner reserves the right to address Petitioner's proposals should trial be instituted.

V. GROUNDS 1 AND 3 SHOULD BE DENIED BECAUSE PETITIONER HAS FAILED TO SHOW THAT THE JAKAFI® LABEL (EX. 1004) AND CONCERT BACKGROUNDER (EX. 1006) ARE "PRINTED PUBLICATIONS"

IPR must be based on patents or printed publications. 35 U.S.C. § 311(b). Here, the Board need not address the merits of Grounds 1 and 3, because Petitioner has failed to carry its burden of proving that the Jakafi® label (Ground 1) and Concert Backgrounder (Grounds 1 and 3) constitute printed publications. *See, e.g.*, *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378-79 (Fed.

Cir. 2015). On this basis alone, the Board should deny institution of Grounds 1 and 3.

A. Jakafi® Label

In Ground 1, Petitioner relies in part on the purported prescribing information (label) for Jakafi® (Ex. 1004). Petitioner's attempt to carry its burden of proving printed publication status consists of two conclusory sentences:

> The Jakafi® (ruxolitinib) Prescribing Information (Ex. 1004) was first published in November of 2011. Thus, the publication is prior art under at least pre-AIA 35 U.S.C. § 102(a).

Petition at 27.

Petitioner does not specify what information in Ex. 1004 supports the alleged November 2011 publication date. The document itself references "2011" three times: (1) page 1 recites "Revised: 11/2011;" (2) page 23 recites "Issued: November 2011;" and (3) page 1 recites "Initial U.S. Approval: 2011." Petitioner has not even cited these dates, let alone established that they are synonymous with publication.

The Board has previously found that exactly these types of dates on drug labels do not establish publication date. *See, e.g.*, *Mylan Pharms. Inc. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01565, Paper 17, at 19-20 (P.T.A.B. Feb. 9, 2017) (finding no showing that a drug label constituted a printed

publication because "a date merely printed on a reference is not synonymous with a publication date"); *Frontier Therapeutics, LLC v. Medac Gesellschaft Fur Klinische Spezialpraparate MBH*, IPR2016-00649, Paper 10 at 22 (P.T.A.B. September 1, 2016) (denying institution where dates on the face of a purported package insert were insufficient to satisfy petitioner's burden of proof).

Petitioner asserts that Ex. 1004 is listed on the face of the '149 Patent. Petition at 27. Petitioner does not appear to be relying on this assertion to prove printed publication status, but even if it is, this assertion says nothing about the publication date of Ex. 1004 itself. The '149 Patent issued on February 2, 2016, and Petitioner has not established when the document became part of the prosecution history, or even substantiated that the document referenced on the face of the '149 Patent is the same document presented as Exhibit 1004. Further, Petitioner provides no information extrinsic to Ex. 1004 tending to show its publication date, that it was publicly accessible, or how one could have obtained a copy of it.

Because Petitioner has not established that Exhibit 1004 is a printed publication, Ground 1 should be denied.[6]

[6] Petitioner asserts that "[T]he understanding that ruxolitinib was an effective pharmaceutical compound was shown in printed publications well over a year before the earliest effective filing date, for example, in Shilling (Ex. 1005)."

B. Concert Backgrounder

Petitioner has failed to carry its burden of demonstrating that the Concert Backgrounder is a printed publication. Petitioner does not specify where on the internet this document was originally located, but instead relies on its purported availability on a "cached WebCite® page" to demonstrate public accessibility. Petition at 27-28. Even taking this assertion at face value, Petitioner has at most established that the Concert Backgrounder was available at www.webcitation.org. But availability on the web, without more, is not sufficient to carry Petitioner's burden. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349 (Fed. Cir. 2016). Petitioner must also demonstrate that the document was accessible to POSAs, *e.g.*, by showing that it was disseminated or otherwise made available to the extent that POSAs exercising reasonable diligence could locate it. *Id.* at 1348-49; *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006) (citation omitted); *see also Hospitality Core Servs. LLC v. Nomadix Inc.*, IPR2016-00052, Paper 8, at 8 (P.T.A.B. Apr. 27, 2016).

Petition at 27. This statement does not save Ground 1 from denial. Petitioner has chosen to make the Jakafi® label integral to Ground 1. The Board should refrain from rewriting Ground 1 to exclude Ex. 1004. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (noting that petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable).

In *Blue Calypso*, the Federal Circuit affirmed the Board's finding that petitioner failed to establish that a POSA, exercising reasonable diligence, would have a located a report ("Ratsimor"), which Dr. Ratsimor published on a University of Maryland webpage. 815 F.3d at 1350-51. That outcome was compelled because the "record [was] devoid of any evidence that a query of a search engine before the critical date, using any combination of search words, would have led to Ratsimor appearing in the search results." *Id*. at 1349-50.

Here, too, Petitioner has failed to make any allegations about how a POSA would have known to look for the Concert Backgrounder on WebCite®, whether the document was indexed on that site, or how a POSA might have otherwise located the cached document on WebCite® via a search. Indeed, WebCite®'s search function appears to be limited to URL, date, and "snapshot ID" (unique numeric ID) searches, and to lack any ability to perform keyword searches of the cached documents. Ex. 2026 at 1, 9. As such, Petitioner has failed to carry its burden of proving accessibility by POSAs.

Petitioner contends that the public accessibility of the Concert Backgrounder is "evidenced by its use in a law review article published in 2009, which cited the same WebCite® page used in th[e] petition." Petition at 28. Again, this at most establishes that the document was available on WebCite®. The Petition is devoid of evidence as to how the author of the law review article located the document,

whether she qualifies as a POSA, and whether POSAs, exercising reasonable diligence, also could have located it.

Petitioner also points to mention of the WebCite® page in an International Search Report (ISR) for a Concert patent application. Petition at 28. But again, the Petition is devoid of evidence as to how the examiner obtained the document (including whether Concert submitted it, or whether the examiner searched for it, and if so, by what methods and what keywords, if any), whether he qualifies as a POSA, and whether POSAs exercising reasonable diligence could have also located it.[7] Additionally, Petitioner fails to establish that the version cited in the ISR is the same as Ex. 1006. The ISR references a document cached on 26.01.2009, while Ex. 1006 was purportedly cached on 27.01.2009. *Compare* Ex. 1021 at 3, *with* Ex. 1006 at 1.

Petitioner does not contend that either the law review article or the ISR is a "research aid" that would have led POSAs to the Concert Backgrounder. *Blue*

[7] Petitioner asserts that other patent applicants have also cited the Concert Backgrounder. Petition at n.2. Two of the cited patents have purported priority dates after the '149 Patent priority date, and thus fail to inform whether the Concert Backgrounder is prior art to the '149 Patent claims. The other two patents issued after the '149 Patent's priority date, and Petitioner has not shown when the document became part of the prosecution histories.

Calypso, 815 F.3d at 1350. However, to the extent the Board entertains this argument, it similarly lacks merit. The Petition lacks evidence or argument that a POSA—whom Petitioner defines as scientists—would have read the law review article or accessed the ISR.

Petitioner's failure to carry its burden of showing that the Concert Backgrounder was accessible to POSAs is especially pertinent here, where the document is a marketing document, as opposed to the type of information POSAs would typically rely on, such as peer-reviewed scientific articles. The Concert Backgrounder is designed to find business partners for Concert's proprietary product platform. Page 2 highlights several features and benefits of the product platform. The document then describes the potential benefits of deuterating drugs (pg. 2-3), provides a case study for deuterated torcetrapib (pg. 4-5), provides an overview of Concert's patent portfolio (pg. 6), and ends with a statement that Concert is interested in identifying business partners "[t]o fully exploit the commercial opportunity." Ex. 1006 at 6. Consistent with the marketing thrust of the document, the only contact information provided is for Concert's Chief Business Officer. Ex. 1006 at 6.

In sum, Petitioner has not established that POSAs, doing the type of searches a POSA would have performed, would have located this marketing document, including because WebCite® does not appear to permit keyword searching.

Accordingly, because Petitioner has failed to carry its burden of proving that the Concert Backgrounder is a printed publication, Grounds 1 and 3 should be denied.

VI. GROUNDS 1 AND 3 SHOULD BE DENIED BECAUSE PETITIONER HAS NOT DEMONSTRATED EITHER A MOTIVATION TO MAKE THE CLAIMED DEUTERATED ANALOGS, OR A REASONABLE EXPECTATION OF SUCCESS OF ACHIEVING A COMPOUND WITH IMPROVED METABOLIC STABILITY

In Ground 1, Petitioner argues obviousness over the combination of the Jakafi® label, Shilling, and the Concert Backgrounder. Ground 3 is similar, except Petitioner substitutes Rodgers for the Jakafi® label. Petitioner has failed to articulate a legitimate motivation to combine the cited references to make the claimed deuterated analogs, or a reasonable expectation of success of making octa- and tetra-deuterated ruxolitinib analogs with improved metabolic stability compared to undeuterated ruxolitinib.

Whether a claimed compound would have been obvious over a particular prior art compound typically follows a two-step inquiry. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-93 (Fed. Cir. 2012). First, the Board determines whether a POSA would have selected the asserted prior art compound as a lead compound for further development efforts. Second, the Board analyzes whether there was a reason to modify the lead compound to make the claimed compound with a reasonable expectation of success. *Id.* at 1291-92; *see also KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 401 (2007) (patent challenger must "identify a reason

that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does"). Petitioner ignores this framework, and otherwise fails both steps of the inquiry.

A. Petitioner Fails to Engage in a Lead Compound Analysis

1. Petitioner Has Not Established a Motivation to Select Ruxolitinib as a Lead Compound for Modification

"In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Otsuka*, 678 F.3d at 1292. In Ground 1, Petitioner argues that because ruxolitinib is an FDA-approved drug with known metabolic hotspots, a POSA would have selected it for deuteration. Petition at 29, 32. In Ground 3, Petitioner argues that because ruxolitinib is claimed in Rodgers and has known metabolic hotspots, a POSA would have selected it for deuteration.[8] Petition at 54.

Petitioner's generic arguments could apply to any number of the thousands of FDA-approved drugs, or to any of the hundreds of compounds recited in Rodgers. Petitioner provides no reason why a POSA would have specifically

[8] Petitioner also argues that Rodgers discloses a genus of deuterated ruxolitinb analogs. Petition at 50-51. For the same reasons discussed below in connection with Ground 2, without using the '149 Patent as a roadmap, a POSA would not have recognized Rodgers to disclose deuterated ruxolitinb. *See* Section VIII.

chosen ruxolitinib as a lead compound over any of these other options.[9] For example, the prior art indicates that candidates for deuteration include drugs "that give rise to undesirable metabolites, are cleared from the bloodstream too quickly, are metabolically broken down in the intestines or liver before reaching the bloodstream, or interfere with the clearance of other medications a patient is taking." Ex. 1013-p.3. Exposing the hindsight nature of its argument, Petitioner points to nothing in its cited references that raises any such issue for ruxolitinib, or any other reason why a POSA would have selected this particular compound for modification. *See, e.g.*, *Fustibal v. Bayer Corp.*, IPR2016-01490, Paper 9, at 17-18 (P.T.A.B. Feb. 8, 2017) (finding that nothing in the prior art highlighted the purported lead compound); *see also Sawai USA, Inc. v. Nissan Chem. Indus. Ltd.*, IPR2015-01647, Paper 9, at 14 (P.T.A.B. Feb. 4, 2016) (same); *Apotex Inc. v. Merck Sharp & Dohme Corp.*, IPR2015-00419, Paper 14, at 11-12 (P.T.A.B. June 25, 2015) (rejecting proposed lead compound where petitioner did not explain why POSA would have picked that compound from among 600 others).

[9] As discussed below, Rodgers does not disclose any *in vitro* or *in vivo* data for any compound that falls within its vast disclosure. *See* Section VIII.A.1.

2. Structural Similarity Alone is Insufficient to Provide Motivation

In Ground 1, Petitioner argues that the structural similarity between ruxolitinib and deuterated ruxolitinib is, standing alone, sufficient motivation to choose ruxolitinib. Petition at 29-31. This argument is contrary to law. As the Federal Circuit stated in *Otsuka*, "mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Otsuka*, 678 F.3d at 1292; *Sawai USA, Inc.*, IPR2015-01647, Paper 9, at 14; *Apotex Inc.*, IPR2015-00419, Paper 18, at 3-4 (petitioner must provide "'some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness,' independent of the structural similarity") (*quoting Otsuka*, 678 F.3d at 1291).

Petitioner's reliance on *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) and *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) is unavailing. In *Aventis*, the relevant claim was directed to an isolated isomer. The prior art taught mixtures containing the claimed isomer, and that isomers with the claimed configuration were more biologically active. *Aventis*, 499 F.3d at 1302. Accordingly, because the prior art provided a motivation to isolate the claimed isomer, the Federal Circuit found the claims obvious. *Id*. These facts are not analogous here, because the '149 Patent claims are not directed

to an isolated component of a previously-known mixture, but are rather directed to a novel drug compound.

In *In re Dillon*, the claims covered a tetraorthoester. *Dillon*, 919 F.2d at 716. The prior art taught that triorthoesters could be used to reduce water in fuels, and that tetraorthoesters behaved similarly to the prior art triorthoesters in relevant fluids. *Id.* at 691, 718. The court's obviousness finding was grounded on the prior art teaching that these structurally-similar compounds behave similarly. *Id.* at 719. Here, in contrast, the prior art teaches that the metabolism of a deuterated analog can be materially different than that of the undeuterated form. *See* Section II.B.3 above.

Because Petitioner fails to establish a valid reason why a POSA would have chosen ruxolitinib as "a natural choice for further development efforts," institution should be denied. *See, e.g.*, *Fustibal*, IPR2016-01490, Paper 9, at 17-18; *Sawai USA, Inc.*, IPR2015-01647, Paper 9, at 14; *Apotex Inc.*, IPR2015-00419, Paper 14, at 12.

B. Petitioner Fails to Identify a Reason to Modify Ruxolitinib to Make the Claimed Compounds

Even if there were a motivation to choose ruxolitinib as a lead compound (which there is not), Petitioner does not identify a persuasive reason to either modify ruxolitinib with deuterium, or pursue the specific claimed analogs, which have specific deuteration patterns. It "remains necessary to identify some reason

that would have led a chemist to modify a known compound in a particular manner." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

1. Petitioner Has Not Established a Motivation to Make the Claimed Deuterated Ruxolitinib Analogs

Petitioner suggests that a POSA would have been motivated to deuterate ruxolitinib to obtain a compound with "comparable" selectivity and potency as ruxolitinib. Petition at 30. But Petitioner never explains why a POSA would have gone through the time and expense of making deuterated ruxolitinib analogs only to obtain something very similar to ruxolitinib itself. *See, e.g.*, Ex. 1010-p.6 (noting that "deuterated compounds are expensive to make" and "will necessitate a new clinical package"); Ex. 1039-p.3 ("For [deuterated] drugs intended for use in humans there will be a substantial additional cost, namely, that associated with preclinical toxicology and clinical trials."). Petitioner also argues that a POSA would have been motivated to deuterate ruxolitinib "potentially to obtain superior ADME properties." Petition at 32. This argument is similarly lacking, because Petitioner has not identified any specific ADME property of ruxolitinib that a POSA would have been motivated to improve or why the POSA would have been motivated to improve it.

2. Petitioner Has Not Established a Motivation to Make the Tetra-Deuterated Analogs

Even if a POSA would have focused on ruxolitinib as a lead compound (which s/he would not) and would have been motivated to modify ruxolitinib by deuterating it (again, s/he would not), Petitioner has not established any motivation to prepare the tetra-deuterated analogs discussed in the Petition, *i.e.*, 3,3,4,4-tetra-deuterated ruxolitinib and 2,2,5,5-tetra-deuterated ruxolitinib. It is only with impermissible hindsight that Petitioner zeros in on these particular analogs. As confirmed by Dr. Baillie, even accepting Petitioner's own rationale, a POSA would not have been motivated to make these analogs.

Shilling states that the major circulating ruxolitinib metabolites in humans are formed by oxidation at ***both*** the 2- and 3-positions of the cyclopentyl ring. Ex. 1005-p.6, 8; *see also* Ex. 1002, ¶ 70. Further, Shilling states that the plasma concentration of metabolites formed by oxidation of each of the 2- and 3-positions are comparable (30% resulting from oxidation at the 2-position vs. 34.5% resulting from oxidation at the 3-position). Ex. 1005-p.6, 8. However, for each of the tetra-deuterated analogs on which Petitioner focuses, deuterium is absent in either position 2 or position 3. Under Petitioner's own rationale, a POSA would not have been motivated to prepare tetra-deuterated compounds where a major site of metabolism is undeuterated. In fact, Dr. Guengerich effectively acknowledges as much, stating: "It would make no scientific sense to deuterate selectively only

some of one of the sites of the cyclopentyl ring (i.e., some of Y^2 or some of Y^3) because Shilling explains that metabolism occurs at each of the four secondary methylenes of the cyclopentyl ring." Ex. 1002, ¶ 85.

A POSA also would not have had a reasonable expectation that this partial substitution would result in a significant KIE, due to the possibility of metabolic switching. Ex. 2002 (Baillie), ¶¶ 72-75. Metabolic switching could result in no change in $t_{1/2}$, or even shorter $t_{1/2}$ values, as seen with iloperidone and maraviroc. *Id.*, ¶ 75. Accordingly, even accepting Petitioner's theory, a POSA would not have been motivated to prepare tetra-deuterated ruxolitinib analogs with a reasonable expectation of success, and for at least that reason, these analogs would not have been obvious to a POSA.

The Board has routinely denied institution where Petitioner fails to satisfy the two steps of the lead compound inquiry, and in view of the above deficiencies in Petitioner's arguments, should do so here as well. *See, e.g.*, *Fustibal*, IPR2016-01490, Paper 9, at 17-18; *Sawai USA, Inc.*, IPR2015-01647, Paper 9, at 14-15; *Apotex Inc.,* IPR2015-00419, Paper 14, at 12.

C. Petitioner Has Not Established a Reasonable Expectation of Success of Achieving a Compound with Improved Metabolic Stability

To establish obviousness, Petitioner must also show a reasonable expectation of both making the new compound, and its advantageous properties.

Mylan Labs. Ltd. v. Aventis Pharma S.A., IPR2016-00627, Paper 10, at 11 (P.T.A.B. Aug. 23, 2016) (*quoting Otsuka*, 678 F.3d at 1292); *Neptune Generics, LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25, at, *e.g.*, 19 (P.T.A.B. Dec. 9, 2015) (denying institution of IPR on a patent to a deuterated drug compound, where the prior art supported the unpredictability of the effect of substituting deuterium for hydrogen on the pharmacological and toxicological effects of a drug). Petitioner has not satisfied either of these requirements.

Petitioner's reasonable expectation of success argument is founded on the incorrect assumption that deuterating at metabolic hotspots "predictably" leads to "altered" metabolism. Petition at 35. Petitioner argues that the torcetrapib example in the Concert Backgrounder establishes "a reasonable level of predictability" because it shows that blocking metabolic "hotspots" led to enhanced metabolic stability. *Id.* at 34-35. Petitioner also argues that the "reemergence of deuteration strategy" and "numerous patent filings" support a reasonable expectation of success. *Id.* at 37.

Petitioner's arguments are at odds with the state of the art. Appreciating the complexity of biological systems and in view of examples such as those described in Section II.B.3, a POSA would have known that deuterating "hotspots" does not predictably lead to increased metabolic stability. Indeed, the Board has previously rejected the contention that deuteration at only metabolic hotspots would have been

obvious, stating that "the ordinary artisan would not have had a reasonable expectation that deuteration of those sites [hotspots] would result in enhanced bioavailability and maintaining the activity of [the drug at issue] for a longer period of time." *Neptune Generics, LLC*, IPR2015-01313, Paper 25, at 20-21. The more complete picture of metabolism and actual examples showing a wide range of results aptly demonstrate that the effect of deuteration on the metabolic properties of a drug are unpredictable. Neither the single torcetrapib example, cited in a marketing document, nor the purported industry interest in deuterating drugs, are sufficient to overcome the known unpredictability that results from deuteration.

As will be more fully discussed below, a POSA would have known that any KIE could be masked, such that no benefits from deuteration are observed.

1. Whether the Breaking of the C-H Bond Is Rate-Limiting Was Not Known and Could Not be Predicted

As discussed above (*see* Section II.B.1), a KIE will only be observed if the breaking of the C-H bond is at least partially rate-limiting in the metabolism of ruxolitinib. At the time of the invention, a POSA would not have known or been able to predict whether the breaking of the C-H bond would be the rate-limiting step in the CYP450 3A4-mediated metabolic oxidation of ruxolitinib. *See supra* Section II.B.1. It is not known even today. As Dr. Guengerich acknowledged in publications outside of the context of this proceeding, "[r]elatively little

information is available regarding what step is rate-limiting in P450 3A4 reactions," and "[w]ithout information on the extent to which chemical steps (e.g. substrate oxidation) limit catalysis, it will not be possible to understand or predict the behavior of this system." Ex. 1035-p.1. Even if C-H bond breaking is involved in the rate-limiting step, a POSA would not have been able to predict the magnitude of the KIE, and thus whether there would be any net benefit *in vivo*. *See* Ex. 1027-p.4-5 (discussing complexities involved in CYP450 metabolism, and concluding that the observed magnitude of a KIE is unpredictable).

2. Whether Metabolic Switching Would Occur Was Not Known and Could Not be Predicted

When deuteration inhibits metabolism at a preferred site, "metabolic switching," *i.e.*, an increase in metabolism at an alternate site, may occur. Ex. 2023 (Miwa), at 2. The pharmacological and toxicological consequences of metabolic switching depend on whether it enhances or inhibits the production of toxic metabolites, or changes the ratio of metabolites that may or may not be active. *Id.* at 4. It was well-known that metabolic switching can mask a KIE. *See, e.g.*, Ex. 1040-p.4; Ex. 1027-p.4; Ex. 1008-p.50.

Petitioner cites no prior art that taught whether metabolic switching would occur with deuterated ruxolitinib. Petitioner suggests that the degree of metabolism at an alternate site will influence whether this phenomenon occurs. Petition at 38. However, Petitioner presents no evidence to establish that the

relative amount of metabolites will dictate whether metabolic switching will occur. For example, Harada *et al*. observed metabolic switching upon deuterating 7-ethoxycoumarin, which caused a five-fold increase in a metabolite previously formed in only a minor amount relative to the major metabolite. Ex. 1033-p.1, 5. Rather, it is the relationship between the topology of the enzyme's active site and the structure of the substrate that drives metabolic switching. Ex. 2023 (Miwa), at 1-2. Petitioner has not posited any prior art information about this relationship with respect to ruxolitinib.

Further, if deuteration of ruxolitinib led to metabolic switching, a POSA would not have been able to predict the ratio of metabolites that would be formed, nor the impact of those metabolites. Ex. 1010-p.6; Ex. 1008-p.50.

3. Several of Petitioner's Arguments are Unsupported and Should be Rejected

Petitioner makes a number of additional arguments in support of a reasonable expectation of success—specifically, relating to sp^3-hybridization, aryl vs. alkyl bond breakage, and ability of a POSA to make the claimed analogs—but they are not properly supported and should be rejected.

For example, Petitioner states, without elaboration, that ruxolitinib's "cyclopentyl sites are sp^3-hybridized, which is a hybridization that is very capable of producing kinetic isotope effects upon deuteration." Petition at 34. Dr.

Guengerich repeats this statement, but similarly does not elaborate or explain why sp^3 hybridization favors a KIE. Ex. 1002, ¶ 84.

Additionally, in paragraphs 94-103 of his declaration, Dr. Guengerich argues that a POSA would have expected a KIE from deuterium substitution at an alkyl C-H bond, but not from an aryl C-H bond. Although these ten paragraphs are cited in the Petition (*see* Petition at 33-34), this argument should be rejected as improper incorporation by reference because Dr. Guengerich's theory is not discussed anywhere in the Petition. Moreover, in developing this theory, Dr. Guengerich relies on several exhibits that are not cited in the Petition, including Exhibits 1012, 1030, 1031, and 1032. He also fails to pinpoint what disclosure he is relying on in these exhibits. *See* Ex. 1002, ¶¶ 94-95. Further compounding the incomplete disclosure, he relies on the "references cited" in Exhibit 1012 (*id.*, ¶ 98), most of which are not of record in this proceeding.[10]

Petitioner also argues that the synthesis of the claimed analogs was "well within the abilities of a POSA from commercially available starting materials." Petition at 32-33. Dr. Guengerich, however, opines only on the synthetic methods disclosed ***in the '149 Patent itself***, but did not point to any ***prior art*** information

[10] Even if one accepts the importance of sp^3-hybridization, the arguments lack merit because Petitioner has not established that the C-H bond-breaking step for an sp^3-hybridized carbon is rate-limiting for ruxolitinib.

indicating that these synthetic methods for the claimed analogs were known. Ex. 1002, ¶¶ 104-105. Dr. Guengerich also asserts that the starting materials the inventors used were commercially available, but relied solely on a page of an Aldrich catalog that is not of record. *Id.*

Accordingly, the Board should disregard Petitioner's arguments regarding sp3-hybridization, aryl vs. alkyl bond breakage, and ability of a POSA to make the claimed analogs, because Petitioner has failed to satisfy its burden to identify the basis for and evidence that supports these challenges. 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."); *Verlander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003) (noting that the Board has discretion to accord little weight to broad conclusory statements from expert witness); *Apple, Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00449, Paper 10, at 11 (P.T.A.B. July 15, 2015) (denying institution where confusing citations left the Board "to play archeologist with the record").

Given Petitioner's failure to establish a reasonable expectation of success, the Board should deny institution. *Neptune Generics, LLC*, IPR2015-01313, Paper 25, at 18 (denying institution of IPR on a patent to a deuterated drug compound).

VII. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS COMPEL DENIAL OF GROUNDS 1 AND 3

Objective indicia of nonobviousness play a critical role in the obviousness analysis. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). They "can be the most probative evidence of nonobviousness in the record, and enable[] the court to avert the trap of hindsight." *Id*. Unexpected results revealed even after the patent's filing or issue are pertinent. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) (citation omitted); *Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, IPR2015-01993, Paper 63, at 7 (P.T.A.B. March 21, 2017).

The Petition fails to rebut the unexpected results presented during prosecution and further fails to recognize that CTP-543 has improved PK properties over ruxolitinib in humans. Crediting these results is crucial in avoiding the hindsight trap and compels denial of institution. *See, e.g.*, *Omron Oilfield & Marine, Inc. v. MD/TOTCO*, IPR2013-00265, Paper 11, at 12-13 (P.T.A.B. Oct. 31, 2014) (denying institution based on secondary considerations).

A. Petitioner Has Shown No Valid Basis to Discard the Results Submitted During Prosecution and Retreads Arguments That Were Previously Before the Office

As discussed above in Section III.B, during prosecution Concert overcame an obviousness rejection by demonstrating that the three octa- and tetra-deuterated compounds on which Petitioner focuses are substantially more metabolically stable

than ruxolitinib. *See* Ex. 1009 at 285-88. Petitioner advances a number of criticisms of these results, none of which withstands scrutiny. In failing to discredit the *in vitro* results submitted during prosecution, Petitioner merely retreads arguments that were previously presented to the Office, and thus the Petition should be denied under 35 U.S.C. § 325(b).

First, Petitioner contends that Concert's *in vitro* results are not unexpected because "most compounds metabolized by P450 reactions show at least some primary isotope effect." Petition at 41. This statement is belied by the known unpredictability of the KIE, due to the known complexity of metabolic processes and examples of deuterated analogs that failed to show improved metabolic stability. As discussed in Section II.B.2, a KIE is observed only when C-H bond breakage is at least partially rate-limiting, which could not be predicted for ruxolitinib. Furthermore, as reflected in the examples in Section II.B.3 above, deuterated analogs of both iloperidone and maraviroc showed *less* metabolic stability than the undeuterated drug. Petitioner also argues that reported KIEs are relatively low (Ex. 1002, ¶ 121), but fails to explain the relevance of the magnitude of the KIE or how this point undercuts the value of the experimental data.

Second, Petitioner argues that Concert's assays were not robust as one would see in a peer-reviewed publication. However, Dr. Guengerich's opinion on

this point is conclusory and not supported by any evidence of record. *See* Ex. 1002, ¶ 122.[11]

Third, Petitioner's arguments that the results are misleading because the assays used two different protein concentrations—which he identifies as "0.5 vs. 5.0 mg/mL"—and "do[] not show a standardized half-life that is independent of protein concentration" appear to be based on Dr. Guengerich's misunderstanding of the experiments presented. *Id.*, ¶ 123; Petition at 42. Initially, it should be noted that contrary to Dr. Guengerich's assertion, there are no experiments described in the Uttamsingh Declaration that use a protein concentration of 0.5 mg/mL. Ex. 2002 (Baillie), ¶ 56. In any event, the Uttamsingh Declaration describes two different experiments that use two very different *in vitro* assay systems, and Petitioner cites no objective evidence as to why the protein concentration should be the same in experiments that are so different. *See* Ex. 1009-p.285-88; Ex. 2002 (Baillie), ¶ 56. Further, Dr. Guengerich's argument that the "relatively high" protein concentration in one of the assays "skew[ed]" the results (Ex. 1002, ¶ 123) is refuted by the results themselves, which are consistent with each other. Ex. 2002 (Baillie), ¶ 57. Moreover, the 5 mg/mL concentration of HLM protein that was used in the Uttamsingh experiment is well within the

[11] Further, as Petitioner acknowledges, Concert had no obligation to meet this standard. Petition at 41-42.

range of protein that is commonly employed in the HLM assays for a basic compound such as ruxolitinib. *Id.*, ¶ 58; Ex. 2018 (Obach), at 1353, Table 3.

Finally, Petitioner contends that the *in vitro* data is not probative of how the compound might function *in vivo*, and that the data should thus be converted to a theoretical systemic clearance. Petition at 42; Ex. 1002, ¶¶ 123, 124. However, Concert nowhere suggested that the *in vitro* half-life data was "used to report percent increase in *in vivo* half-life," as Petitioner contends. Ex. 1002, ¶ 123. To the contrary, the Uttamsingh Declaration stated: "The state of the art requires actual testing to determine the effect, if any, of deuterium substitution on metabolism." Ex. 1009-p.288. Further, as appreciated by POSAs, the purpose of *in vitro* testing in the context of deuterated drug analogs is to determine whether deuterium causes *in vitro* differences in drug metabolic stability. These assays are not typically used as quantitative predictors of human PK properties. Ex. 2002 (Baillie), ¶ 59. The Uttamsingh data was presented for the purpose of comparing the test compounds to ruxolitinib, and on that basis, showed unexpected differences in half-life measured *in vitro* compared to ruxolitinib. *Id.*

The Board should reject Petitioner's conclusory and unfounded criticisms of the unexpected results used during prosecution to establish patentability of the three compounds addressed in the Petition. Petitioner's obviousness arguments then boil down to the same core arguments that the Office already considered,

which were overcome during prosecution. *See, e.g.*, Ex. 1009-p.111; *supra* Section III.B. Accordingly, the Board should deny institution of Grounds 1 and 3 because substantially the same unpatentability arguments were previously presented to the Office. 35 U.S.C. § 325(d).

B. The Petition is Based on a Mischaracterization of CTP-543's Clinical Profile

Petitioner fails to recognize that CTP-543 has improved PK properties over ruxolitinib in humans. Instead, Petitioner disparages Concert's earlier *in vitro* results, asserting that a POSA would not have expected the *in vitro* differences from ruxolitinib to translate to an *in vivo* setting. Petition at 42. Petitioner further argues that Concert's clinical data showed that deuterium modification had little effect, and that this clinical data was more probative than Concert's *in vitro* data. *Id.* at 42-43. Based on this assessment, Petitioner concludes that Concert failed to overcome *prima facie* obviousness.[12]

[12] Petitioner's attempt to shift the burden of proving patentability to Patent Owner in this proceeding is legal error. The "burden-shifting framework does not apply in the adjudicatory context of an [IPR]." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016). Rather, "the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee." *Dynamic Drinkware*, 800

Petitioner's assertions regarding little or no *in vivo* effect resulting from deuteration of ruxolitinib are incorrect. CTP-543 has a significantly longer $t_{1/2}$ than ruxolitinib in humans. Ex. 2001 (Harbeson), ¶¶ 12-13, Table 3; Ex. 2002 (Baillie), ¶ 47. While it is true that Concert reported a $t_{1/2}$ that was similar to ruxolitinib in a Phase 1 clinical trial (Petition at 40), that trial only tested CTP-543. Ex. 2002 (Baillie), ¶¶ 47-48. There was no direct comparison of CTP-543 to ruxolitinib. Instead, CTP-543 was compared to historical data for ruxolitinib. *Id*.

As discussed above in Section II.C, Concert later conducted a crossover study that directly compared CTP-543 and ruxolitinib. The results revealed a statistically significant improvement in $t_{1/2}$, clearance ("CL/F"), and AUC for CTP-543 compared to ruxolitinib:

Comparison of CTP-543 and Ruxolitinib PK Parameters		
PK Parameter	**p-value**	**Statistically different ($p < 0.05$)**
C_{max}	0.0941	No
AUC_{inf}	0.0006	Yes
C_{12hr}	0.007	Yes
$t_{1/2}$	0.003	Yes
CL/F	0.0001	Yes

Ex. 2001 (Harbeson), ¶ 13; Ex. 2002 (Baillie), ¶ 48.

F.3d at 1378 (citation omitted); *E.I. Du Pont de Nemours and Co. v. Furaniz Techs. B.V.*, IPR2015-01838, Paper 43, at 14-15 (P.T.A.B. Mar. 3, 2017).

Importantly, Petitioner's argument that the clinical differentiation of CTP-543 does not support patentability is based on a characterization of CTP-543 that is contrary to the data from this human crossover study. Without the benefit of this later clinical data, the Petition incorrectly assumes little or no clinical differentiation. However, the data herein demonstrate that there *is* significant PK differentiation between CTP-543 and ruxolitinib. Ex. 2002 (Baillie), ¶ 48. Accordingly, Petitioner's assertion that a POSA would not have expected the *in vitro* differences from ruxolitinib to translate to an *in vivo* or clinical setting serves only to highlight the unexpected nature of the clinical PK profile of CTP-543.

C. The Petition Fails to Address CTP-543's Important Clinical Advantages

In addition, two important and clinically meaningful unexpected advantages of CTP-543 over ruxolitinib were not addressed in the Petition. These unexpected advantages are: (a) an increased therapeutic window; and (b) increased clinical response at a given dose.

1. Increased Therapeutic Window

Both non-clinical and clinical studies show that, relative to ruxolitinib, CTP-543 has the potential for an increased therapeutic window that is unexpected. The increased therapeutic window is due to PK differences between the drugs that are especially favorable for CTP-543 with respect to its potential safety and efficacy in treating alopecia areata. Ex. 2002 (Baillie), ¶ 50. In particular, as discussed above

(Section II.C.2), doses of CTP-543 that are likely to be effective in the treatment of alopecia areata are less likely to cause anemia than similarly effective doses of ruxolitinib. Ex. 2002 (Baillie), ¶¶ 51-52.

Neither Shilling nor the Concert Backgrounder explain this increased therapeutic window or suggest why it would be expected. Figure 1 of the Concert Backgrounder provides two reasons for why deuterium modification might improve either safety or tolerability: (1) by inhibiting formation of a toxic metabolite, or (2) by reducing C_{max}-driven side effects. Ex. 1006-p.2. However, neither of these reasons explains the increased therapeutic window for the deuterated ruxolitinib analog. The clinical data shows that CTP-543 has the potential for better safety without lowering C_{max}, and there is no evidence that a toxic metabolite is being avoided. Thus, the Concert Backgrounder provides no reason to believe that a deuterated ruxolitinib analog having the PK profile observed in the CTP-543 clinical study would have an increased therapeutic window. Petitioner's analogy to torcetrapib is likewise inapposite, because that argument also relies on the lowering of C_{max}, which is not the case for CTP-543.

2. Increased Clinical Response at a Given Dose

As discussed above (*see supra* Section II.C.3), another unexpected advantage of CTP-543 is the potential for an increased clinical response at a given dose. Patient populations are heterogeneous and display a range of PK profiles for

a given dose of drug. Ex. 2002 (Baillie), ¶ 49. As a result, not all patients receiving drug will benefit to the same degree. *Id.* In Concert's crossover study, individuals with the shortest ruxolitinib $t_{1/2}$ values unexpectedly and beneficially had the greatest improvement in $t_{1/2}$ values when given CTP-543. Ex. 2001 (Harbeson), ¶ 14; Ex. 2002 (Baillie), ¶¶ 49-50. An increased clinical response at a given dose would be clinically meaningful because a patient would be more likely to benefit from treatment.

Petitioner does not cite any prior art disclosure of a deuterated analog of a non-deuterated drug providing a greater benefit in $t_{1/2}$ to more rapid CYP3A4 metabolizers, much less any reason why a POSA would have expected to observe such a benefit for any drug, let alone for a deuterated analog of ruxolitinib. Patent Owner and Dr. Baillie are not aware of any other reported examples where a deuterated analog of a CYP3A4-metabolized drug provides a proportionately greater benefit in $t_{1/2}$ to those subjects with the shortest $t_{1/2}$ for the non-deuterated drug. Ex. 2001 (Harbeson), ¶ 15; Ex. 2002 (Baillie), ¶ 53.

D. The Surprising and Unexpected Potential for an Increased Therapeutic Window and Increased Clinical Response at a Given Dose Support Nonobviousness

The Petition does not address data showing that deuterium modification of ruxolitinib has the potential to increase the therapeutic window or provide an

increased clinical response at a given dose. Furthermore, Petitioner does not refute the unexpected nature of these advantages.

The potential for improved safety and tolerability in treating alopecia areata is not explained by either Shilling or the Concert Backgrounder. Ruxolitinib is not known to form a toxic metabolite and the CTP-543 clinical data shows that C_{max} is not lowered compared to ruxolitinib, the two reasons why deuterium modification might provide a greater therapeutic window according to the Concert Backgrounder. Therefore, Petitioner's cited prior art does not explain the increased therapeutic window.

The clinical data for CTP-543 also shows a surprising potential for an increased clinical response. Ex. 2001 (Harbeson), ¶ 14; Ex. 2002 (Baillie), ¶ 49. This is a potential benefit for alopecia areata as well as for the treatment of blood cancers for which Jakafi® is approved. Ex. 2002 (Baillie), ¶ 54. As noted, Patent Owner and Dr. Baillie are not aware of any other reported examples of this type of result flowing from a deuterated analog of a CYP3A4-metabolized drug. Ex. 2001 (Harbeson), ¶ 15; Ex. 2002 (Baillie), ¶ 53.

It is important to note that while the metabolic stability of the deuterated ruxolitinib analogs is unexpected, that alone does not explain the advantages of an increased therapeutic window and increased clinical response. Even assuming, *arguendo*, that improved metabolic stability might be expected when the metabolic

hotspots of ruxolitinib are substituted with deuterium, the Petition offers no explanation for why these other, clinically meaningful advantages would result. These unexpected results are therefore "different in kind," and are thus highly probative of non-obviousness. *See Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) (finding nonobviousness where unexpected results differed in kind from what would have been expected); *Coalition for Affordable Drugs VII LLC v. Pozen Inc.*, IPR2015-01718, Paper 40, at 26, 29 (P.T.A.B. Feb. 21, 2017) (same).

E. Conclusion on Nonobviousness

As discussed above, Petitioner has failed to establish obviousness for any embodiment of the claim, including because it has failed to establish a motivation to select ruxolitinib for deuteration or a reasonable expectation of success, and has failed to identify a reason to discard the unexpected results presented during prosecution. Moreover, as to the three embodiments on which it focused its Petition (Petition at 8-9), Petitioner has failed to establish a motivation to make the two tetra-deuterated species, and has not addressed the surprising and unexpected benefits demonstrated by the octa-deuterated species. Accordingly, Petitioner has failed to carry its burden of proving that it is more likely than not that at least one challenged claim is unpatentable, and the Board should therefore deny institution of Grounds 1 and 3. *See Allergan, Inc.*, 796 F.3d at 1307; *Coalition for Affordable*

Drugs V LLC, IPR2015-01993, Paper 63, at 27; *Coalition for Affordable Drugs VII LLC*, IPR2015-01718, Paper 40, at 29; *see also Dynamic Drinkware*, 800 F.3d at 1378 (burden of persuasion is on petitioner and never shifts to the patentee).

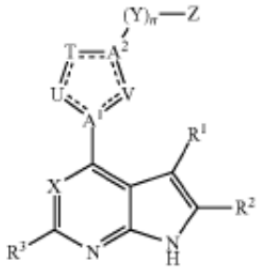
VIII. GROUND 2 SHOULD BE DENIED BECAUSE RODGERS FAILS TO ANTICIPATE

Ground 2 should be denied because Rodgers, which discloses a vast genus comprising trillions of compounds, none of which are deuterated, in no way discloses a small genus from which a POSA would "at once envisage" the specific deuterated ruxolitinib analogs claimed in the '149 Patent.

A. The Rodgers Disclosure

1. Rodgers' Specification

Rodgers is a published patent application of breathtaking scope. It is directed to an enormous class of compounds, depicted by Formula I, that modulate JAK activity:



Ex. 1007-p.1 (Abstract); 61:64-62:17. Plugging in the constituent members disclosed in the specification (R^1, R^2, etc., *see* Ex. 1007-p.7-18), Formula I covers

a genus of trillions of potential compounds, about 600 of which are recited in the specification. Ex. 1007-p.38-188 (Examples).

Rodgers does not stop at these trillions of compounds. It also purports to cover pharmaceutically acceptable salt forms and prodrugs of the compounds of Formula I. Ex. 1007-p.6-7 (Summary of the Invention); 33:1-21. It also purports to cover "[a]ll stereoisomers, such as enantiomers and diastereomers" of the Formula I compounds, including in isolated optically active or racemic forms. Ex. 1007, 31:32-35. Rodgers further purports to cover all geometric isomers, including cis and trans isomers of the compounds of Formula I, which can be "isolated as a mixture of isomers or as separated isomeric forms." *Id.*, 31:38-44. It also purports to cover tautomeric forms, hydrates, solvates, anhydrous forms, and non-solvated forms of the compounds of Formula I. *Id.*, 31:64-65, 32:11-12.

With respect to isotopes, Rodgers generically states that "[c]ompounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds . . . . For example, isotopes of hydrogen include tritium and deuterium." *Id.*, 32:13-17. Rodgers also indicates that "[a]nother aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating JAK in tissue samples, including human, and for identifying JAK ligands by inhibition

binding of a labeled compound." *Id.*, 67:65-68:5; *see also* 68:36-52 (discussing binding assays).

Rodgers also states that "[t]he present invention further includes isotopically-labeled compounds of the invention." *Id.*, 68:7-8. Rodgers goes on to broadly define an "isotopically" or "radio-labeled" compound 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.*, 68:8-13. It then goes on to exemplify "[s]uitable radionuclides," 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." *Id.*, 68:13-17. Rodgers further states that "The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound." *Id.*, 68:17-24. Rodgers further purports to cover compounds with more than one incorporated radionuclide. *Id.*, 68:25-27. Five specific nuclides are singled out—^{3}H, ^{14}C, ^{125}I, ^{35}S, and ^{82}Br—none of which are deuterium. *Id.*, 68:27-29.

Still further, Rodgers seeks to cover all pharmaceutical formulations and dosage forms comprising the purported inventive compounds, as well as

combination therapies of an additional pharmaceutical agent combined with the compounds of Formula I. *Id.*, 65:23-63; 64:30-39.

Rodgers reports no *in vitro* or *in vivo* data for any of the disclosed compounds, and nowhere indicates that any particular compound is "preferred." Rodgers reports no working example of any formulation or dosage form that contains any of the disclosed compounds.

2. Rodgers' Claims

From this extremely broad disclosure of trillions of compounds and innumerable additional compositions and possibilities, Rodgers claims three compounds, 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propane-nitrile (claim 1), and the (3R) and (3S) stereoisomers of this compound (claims 2 and 3, respectively).

B. Rodgers Does Not Anticipate the '149 Claims

Petitioner's contention that Rodger's vast disclosure anticipates the '149 Patent claims, which are directed to specific deuterated ruxolitinib analogs and pharmaceutical compositions comprising the same, is contravened by black letter law. "Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim." *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013). The challenged claims recite certain ruxolitinib analogs where certain hydrogen positions are instead deuterium

in an abundance that is at least 3,000 times greater than the natural abundance of deuterium, and compositions containing the same. Petition at 24. It is undisputed that Rodgers does not disclose the claimed deuterated ruxolitinib analogs *in haec verba*.

Rather, to get from Rodgers' disclosure to the challenged claims, Petitioner must do at least five things: (1) focus on Rodgers' claimed compounds to the exclusion of the trillions of other disclosed compounds; (2) import into the scope of Rodgers' claims the discussion of isotopes and radiolabeling; (3) somehow exclude every isotope and radionuclide, including the preferred radionuclides, to focus on just deuterium; (4) imagine that Rodgers directs POSAs to the small genus of analogs deuterated only at the sites recited in the challenged claims; and (5) imagine that Rodgers directs POSAs to substitute deuterium at the level of incorporation that Petitioner admits is required.

In limited circumstances, disclosure of a genus can anticipate every species in that genus. For example, in *In re Petering*, the court found claims to certain compounds anticipated where the prior art reference disclosed a genus that contained the later-claimed compounds, among only twenty other species. 301 F.2d 676, 681-82 (C.C.P.A. 1962). The key to anticipation in *Petering* was the pattern of specific preferences disclosed in the prior art reference that transformed the generic formula into a limited class of specific, defined compounds. *Id.* at 681.

Here, unlike *Petering*, Petitioner points to no pattern of preferences in Rodgers that would result in a POSA "at once envisaging" a genus that covers the specific deuterated analogs in the challenged claimed. As described above, Rodgers discloses a vast array of trillions of compounds, together with their salts, prodrugs, stereoisomers, geometric isomers, hydrates, solvates, etc. Rodgers also discloses approximately 600 specific example compounds, but fails to point to any individual compound as "preferred." Even assuming Rodgers discloses deuterated ruxolitinib analogs, it certainly does not point to analogs deuterated at the specific hydrogen positions claimed in the '149 Patent.

Using the '149 Patent claims as a guide to pick and choose among disparate portions of Rodgers, Petitioner focuses solely on the claims (which relate to ruxolitinib and related isomers), and on col. 32, lines 13-17 (which discusses isotopes). Petition at 44; Ex. 1002, ¶ 130. Rodgers' claims are directed to undeuterated ruxolitinib (claim 2), the opposing isomer (claim 3), and the ruxolitinib base compound without mention of stereochemistry (claim 1). Because the Rodgers claims, standing alone, fail to mention deuterium, they cannot alone anticipate the '149 Patent claims.

The mention of deuterium in Rodgers column 32, lines 13-17 does not transform the Rodgers claims into anticipatory subject matter. First, combining the claims with one cherry-picked sentence plucked from the vast Rodgers disclosure

is the exactly the type of "mechanistic dissection and recombination" of a prior art reference to create "hindsight anticipations with the guidance of an applicant's disclosures" that the case law prohibits. *See, e.g.*, *In re Ruschig*, 343 F.2d 965, 973-74 (C.C.P.A. 1965) (distinguishing the "very special situation" of *In re Petering* and finding no anticipation where prior art disclosures could be recombined to describe 130 and 156 potential compounds). Second, while column 32 mentions tritium and deuterium, it is not limited to these two isotopes, but rather references "all isotopes of atoms." Ex. 1007, 32:13-17. Thus, to the extent this passage can be combined with Rodgers' claims, it discloses a vast genus of ruxolitinib analogs that contain any isotope of any atom, in any combination. Nothing limits the disclosure to the specific claimed deuterated ruxolitinib analogs of the '149 Patent claims.

More importantly, as Petitioner acknowledges, the '149 Patent claims require "'deuterium at an abundance that is at least 3,000 times greater than the natural abundance of deuterium, which is 0.015% (*i.e.*, at least 45% incorporation of deuterium).'" Petition at 24 (*quoting* the '149 Patent). Accordingly, even if it were proper to combine the claims with the cited excerpt from column 32 to create a purportedly anticipatory genus (which it is not), Petitioner fails to match up this disclosure with the properly-construed '149 Patent claims. Rodgers column 32 is silent about the level of deuterium enrichment, and certainly does not disclose the

level required by the '149 Patent claims. For this reason alone, Ground 2 must be rejected.

Although Petitioner did not cite Rodgers columns 67-68 to support its argument that the deuterated analogs were disclosed in Rodgers, out of an abundance of caution, Patent Owner also analyzes this disclosure.[13] Petition at 49-50. It is not surprising that Petitioner avoided this section. For anticipation purposes, Petitioner attempts to artificially narrow Rodgers' disclosure to create a small genus. Rodgers column 68, however, discloses labeling the trillions of disclosed compounds with one or more of twenty-one example radionuclides. Ex. 1007, 67:65-68:52. It singles out a number of particular radionuclides, but none of them are deuterium. *Id.* at 68:19-29. Nothing in Rodgers shows a preference for

[13] In arguing anticipation of claims 8 and 15 (which relate to pharmaceutical compositions), Petitioner cited these columns of Rodgers as purportedly disclosing pharmaceutical compositions comprising a pharmaceutical carrier, but did not argue that the discussion of radio-labeled compounds in this section of Rodgers purportedly anticipates the claims. Petitioner also cited col. 347, line 21-25, but this citation is nonsensical. Patent Owner cannot discern why Petitioner cited this section, or, assuming it was cited in error, what citation was intended. Accordingly, Patent Owner will not further address this citation.

deuterium, or even indicates that the Rodgers inventors ever made a single radio-labeled compound, let alone a deuterated compound.

There is no legal support for establishing anticipation under such circumstances. To anticipate a later-claimed species, the prior art reference must disclose a pattern of preferences that leads to a genus small enough such that a POSA would at once envisage the claimed species. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377-78 (Fed. Cir. 2006). Here, absolutely no "pattern of preferences" narrows Rodgers' vast disclosure such that a POSAs would immediately envisage a small class containing the '149 claimed compounds. As to steps 1 and 2 above, nothing in the specification suggests that ruxolitinib is preferred, let alone that an isotopically-enriched ruxolitinib analog is preferred. *See id.*; *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1083-84 (Fed. Cir. 2008). As to step 3 above, nothing suggests that POSAs should selectively enrich ruxolitinib with deuterium to the exclusion of the other isotopes and radionuclides.

As to step 4 above, nothing suggests that POSAs should create the specific deuterated ruxolitinib analogs recited in the challenged claims. Ruxolitinib has 18 hydrogens, which can create $2^{18} - 1 = 262{,}143$ different deuterated ruxolitinib analogs. Petitioner first imagines an undisclosed genus of deuterated ruxolitinib analogs, then attempts to artificially narrow that genus by contending that a POSA

would deuterate at only 10 of the 18 hydrogens. Petition at 45-46. For this argument Petitioner relies on Dr. Guengerich's Declaration at ¶ 131 (Petition at 45-46). While that paragraph states "there is simply no reason to deuterate only one hydrogen at a given position," it never explains the reason why this is purportedly true. Accordingly, for this reason alone, Petitioner's argument should be rejected as unsupported. *See* 37 C.F.R. § 42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Neptune Generics, LLC v. Nektar Therapeutics*, IPR2016-00049, Paper 16, at 22 (P.T.A.B. Apr. 27, 2016) (denying institution where, *inter alia*, expert's conclusory statements lacked evidentiary support).

However, out of an abundance of caution, Patent Owner will address paragraph 85 of Dr. Guengerich's Declaration.[14] In paragraph 85, Dr. Guengerich opines that "[i]t would make no scientific sense to deuterate selectively only some of one of the sites of the cyclopentyl ring (i.e., some of Y^2 or some of Y^3) because Shilling explains that metabolism occurs at each of the four secondary methylenes of the cyclopentyl ring." Ex. 1002, ¶ 85. Even if Petitioner had made this argument in connection with Ground 2 (which it did not), it does not establish

[14] Patent Owner objects to petitioner or the Board relying on this paragraph in support of Ground 2, because neither Petitioner nor Dr. Guengerich cited it in connection with Ground 2.

anticipation. Nothing in Rodgers suggests modifying any compound (let alone ruxolitinib) with deuterium in an effort to obtain a compound with improved metabolic or PK properties. Thus a POSA reading Rodgers would have had no reason to look to Shilling for information on ruxolitinib's metabolic "hotspots" in order to determine appropriate deuteration sites. *See In re Arkley*, 455 F.2d 586, 589 (C.C.P.A. 1972) ("We do not read into references things that are not there.").

Petitioner also points to two issues that supposedly militate in favor of a POSA envisioning a small genus that includes the claimed analogs. First, it argues that the choice between hydrogen or deuterium is binary. Petition at 47. Second, it argues that deuterium-substituted analogs are closely related to each other. *Id.* at 49. However, it is not the purported ease with which a POSA could imagine the later-claimed compounds that establishes anticipation, but rather whether the prior art reference contains a pattern of preferences such at a POSA could envisage the members of the genus as readily as if the members had been described in words. *See, e.g.*, *In re Ruschig*, 343 F.2d at 973-74.

Finally, as to step 5 above, even if Petitioner could get to a small enough genus such that a POSA could "at once envisage" each of the individual species, it has done nothing to establish that those species would necessarily have the isotopic enrichment to anticipate the claims, which requires that certain positions are substituted with deuterium at an abundance that is at least 3,000 times greater than

the natural abundance of deuterium. Ex. 1001, 3:65-4:3; Petition at 24. Accordingly, Petitioner has failed to show that Rodgers discloses each and every limitation of claims 1-15 of the '149 Patent, and the Board should therefore deny Ground 2.

IX. CONCLUSION

For all of the foregoing reasons, the Board should decline to institute IPR on any ground.

Respectfully submitted,

Date: July 24, 2017

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this CONCERT PHARMACEUTICALS INC.'S PATENT OWNER PRELIMINARY RESPONSE complies with the word count limitation of 37 C.F.R. § 42.24(a)(l)(i) because the Petition contains 13,951 words, excluding the cover page, signature block, and the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(l).

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on July 24, 2017, copies of the foregoing CONCERT PHARMACEUTICALS INC.'S PATENT OWNER PRELIMINARY RESPONSE and all Patent Owner exhibits cited therein were served via electronic mail, as agreed to by counsel, upon the following counsel of record for the Petitioner:

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