UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Incyte Corporation
Petitioner,
v.

Concert Pharmaceuticals, Inc.
Patent Owner

Inter Partes Review No. IPR2017-01256

Patent No. 9,249,149

PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. INTRODUCTION

Incyte is challenging Concert's '149 Patent, which claims novel deuterated analogs of ruxolitinib, one of which is in clinical trials for the treatment of alopecia areata ("AA"). Incyte's challenges to this patent fail at every turn. Incyte has not established that its key references qualify as printed publications; has failed to establish motivation to deuterate ruxolitinib and rebut the unpredictability of the deuterium isotope effect that is observed *in vitro*; and has ignored the added complexity of predicting how the deuterium effect would translate in humans.

Furthermore, Incyte has failed to rebut Concert's unexpected results. By arguing PK parameters individually, Incyte ignores the clinical significance of the half-life improvement in more rapid metabolizers, and that the PK advantages *taken together* provide an unexpectedly flatter PK curve that is advantageous for treating AA, where there has long been a need for adequate treatment. In short, Incyte fails to demonstrate unpatentability, and its challenge to the '149 Patent should be rejected.

II. CONCERT BACKGROUNDER AND JAKAFI® LABEL ARE NOT PRINTED PUBLICATIONS

Perhaps recognizing its failures of proof in the Petition, Incyte now proffers new theories and evidence on printed publication. Incyte's belated arguments should be ignored. 37 C.F.R. §42.23(b); Trial Practice Guide Update (Aug. 2018)

("TPG Update"), 15 ("'[R]espond,' in the context of §42.23(b), does not mean embark in a new direction with a new approach"); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1370 (Fed. Cir. 2016) (rejecting argument first presented in reply). Even if considered, the new theories fail to establish that two key documents underlying Incyte's grounds of alleged unpatentability are printed publications, necessitating denial of its IPR.

A. Concert Backgrounder Was Not Accessible to POSAs

Abandoning its original argument that the Concert Backgrounder was publically accessible "via the cached WebCite® page" (Petition, 28), Incyte newly argues accessibility based on purported dissemination to alleged POSAs, including to four patent examiners/searchers. (Reply, 24-25.) But Incyte makes no attempt to show that these examiners/searchers meet the educational and experience requirements of a POSA.[1] (*Id*.) Accordingly, these purported disseminations carry no weight.

Incyte also relies on dissemination to Ms. Buteau, a purported POSA. But dissemination to one or even a few POSAs does not suffice to demonstrate public accessibility. *See, e.g.*, *Preemption Devices v. Minn. Min. & Mfg. Co.*, 732 F.2d 903, 906 (Fed. Cir. 1984) (single dissemination insufficient); *Application of Bayer*,

[1] Of the patent materials Incyte now cites, only Ex. 1021 was included in the Petition.

568 F.2d 1357, 1361 (C.C.P.A. 1978) (three disseminations insufficient). Incyte's lack of evidence of actual dissemination is compounded by the lack of indexing or search capabilities on WebCite®.[2] (POR, 41-44; *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1195 (Fed. Cir. 2008) (access by one person, in view of lack of indexing, insufficient); *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989) (thesis presented to handful of faculty and not meaningfully indexed insufficient).)

Incyte's other new argument that the Buteau article is a "research aid" that would guide POSAs to the Concert Backgrounder (Reply, 25-26) also fails. Incyte cites *Cornell*, but there the asserted prior art was cited in a "seminal publication" in the relevant field. *Cornell Univ. v. Hewlett-Packard Co.*, No. 01-cv-1974, 2008 U.S. Dist. LEXIS 39343, at *20 (N.D.N.Y. May 14, 2008). Here, Incyte has made no showing that POSAs—who are defined as scientists—seek out law review articles. That the Buteau article was cited in a 2011 scientific article and in various patent materials is also unavailing. Incyte provides no evidence that POSAs would navigate through the chain of these materials, to the Buteau article, and then to the Concert Backgrounder. Indeed, the "research aid" rationale is insufficient where the link between the purported research aid and the asserted prior art is attenuated.

[2] Incyte has not proven, or even alleged, that Ms. Buteau or the searchers/examiners obtained the Concert Backgrounder from WebCite® or via a search a POSA would conduct.

See, e.g., *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016) (no evidence that POSA "could navigate from [a university] website to Dr. Ratismor's personal page, whether through a direct link or a chain of links, to access the Ratismor Reference").

In view of Incyte's lack of proof of both meaningful dissemination and indexing, Incyte has failed to carry its burden of demonstrating the public accessibility of the Concert Backgrounder, necessitating denial of both grounds of unpatentability.

B. The Board Should Not Rewrite the Grounds

Incyte suggests that even if the Concert Backgrounder does not qualify as a printed publication, the Board should still consider it because it goes only to motivation, and purportedly "is not relied on to teach or suggest any claim element." (Reply, 26-27.) This argument misrepresents the full scope of Incyte's reliance on the Concert Backgrounder, which Incyte additionally used for purportedly teaching the claim limitations directed to deuteration of specific sites on ruxolitinib (Petition, *e.g.*, 32, 52-53), and for teaching an alleged expectation of success (*id.*, 34-35, 54; *see also* ID, 24). Accordingly, even if documents pertaining to motivation need not be printed publications, Incyte has chosen to make the Concert Backgrounder integral to its grounds. IPR can be based only on

patents and printed publications (35 US.C. §311(b)), and Incyte has failed to show that the Concert Backgrounder meets this threshold.

C. Incyte Has Not Proven that Jakafi® Label is a Printed Publication

The Board found that Incyte has not met its burden of proving that Jakafi® Label (Ex. 1004) is a printed publication. (ID, 15.) That decision was correct and should be adopted in the final decision.

As purported evidence of public accessibility, Incyte relies on Dr. Guengerich's observation that ruxolitinib was "a well-established, pharmaceutical drug." (Reply, 28.) As the Board correctly found, this says nothing about whether the Jakafi® Label was publicly accessible, nor provides any personal knowledge regarding dissemination. (ID, 13-14.)

Incyte improperly cites new evidence on reply in an attempt to gap-fill its *prima facie* case. (Reply, 28.) Such "gap-filling" is expressly forbidden. (TPG Update, 15; *Intelligent Bio-Sys.*, 821 F.3d at 1370; *Neste Oil Oyj v. REG Synthetic Fuels, LLC*, IPR2013-00578, Paper 54, 19-20 (P.T.A.B., Mar. 12, 2015).) The Board should reject Incyte's belated arguments and evidence, and confirm that Incyte failed to carry its burden on the Jakafi® Label.[3]

[3] The Board denied Concert authorization to file a motion to strike new arguments and evidence regarding the Jakafi® Label. (Paper 74, 3.)

III. INCYTE HAS FAILED TO CARRY ITS BURDEN OF MOTIVATION TO COMBINE

As explained, ruxolitinib's known dose-limiting toxicities would have affirmatively motivated POSAs to *not* deuterate ruxolitinib due to the risk of increasing the drug's toxicity. (POR, 46-50.) Although Incyte's experts, Drs. Shapiro and Reider, agree that patient safety is paramount (Ex. 2121, 74:21-75:18; Ex. 2118, 21:19-22, 74:10-76:19), they did not addresses the impact of ruxolitinib's known dose-dependent side effects on motivation to combine ruxolitinib with deuteration.

Incyte instead attempts to side-step the negative impact of this toxicity on motivation by suggesting that *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013) holds that dose-dependent side effects do not teach away from modifications that could exacerbate side effects. (Reply, 13.) But *Galderma's* holding was not so broad. There, the claim was directed to the use of a known drug for a known condition, in a concentration that fell within a range taught in the prior art as useful for that condition. *Galderma,* 737 F.3d at 737. The court found that the prior art lacked any suggestion that "the side effects would be serious enough to dissuade the development" of the claimed concentration, and taught the use of this concentration lacked "intolerable irritability." *Id.*, 737, 739.

Galderma is readily distinguishable. Concert is not claiming a known drug in a known concentration, and the prior art here clearly describes serious side

effects, including hematological adverse events requiring dose adjustments and discontinuations. (POR, 10-11.) As Concert's experts explained, POSAs would have been affirmatively motivated to *not* deuterate the drug due to ruxolitinib's dose-dependent side effects. (*Id.*; Ex. 2057, ¶41; Ex. 2048, ¶27.)

Incyte simplistically argues that POSAs would not be concerned with side effects, because they could lower the dose. (Reply, 13-14.) This attorney argument ignores the impact a lower dose would have on efficacy. Incyte offers no expert analysis of whether POSAs, in lowering the dose of deuterated ruxolitinib, would have expected to achieve a suitable balance of efficacy and side effects.

Incyte has not carried its burden on motivation to combine—an independent reason why its patentability challenges fail.

IV. INCYTE HAS NOT ESTABLISHED A REASONABLE EXPECTATION OF IMPROVED METABOLIC STABILITY

As Concert has demonstrated, the effects of deuteration are unpredictable both in terms of whether POSAs would expect a KIE and whether the KIE, if any, would lead to a beneficial metabolic profile. (POR, *e.g.*, 15-16.) Incyte fails to demonstrate a reasonable expectation that deuteration of ruxolitinib would provide an observable KIE *in vitro* or an improved PK profile *in vivo*.

A. Neither a KIE Nor Its Magnitude Can Be Predicted

Although Incyte alleges that a KIE is predictable based on Dr. Reider's analysis of "184 unique deuterated compounds" (Reply, 17), his analysis is flawed in several respects.

First, to assess the frequency with which KIEs are observed, Dr. Reider analyzed only literature of record, not the prior art as a whole. (Ex. 2118, 92:8-11; *see also Impax Labs. Inc., v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018) (obviousness must be based on prior art as a whole).) Second, Incyte's expert, Dr. Guengerich, admitted that failures to achieve a KIE are underreported. (Ex. 2047, 172:1-15.) As a result, the literature is necessarily skewed towards reporting a higher-than-actual frequency of KIEs. Therefore, Dr. Reider's conclusions drawn from a limited and biased sample set do not reflect the state of the art.[4]

Furthermore, Dr. Reider did not consider whether any reported KIE was *in vitro* or *in vivo*, nor the extent to which the existence of an *in vitro* KIE was predictive of an *in vivo* KIE. (Ex. 2118, 108:13-17.) The majority of the KIEs he

[4] Additionally, Dr. Reider admitted that the total number of unique compounds in his table is less than 184, and that some the compounds he listed as showing a KIE did not, in fact, have data supporting that characterization. (Ex. 2118, 98:9-25; 100:13-17; 109:17-20.)

reported are based on *in vitro* data alone, without any showing that the effect translated to an *in vivo* setting. (*Id.*, 108:18-23.)

To support its argument that the deuterium effect is predictable, Incyte over-simplifies mechanistic pathways that are known to be much more complex, even in *in vitro* systems. For example, Incyte mischaracterizes KIEs as a binary phenomenon (KIE or no KIE). (Reply, 18-20.) In reality, there are many possible outcomes of deuteration. There may or may not be a KIE and, if there is, its magnitude and direction (*i.e.*, whether it accelerates or slows metabolism) cannot be predicted *a priori*. (POR, 15-16.) Regarding the magnitude of the KIE (to the extent one is observed at all), Incyte asserts that a KIE of "1-10 can be predicted." (Reply, 18.) But a KIE of "1" is in fact no KIE at all. (Ex. 2118, 108:3-4.) Incyte's range thus does not support any predictability regarding whether there is a KIE nor the magnitude of the KIE, and ignores the possibility of an inverse KIE.

Faced with Dr. Ortiz de Montellano's testimony refuting the mechanistic views offered by Dr. Guengerich, Incyte attempts to dismiss the details of the pathways underlying the KIE as "academic." (Reply, 18.) Incyte argues that the biological basis for KIE does not matter because, according to Incyte, in every scenario described by Concert's and Incyte's experts, deuteration is expected to inhibit metabolism. (*Id.*) Not so. While Incyte seizes on Dr. Ortiz de Montellano's testimony that an apparent KIE may be expected when there is

"shunting" to a branched pathway preceding the C-H bond breaking step (*id.*, 19), it ignores that Dr. Ortiz de Montellano made clear that whether such shunting occurs, and therefore whether an apparent KIE is observed, is entirely unpredictable.[5]

Incyte similarly attempts to dismiss metabolic switching as a source of unpredictability by downplaying the importance of the variability and unpredictability of KIE magnitude. Incyte concedes that switching can impact the KIE, but argues that when switching occurs, "some effect" would still be expected. (Reply, 20.) This casual dismissal ignores the tremendous variability in the magnitude of any effect deuteration may have on metabolism, and the lack of predictability in that magnitude.

Incyte's attempt to dismiss the unpredictability exemplified by deuterated iloperidone and maraviroc—which both demonstrated *accelerated* metabolism—falls flat. (*Id.*, 20-21.) Regardless of whether iloperidone and maraviroc were deuterated at the most significant metabolic hotspot, a shortening of half-life

[5] Incyte's argument that Dr. Ortiz de Montellano admitted that masking is inapplicable to ruxolitinib (Reply, 22) is a mischaracterization. He did not testify that masking factors are inapplicable to ruxolitinib, but rather that they are not specific to ruxolitinib, and are applicable to any compound. (*See, e.g.*, Ex. 1088, 26:4-10, 30:1-8.)

following deuteration at any position of a molecule exemplifies that deuteration does not necessarily produce the results that Incyte claims are expected.[6]

Incyte's discussion of *in vivo* KIEs is equally flawed. (Reply, 22-23.) For atazanavir, Incyte points to one analogue that exhibited a positive KIE, but ignores another analogue that exhibited the opposite effect, highlighting the unpredictability of deuteration. For tramadol, Incyte fails to credibly explain why the masking seen there is inapplicable to ruxolitinib. (*Id.*, 22.) For tolbutamide, authors of the human study reported two different values for the isotope effect (1.03 and 1.19), contrasting them to larger effects seen with other compounds. (Ex. 2068, 2-3.) For nerispiridine, Incyte dismisses the lack of *in vivo* translation by arguing that N-dealkylation is not predictive of aliphatic oxidation. However, Incyte provides no explanation for why the *in vitro* KIE that was observed for nerispiridine did not translate *in vivo*. (Reply, 23.)

B. Incyte Has Not Demonstrated a Reasonable Expectation of Success of a Safe and Effective *In Vivo* Profile

Incyte incorrectly argues that it need not demonstrate a reasonable expectation of success in making a compound with beneficial *in vivo* properties

[6] Concert also disputes that accelerated metabolism resulting from deuteration, a phenomenon Incyte concedes is observed at least 9% of the time, is "exceedingly rare." (Reply, 20.)

because the claims are directed to compounds, without any recited properties. (Reply, 15.) A compound and its properties are inseparable for purposes of §103. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination."); *Application of Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."). It is therefore no answer for Incyte to argue that the *in vivo* PK profiles are unclaimed; these properties are inseparable from the compound itself.

Furthermore, to demonstrate a reasonable expectation of success for a compound, a challenger must show that the combination would have worked for its intended purpose. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009); *see also Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1360 (Fed. Cir. 2007) (finding "nothing in the prior art [provided] a reasonable expectation that adding a methyl group to [the lead compound] would reduce or eliminate its toxicity"). As such, Incyte's burden goes beyond demonstrating POSAs *could* deuterate ruxolitinib—it includes showing that the resulting compound would be expected to work for its intended purpose as a safe and efficacious drug.

As Concert demonstrated, not only would a POSA have been affirmatively motivated *not* to deuterate ruxolitinib for fear of exacerbating known toxicities, but the results of deuteration on the *in vivo* properties would have been impossible to predict. (POR, 20-21.) In Reply, Incyte is silent on whether POSAs would have expected deuterated ruxolitinib to have acceptable toxicity, PK profile, and efficacy across patients—critical attributes of a safe and effective drug. Incyte's failure to carry its burden requires denial of its challenges.

V. CTP-543'S PHARMACOKINETIC PROFILE LEADS TO UNEXPECTED POTENTIAL BENEFITS

CTP-543 demonstrated clinical superiority to ruxolitinib in two ways that show the potential for the octa-deuterated drug to provide meaningful clinical benefits: it enables faster metabolizers to benefit from a comparable dose of CTP-543, and its flatter PK curve permits CTP-543 to be within the therapeutic window for AA for a longer time than an equally-effective dose of ruxolitinib. (POR, 34-37.) Contrary to Incyte's arguments, these clinical results with CTP-543 in a head-to-head comparison with ruxolitinib are both unexpected and clinically meaningful.

A. Greater Relative Increase in Half-Life for Faster Metabolizers

Incyte does not disagree with Concert that a greater relative increase in half-life for faster metabolizers of ruxolitinib would be clinically beneficial. Rather, it argues that the benefit is not unexpected. (Reply, 10-12.) However, Incyte's

position is not only based on mischaracterizations of testimony from Concert declarants, but its own expert, Dr. Thisted, supports Concert's position.

1. Concert's Declarants Confirmed Unexpectedness

Concert's declarants testified that they had not previously seen this half-life effect for drugs metabolized by CYP3A4. (Ex. 2001, ¶15; Ex. 1089, 70:4-13.) Ignoring the specificity of these statements, Incyte seized on one instance in Concert's brief that phrased this phenomenon with regard to P450 enzymes more generally (POR, 37), when Concert's declarants specifically limited their statements to CYP3A4-metabolized drugs. (Ex. 2001, ¶15; Ex. 2002, ¶53; *see also* POR, 69-70 (explaining that phenomenon had not been observed for CYP3A4 substrates).) Accordingly, Incyte's reliance on Austedo™ (deuterotetrabenazine) and venlafaxine is misplaced, because both drugs are metabolized by CYP2D6. (Ex. 1089, 70:4-71:15; Ex. 1132, 1; Ex. 1008-p.57.) CYP2D6 exhibits genetic polymorphism (Ex. 1008-p.56), such that a differential effect on poor metabolizers versus rapid metabolizers is not unexpected. CYP3A4 does not exhibit genetic polymorphism. (Ex. 2061, 63-64.) Therefore, CTP-543 cannot be compared to drugs metabolized by CYP2D6.

With regard to deuterated atazanavir, Dr. Thisted confirmed that, unlike with CTP-543, the slope he visually observed is not statistically significant (Ex. 2120,

47:3-48:5, 53:12-18; 57:15-58:14), meaning that it is not reliable evidence that atazanavir exhibits the same effect as ruxolitinib.

As Concert's declarants testified, the phenomenon seen with CTP-543 has not been reported for a CYP3A4-metabolized drug, and is unexpected.

2. Dr. Thisted's Testimony Confirms that Concert's Finding Was Unexpected

Where there is an observed KIE, the expectation is that there would be the same relative (percentage) increase in half-life for all metabolizers. (Ex. 2057, ¶51.) For example, if deuteration slows overall metabolism such that normal metabolizers experience a 5% longer half-life, POSAs would have no reason to expect that an increase in half-life in more rapid metabolizers would be statistically longer than 5%. (*Id.*) However, Concert unexpectedly found that CTP-543 provides a greater relative (percentage) increase in half-life for more rapid ruxolitinib metabolizers. (*Id.*)

Dr. Thisted did not disagree with Concert's calculations. (Ex. 2120, 36:18-37:2.) Instead, he proposed that the findings can be explained with an alternate mathematical model, showing that the subjects in the study "actually experienced $t_{1/2}$ values consistent with the same average ***absolute*** increase in $t_{1/2}$ with CTP-543." (Ex. 1129, ¶12 (emphasis added).) But his mathematical model is just that—a mathematical calculation with no biological basis. (Ex. 2120, 19:18-20:18.) Regardless of the mathematical model, the showing is still unexpected. The

important point is that by having the same absolute increase, those who metabolize ruxolitinib more rapidly have a greater relative benefit in half-life. Therefore, Dr. Thisted's testimony *supports* the unexpected nature of Concert's finding.

In any event, Dr. Thisted, a biostatistician, is not a POSA under either party's definition. (Ex. 2120, 9:9-11:2.) Tellingly, Incyte did not provide his analysis to its other experts to evaluate its impact on Concert's unexpected results. (*Id.*, 8:5-20.) In contrast, all of Concert's experts evaluated whether the $t_{1/2}$ effect was important and unexpected, and concluded that it is. Dr. Thisted's testimony, which is all that Incyte offers, does not suffice to rebut these experts concerning the only pertinent question here, *i.e.*, what would be unexpected to POSAs.

B. The Prior Art Did Not Predict CTP-543's PK Profile

Incyte incorrectly asserts that the prior art predicted the PK profile Concert observed for CTP-543 in its cross-over study. Incyte's first contention is that increased AUC and half-life are the "*expected* result of inhibiting P450 metabolism." (Reply, 5.) But Incyte puts the cart before the horse because it assumes that deuteration will inhibit P450 metabolism *in vivo*. This assumption is incorrect—the impact of deuteration, if any, is unpredictable. (POR, 19-20.)

Even if one were to assume *in vivo* inhibition of metabolism leading to an observed KIE, Incyte fails to show why CTP-543's particularly advantageous PK profile would be the result. Incyte focuses on differences in the individual PK

parameters, such as AUC and $t_{1/2}$, missing the larger point that *taken together* the changes in the PK parameters provide a more favorable profile. Its arguments on individual PK parameters miss the more relevant finding that half-life and AUC increase relative to C_{max}, thereby providing a flatter PK curve better suited for the AA therapeutic window. (POR, 34-35.)

Incyte next characterizes the schematics in the Concert Backgrounder as showing only two possible PK outcomes, both of which Incyte incorrectly argues are expected.[7] Incyte's argument that POSAs would be picking from only two possible results ("heads or tails") is greatly misleading. There is no reason to believe that the schematics are anything but illustrative, and certainly not limiting or equally likely occur. (POR, 68-69; Ex. 2047, 180:15-181:6.) Many PK profiles are possible, and POSAs cannot predict which will occur. There is nothing in the Concert Backgrounder pointing to any particular profile that would apply to deuterated ruxolitinib. Indeed, Incyte's Petition is silent regarding ruxolitinib's expected PK profile following deuteration. It is only after Concert disclosed CTP-543's profile that Incyte first argued (incorrectly) that the profile was expected. This is the epitome of hindsight.

Incyte further argues that POSAs would have expected the panel (A) profile based on (1) published metabolic properties of ruxolitinib when its P450-mediated

[7] For clarity, the Concert Backgrounder is relied upon by Incyte, not Concert.

clearance was reduced by a metabolic inhibitor; and (2) the alleged lack of first pass metabolism of ruxolitinib. (Reply, 7.) These assertions are unsupported. First, Incyte has not provided any evidence that a metabolic inhibitor would predict the effects of deuteration. In any event, the metabolic inhibitor ketoconazole significantly *increased* ruxolitinib's C_{max} (Ex. 1071, 4-5), which panel (A) does not show. Further, Incyte mischaracterizes Dr. Ortiz de Montellano's testimony as suggesting that Shilling rules out first pass metabolism, when in fact he testified that Shilling provides insufficient information to distinguish between parent drug in systemic circulation (not subject to first pass metabolism) and metabolites (resulting from first pass metabolism). (Ex. 1005, 1; Ex. 1088, 33:14-36:11.) Incyte's other reference, Shi, provides no definitive statement regarding first-pass metabolism. (Ex. 2012, 1.)

Incyte's additional unsupported assertions about the purported known effects of deuteration on P450 metabolism fare no better. For example, Incyte suggests that the PK profiles of deuterated ivacaftor and venlafaxine are somehow indicative of what profile would have been expected for deuterated ruxolitinib.[8]

[8] The Board previously denied institution of an IPR directed to deuterated venlafaxine, because the prior art supported the unpredictability of deuteration on the pharmacology and toxicity of the drug. *Neptune Generics, LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25, 19-20 (P.T.A.B. Dec. 9, 2015).

(Reply, 6.) This contention is not supported by citation to any literature or expert opinion. Further, unlike CTP-543, deuteration of venlafaxine led to a doubling of C_{max}. (Ex. 1008-p.57-58.) As for deuterated ivacaftor, the poster Incyte cites actually discloses that different deuterated ivacaftor analogues provided different PK results depending on the animal species. Not only has Incyte failed to demonstrate that this poster qualifies as prior art, but the poster itself questions which of the animal models are predictive of human PK results. (Ex. 1029.)

Incyte also appears to question whether CTP-543 would have lower C_{max} side effects than ruxolitinib, given that CTP-543's C_{max} was numerically greater than that of ruxolitinib. (Reply, 10.) Incyte attempts to dismiss the fact that there was no statistically significant change in C_{max} between ruxolitinib and CTP-543.[9]

[9] Incyte fails to explain why "nothing can be inferred here from the absence of statistical significance." (Reply, 10.) To the extent Incyte seeks to incorporate arguments by reference to Dr. Thisted's declaration, such attempt should be refused. *See* 37 C.F.R. §42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."); *Electronic Arts Inc. v. Terminal Reality, Inc.*, IPR2016-00928, Paper 48, 36-37 (P.TA.B. Oct. 23, 2017). Moreover, unlike Incyte, Concert does not rely *only* upon a statistical analysis. Dr. Ortiz de Montellano explained why this statistical result is important. (Ex. 2057, ¶¶51-53.)

(*Id*.) But Dr. Thisted does not dispute the statistical analysis—that there was no statistically significant change in C_{max}—and that is all he is qualified to analyze.

C. Unexpected PK Profile in Relation to "Therapeutic Window"

From the cross-over study data, Concert calculated that, for AA, a dose of 27 mg ruxolitinib would be needed to have efficacy that is comparable to a 16 mg dose of CTP-543. (POR, 34.) Contrary to Incyte's allegation, this comparison is neither artificial nor exaggerated. When efficacy and safety are considered together (as shown by reference to the therapeutic window), the difference between CTP-543 and ruxolitinib is significant.[10] As explained, these very different doses are required for the two drugs to maintain exposure levels for the same length of time over the IC_{50} for IFN-γ, a cytokine implicated in AA. (*Id*.) Incyte does not

[10] While Dr. Shapiro did not consider CTP-543's PK profile as a whole, he did acknowledge that safety and efficacy must be considered together (Ex. 2121, 74:21-75:8), and that given equal efficacy, he would choose the safer drug (*id.*, 76:4-10).

dispute that the two different doses would provide exposure levels above the IC_{50} for IFN-γ for the same length of time.[11]

Also significant is the increased time CTP-543 spends within the therapeutic window. In the cross-over study, following a single dose of each drug, CTP-543 levels were within the therapeutic window 2.2 hours longer on average than ruxolitinib levels. Incyte argues that the 2.2 hour average difference is clinically irrelevant given that both drugs are to be dosed twice daily,[12] which it argues would diminish CTP-543's benefit in that the PK profile of ruxolitinib would be just as suitable with respect to the therapeutic window. (Reply, 9.) Incyte, however, offers little credible evidence for this argument. Incyte relies on Ex. 1072 (Shi) to support its contention that 15 mg ruxolitinib BID had a steady state C_{min} above 50 nM and a steady state C_{max} of 649 nM, which is within the

[11] Incyte's complaint that Concert had earlier compared 16 mg CTP-543 to 20 mg ruxolitinib (Reply, 8) is irrelevant. Concert never claimed that 16 and 20 mg doses were comparable with respect to time over IFN-γ IC_{50}.

[12] To be clear, there is no requirement that CTP-543 must be administered twice daily, except in the current Phase 2a clinical trial. Further study may reveal the possibility of reduced dose frequency in light of CTP-543's more favorable pharmacokinetics.

therapeutic window (Reply, 9-10), but Incyte's portrayal of the Shi data is misleading. The mean C_{max} reported by Shi is close to the upper limit of the therapeutic window. If there is a normal distribution, half of the population would have a C_{max} above that mean value. Furthermore, the Shi study did not include CTP-543. Comparing data across two separate studies with two different drugs is not nearly as reliable as the head-to-head, direct comparison performed by Concert in its cross-over clinical trial. (*See, e.g.*, Ex. 1095, 73:24-74:6.)

VI. CTP-543 SATISFIES A LONG-FELT NEED

Incyte asserts that there is no long-felt need for an FDA-approved AA treatment because the "full technical solution of using JAK inhibitors to treat AA" was purportedly taught before the priority date.[13] (Reply, 3-4.) Incyte's Dr. Shapiro based this opinion on Ex. 1014, a patent application that published just one month before the priority date. (Ex. 1117, ¶18.) However, contradicting ¶25 of his declaration, Dr. Shapiro now concedes that this patent application contains no clinical data demonstrating the use of ruxolitinib in AA.[14] (Ex. 2121, 89:17-90:22, 95:15-96:1; Ex. 1014, [0288].) Indeed, he confirmed that the first reports of JAK inhibitor use in AA patients occurred in 2014—well *after* the 2012 priority date.

[13] Incyte's argument lacks clarity, because it fails to cite any legal authority for its "full technical solution" framework.

[14] Dr. Shapiro also did not cite any data from any other *in vivo* or *in vitro* testing.

(Ex. 2121, 77:15-79:13, 82:7-83:2.) Although a commercial solution is not necessary (Reply, 4), Incyte fails to adequately link the prophetic pronouncements in Ex. 1014 with its contention that the "full technical solution" of using JAK inhibitors to treat AA—or of a JAK inhibitor with a safety profile sufficient to achieve FDA approval for AA—was available as of the priority date. Indeed, Dr. Shapiro's own December 2013 article titled "Current Treatment of Alopecia Areata" nowhere mentions JAK inhibitors as a current treatment, belying their use for AA in 2012. (Ex. 2102, 1-2; Ex. 2121, 84:10-12, 85:14-25.)

There remains a long-felt need for an FDA-approved treatment for AA.[15] None of the three approved JAK inhibitors—ruxolitinib, tofacitinib, and baricitinib—are indicated for AA. (Ex. 2006; 2106; 2110.) And both tofacitinib and baricitinib carry black-box warnings (Ex. 2106, 1; Ex. 2110, 1), which may limit their use in AA. (*See, e.g.*, Ex. 2048, ¶37 (noting that serious side effects are of concern in treatment of a chronic, non-fatal condition like AA).)

Incyte's bare allegation that Concert's reliance "on JAK inhibitor side-effect profile[s] in cancer patients is inapplicable to AA patients" (Reply, 4-5) should be

[15] Contrary to Incyte's contention (Reply, 3), Concert never asserted that CTP-543 is currently FDA-approved. As Concert noted, the FDA has granted CTP-543 a "Fast Track" designation, in recognition of its potential to fill the unmet medical need. (POR, 38-39.)

rejected under Rule 42.6(a)(3). *Supra* n.9. In any event, its allegation is refuted by its own expert. Although Dr. Shapiro asserts here that the side-effect profile in cancer patients is irrelevant to AA patients (Ex. 1117, ¶¶31-32, 36), his own AA-related article discusses side effects seen in myelofibrosis patients. (Ex. 1122, 8 (citing Ex. 2053).) He also failed to disclose that AA patients are more likely than healthy people to have anemia.[16] (Ex. 2097 at 3, Table 2; Ex. 2098 at 2, Table 1.) Moreover, the prior art reported that even healthy subjects and patients with other autoimmune diseases—populations that Dr. Shapiro contends are more relevant than myelofibrosis patients—experienced hematological adverse events when administered JAK inhibitors. (Ex. 2105, 7-11 (neutropenia and thrombocytopenia); Ex. 2012, 6 (dose-dependent neutropenia in short-term study); Ex. 2106, 8, 16, 18; Ex. 2121, 132:17-133:18, 134:8-135:7.) While Incyte tries to downplay these side effects, as both Dr. MacKay-Wiggan and Dr. Reider stated, drug toxicity is less tolerable in AA than in cancer indications (Ex. 2048, ¶37; Ex. 2118, 27:11-17), and thus they would be of concern to POSAs.

[16] Dr. Shapiro was not even familiar with rates of anemia in AA patients, which is not surprising because he does not check his patients for co-morbidities such as anemia. (Ex. 2121, 47:19-48:7.)

VII. CONCERT'S EVIDENCE OF SECONDARY INDICIA IS COMMENSURATE IN SCOPE

Incyte expressly limited its patentability arguments to the three compounds recited in claim 7—one "octa-deuterated ruxolitinib" derivative, and two "tetra-deuterated ruxolitinib" derivatives. (Petition, 8.) In response, Concert focused its POR on those same three compounds. (POR, 39.)

With regard to the tetra-deuterated derivatives (including those in claims 3, 4, 11, and 12), Concert demonstrated that Incyte's own unpatentability arguments make no sense as applied to these compounds. (POR, n.12.) In its Reply, Incyte did not even attempt to rebut this showing.

With respect to octa-deuterated ruxolitinib, Concert demonstrated unexpected results for CTP-543, an octa-deuterated compound. Where there is "adequate basis to support the conclusion that other embodiments . . . will behave in the same manner," evidence of unexpected results is generally considered commensurate in scope with the claims. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011); *In re Cescon*, 474 F.2d 1331, 1334 (C.C.P.A. 1973) (concluding that evidence of correlation with result is sufficient to establish unexpected results even though limited embodiments tested). Here, Incyte concedes that POSAs would have known how degree of deuterium enrichment influences metabolic properties (Reply, 18), and therefore would have known the correlation between degree of isotopic enrichment and unexpected

results. Because the only variation between the proffered evidence and the octa-deuterated compound at issue is the level of deuterium enrichment, a POSA would understand the scope of the unexpected results to be commensurate with the claims. Incyte's failure to offer any experimental evidence that any embodiments falling within the claims would not demonstrate unexpected results further supports this conclusion. *Cephalon Inc. v. Mylan Pharms. Inc*., 962 F.Supp.2d 688, 719-20 (D. Del. 2013).

VIII. CONCLUSION

For the foregoing reasons, Incyte has failed to carry its burden of proving unpatentability, and the Board should therefore refuse to cancel the claims.

Dated: November 2, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42

Pursuant to 37 C.F.R. §42.24(d), I hereby certify that this PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE complies with the word count limitation specified in the Board's Sept. 27, 2018 Order (Paper 74), because this sur-reply contains 5,577 words, excluding the cover page and parts of the document exempted by 37 C.F.R. §42.24(c).

Respectfully submitted,

Date: November 2, 2018 By: /*Cynthia Lambert Hardman*/

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CERTIFICATE OF SERVICE

I hereby certify that I caused the foregoing document captioned "PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE" to be served electronically via e-mail on this 2nd day of November, 2018, as follows:

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