No. 19-2011

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CONCERT PHARMACEUTICALS, INC.,

Appellant,

v.

INCYTE CORPORATION,

Appellee,

KATHERINE K. VIDAL, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

Intervenor.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, No. IPR2017-01256

REPLY BRIEF OF APPELLANT CONCERT PHARMACEUTICALS, INC.

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GLOSSARY

'149 Patent	U.S. Patent No. 9,249,149 [Appx1425-1446, Exhibit 1001 below]
AA	alopecia areata
ADME	absorption, distribution, metabolism, and excretion
Board	Patent Trial and Appeal Board
C_{max}	maximum plasma concentration
Concert	Appellant Concert Pharmaceuticals, Inc.
Concert Backgrounder	Concert Pharmaceuticals, Inc., PRECISION DEUTERIUM CHEMISTRY BACKGROUNDER [Appx1738-1743, Exhibit 1006 below]
CTP-543	Concert's novel deuterated version of ruxolitinib
IFN-γ	interferon gamma
Incyte	Appellee Incyte Corporation
IPR	*inter partes* review
JAK1	Janus Kinase 1
JAK2	Janus Kinase 2
KIE	kinetic isotope effect
PGR	post-grant review
PTAB	Patent Trial and Appeal Board
Shilling	Adam D. Shilling et al., *Metabolism, Excretion, and Pharmacokinetics of [^{14}C]INCB018424, a Selective Janus Tyrosine Kinase 1/2 Inhibitor, in Humans*, 38 DRUG METABOLISM & DISPOSITION 2023 (2010) [Appx1729-1737, Exhibit 1005 below]

INTRODUCTION

Incyte's brief makes clear that there is no disagreement on the basic *facts* about what skilled artisans would have understood on the priority date: they would have expected deuteration not to affect ruxolitinib's selectivity and potency, but would have anticipated, at most, a "potential" improvement in pharmacokinetic properties. The parties part ways over the *legal significance* of that factual backdrop. The Board thought these undisputed facts were enough to find motivation and a reasonable expectation of success. But the Board's legal analysis was flawed. Incyte fails to rehabilitate that analysis on its merits, and cannot shield the Board's decision from review by insisting that this appeal is really about the way in which the PTAB weighed conflicting evidence. The Board's legal errors require reversal.

On the question of motivation, Incyte repeatedly stresses (*e.g.*, Br. 36-39) that ruxolitinib and the claimed deuterated compounds have very similar structures—and that, as a result, a skilled artisan would have expected them to have similar selectivity and potency. But that sidesteps the key issue: whether a skilled artisan would have expected the claimed compounds' *pharmacokinetic properties* to be more advantageous than those of ruxolitinib. Because *those* properties supplied the motivation to deuterate that Incyte asserted and the Board recognized, the Board erred in failing to train its attention on them. Incyte does not meaningfully respond to this legal point. Instead, it just keeps emphasizing expectations about the claimed compounds' other

properties—but neither Incyte nor the Board has suggested that those other properties would motivate anyone to deuterate.

Incyte attempts to bolster its assertions by downplaying the unpredictable nature of deuteration, but its arguments just exchange one legal error for another. The Court "must . . . consider[]" each prior-art reference "in its entirety, i.e., as a *whole*." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). Incyte flouts this principle, plucking scattered statements from each reference on which it relies and ignoring warnings about the unpredictability of deuteration in *the very same references*. Incyte's treatment of the Concert Backgrounder—the centerpiece of its obviousness case—exemplifies this sleight of hand. Incyte argues (*e.g.*, Br. 28) that the Backgrounder would have led a skilled artisan to believe that deuterating ruxolitinib's so-called "hot spots" would reliably improve the drug's ADME properties. But the Backgrounder makes clear that deuteration merely has the "potential" to do so, and that the "magnitude and nature of the deuterium benefit cannot be predicted *a priori*." Appx1740. Indeed, the Board recently found, in rejecting a nearly identical challenge from Incyte to a related Concert patent, that "deuteration of compounds was not predictable." *Incyte Corp. v. Concert Pharms., Inc.*, No. PGR2021-00006, 2022 WL 11703590, at *4 (Oct. 11, 2022) (Paper 70, at 8). Incyte selectively disregards the prior art's teachings about that unpredictability.

Incyte's discussion of reasonable expectations is equally flawed. This Court's structural-obviousness decisions make clear that an examination of a claimed compound's functional properties is an important part of the reasonable-expectation analysis. Because a skilled chemist will often be able to combine different molecular building blocks to arrive at a wide variety of structurally similar compounds, it is a particular claimed compound's *properties* that separates the nonobvious from the predictable. For this reason, Incyte is wrong to insist that the Board did not need to consider the claimed deuterated compounds' pharmacokinetic properties at the reasonable-expectation stage because the '149 Patent claims only the compounds themselves. That misunderstands "success" in compound cases—and effectively neuters the reasonable-expectation inquiry in that context.

Incyte also fails to resuscitate the Board's analysis of objective indicia of nonobviousness. Here, too, the Board committed fatal legal errors, improperly disregarding unexpected properties that allow Concert's invention to satisfy a long-unmet need for a viable AA treatment. Incyte attempts to sweep aside these errors by misstating the law and distorting the record. At bottom, however, the objective indicia confirm what an analysis of Incyte's prima facie case already makes clear: a skilled artisan would not have found Concert's novel deuterated compounds to be obvious. The Court should reverse the Board's erroneous decision.

ARGUMENT

I. The PTAB's structural-obviousness analysis rested on three legal errors.

A. The PTAB's motivation inquiry ignored uncertainty about the effect of deuteration on the very properties that allegedly supplied the motivation to deuterate.

Both the PTAB and Incyte acknowledge that the reason a skilled artisan would consider deuterating a drug substance is to try to improve its *pharmacokinetic properties*. Appx23-24; Incyte Br. 39. So the Board erred in failing to base its motivation inquiry on *those properties*. Incyte cannot explain away that error.

1. Incyte's repeated arguments about two isolated properties—"selectivity and potency"—just reproduce the Board's error.

Incyte attempts to support the Board's motivation analysis by reiterating (Br. 2, 16, 29, 36-39, 50, 54) that a skilled artisan would have known the claimed compounds would have similar "selectivity and potency" to ruxolitinib. As Concert has explained, however, that observation sidesteps the relevant legal question. A belief that a modified compound would have similar properties *in general* to the lead compound is not enough to motivate a skilled artisan to undertake the claimed modifications. *See* Concert Br. 30-40 (citing *Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368 (Fed. Cir. 2006); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009)). Instead, the prior art must have taught something about the

claimed modifications' effect on the properties of interest—that is, the desired properties that *actually would have spurred the claimed modifications*. *See id.* Incyte does not confront, much less dispute, this basic legal principle.[1]

Here, that principle means that Incyte's—and the Board's—exclusive focus on selectivity and potency is misplaced. Selectivity and potency are two properties that describe how a *drug* affects the *body*. Concert Br. 6; Incyte Br. 5-6. But the Board found that a skilled artisan's motivation to deuterate comes from a desire to improve properties that govern how the *body* affects a *drug—i.e.*, the drug's pharmacokinetic properties. Appx5; Appx23-25; Appx31-32; *see* Incyte Br. 39; *see also* Concert Br. 6 (describing the difference between selectivity and potency on the one hand and pharmacokinetic properties on the other). So it is deuteration's effect on these properties of interest that should have grounded the Board's analysis of motivation (and reasonable expectation of success, *see infra*, pp. 18-22).

Focusing on the properties relevant to motivation is not only legally correct—it makes good sense, too. Motivation to modify one set of properties obviously cannot be established by pointing to expectations that a different set of properties would

[1] Incyte argues (Br. 41-42, 49-50) that *Sanofi-Synthelabo* and *Procter & Gamble* are factually distinguishable from this case, but Incyte does not challenge the legal rule that those decisions announced and applied—namely, that a skilled artisan would focus on the properties that actually motivated the chemical modification, not just the general properties of the claimed compound.

remain unchanged. If a claimed modification of a television's design is aimed at improving the device's *video* quality, the modification is not obvious merely because a skilled artisan would have expected the change *not* to affect its *audio* output. If a claimed modification of a car's design is aimed at improving the vehicle's *crash-worthiness*, the modification is not obvious merely because a skilled artisan would have expected the change *not* to affect its *fuel efficiency*. So, too, here: if the reason to deuterate a drug is to improve its pharmacokinetics (as, indeed, it is), the modification is not obvious merely because a skilled artisan would have expected the change not to affect its non-pharmacokinetic properties. Yet that is exactly the flawed syllogism the Board employed. *See* Concert Br. 40-42.

2. The Board's finding that deuteration had the "potential" to improve pharmacokinetic properties is not enough to show motivation.

As a fallback, Incyte argues that the PTAB "*did* consider the effects of deuteration on pharmacokinetic properties" because it "found that skilled artisans would have been motivated to deuterate ruxolitinib 'to achieve the *potential* benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability, and efficacy.'" Incyte Br. 39 (quoting Appx23-24) (emphasis altered); *see also id.* at 44 (similar). But that finding—even if true—does not satisfy the applicable legal standard.

The question is not whether there was a mere "potential" of improving pharmacokinetic properties, but whether those pharmacokinetic properties could actually "be anticipated based on [the deuterated compounds'] structure." *Procter & Gamble*, 566 F.3d at 996; *see also* Concert Br. 37-40; *cf. OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) ("[R]eferences [that] provide no more than hope . . . are not enough to create a reasonable expectation of success in a highly unpredictable art such as this."). Incyte never made *that* showing—and the Board never required it to. Thus, Incyte's fallback argument fails as a matter of law; it, too, fails to establish that the Board considered the right legal question.

3. Incyte fails to show that a skilled artisan would have expected deuteration to improve ruxolitinib's ADME properties.

a. The Board's failure to apply the right legal standard is consequential, because it led the Board to the wrong conclusion in this case. Incyte attempts to prop up the Board's conclusion by claiming (*e.g.*, Br. 43-50) that deuteration's effect on a drug's pharmacokinetic properties is entirely predictable—and, in this case, predictably beneficial. But Incyte's arguments are fundamentally flawed. As Concert has explained, a drug's ADME properties—*i.e.*, the concentrations achieved in the body over time—determine whether the drug will be safe and effective, ineffective, or even toxic. *See, e.g.*, Concert Br. 6. And a skilled artisan could not have predicted on the priority date whether deuteration would have an effect on a given drug's

ADME properties—much less whether that effect would be clinically beneficial. *See* Concert Br. 7-14. Incyte is unable to counter that unpredictability.

First, Incyte selectively quotes the references on which it relies, even though the law requires it to analyze each reference "as a *whole*." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). Incyte does this most notably with the Concert Backgrounder, which formed the backbone of both of Incyte's asserted grounds of obviousness, *see* Appx8. According to Incyte (Br. 1-2, 6-7, 16, 27-28, 33, 39, 40-41, 44-45), the Backgrounder helps establish that deuteration has a predictable—and predictably beneficial—effect on a drug's ADME properties. But the document states that the "magnitude and nature of the deuterium benefit cannot be predicted a *priori*"—in other words, a skilled artisan could not tell whether, or to what extent, deuteration might have a positive or negative effect on a drug's pharmacokinetics. Appx1740; *see* Concert Br. 27. Incyte's failure to read the Backgrounder "in its entirety, . . . including portions that would lead away from the [claimed] invention," *Panduit*, 810 F.2d at 1568, is wrong as a matter of law.

Incyte uses the same selective-quotation strategy with other references. For example, Incyte cites a trio of articles that, it says, likewise support its arguments about predictability. *See* Incyte Br. 7 (citing Appx2404; Appx5525-5526; Appx5548-

5549).[2] As with the Concert Backgrounder, however, Incyte disregards what those references actually say. One article stresses that "[t]he effects of deuteration on drug stability toward CYP metabolism are complex and unpredictable." Appx5526. Another article cautions—in the very first paragraph, no less—that "[w]ithin biological systems, numerous competing effects can mask the deuterium KIE such that the observed magnitude and even direction of the KIEs are unpredictable." Appx5548. The third article recounts an experiment in which deuteration "failed to extend [a] drug's duration of action." Appx2404. The law of obviousness does not allow Incyte "to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

Second, Incyte fails to consider the totality of the prior art. *See Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021) (noting that the prior art must be "taken as a whole"). According to Incyte (Br. 7, 11, 55), its expert found that 79% of "compounds of record" display a KIE when deuterated. But Incyte's description is misleading: Incyte means only that its expert reviewed

[2] Incyte represents (Br. 7) that these three articles are "prior-art references," but at least one of them—a 2017 article by Liu and others—plainly is not: it was published several years after the '149 Patent's priority date. Appx5524.

and catalogued any deuterated compounds disclosed in the 33 specific exhibits that the parties happened to submit *in this proceeding*. Appx6488(¶99); *see* Appx10573(92:8-11). There is nothing to show that this assortment of compounds is representative of the prior art as a whole. Incyte's expert did not survey the broader prior-art literature. Appx10573(92:4-7). He did not analyze other deuterated compounds that he was familiar with from his own experience. Appx10573-10574(92:12-93:5). Nor did he consider how many of the 33 exhibits were submitted by Incyte versus by Concert. Appx10574(93:12-25). Because his analysis does not consider the prior art as a whole, it fails as a matter of law.[3]

b. Incyte argues in the alternative (Br. 11-15, 33, 46, 56) that even if deuteration is unpredictable *generally*, none of the usual sources of unpredictability would have applied to ruxolitinib *specifically*. As an initial matter, however, Incyte entirely fails to address two categories of uncertainty that Concert identified. Concert explained (Br. 8-10, 12-14) that the unpredictability of deuteration stems in part from (1) uncertainty about whether the relevant step in the catalytic cycle is rate-limiting,

[3] Incyte's "79%" analysis is flawed for the independent reason that, as another Incyte expert acknowledged, "failed attempts" to achieve a KIE are usually "neither reported nor published." Appx9258(172:1-15). So even if Incyte's analysis purported to be comprehensive, counting up published prior-art references produces a higher-than-actual frequency of KIEs.

or whether a particular branched pathway exists in that cycle, and (2) unpredictability about whether a particular KIE will be clinically beneficial. Incyte has no response to these points. As for the sources of unpredictability that Incyte *does* address—metabolic switching and masking—its arguments are unpersuasive.

First, Incyte maintains (Br. 13) that a skilled artisan would have thought metabolic switching unlikely because ruxolitinib has "concentrated sites of metabolism." But Incyte identifies no prior art that taught whether metabolic switching would occur in deuterated ruxolitinib. And Incyte's own reference contradicts the notion that switching occurs only in molecules without concentrated sites of metabolism. *See* Appx2843; Appx2847 (reporting an experiment in which deuteration resulted in no change to the overall reaction rate because metabolism switched to a metabolite that, before deuteration, accounted for only 5% of the metabolite mixture); *see also* Appx9573(¶38) (elaborating on the study). Incyte's argument about sites of metabolism also ignores the fact that switching occurs not only when deuteration causes the same enzymatic pathway to metabolize a different site on the drug molecule, but also when deuteration causes the drug molecule to be metabolized by a different enzymatic pathway altogether. Appx9196-9197(110:18-111:9) (Incyte's expert acknowledging this second type of switching). As a backup, Incyte argues (Br. 13) that even where metabolic switching occurs, it only affects the magnitude of a KIE—*i.e.*, deuteration still slows metabolism to some extent. But that

casual dismissal ignores the tremendous variability—and unpredictability—in the magnitude of any deuterium effect. *See* Concert Br. 12-14.

Second, Incyte argues (Br. 14-15) that a skilled artisan would have understood ruxolitinib not to be susceptible to factors that lead to masking. But Concert's expert did not agree that masking is inapplicable to ruxolitinib, as Incyte suggests (Br. 14). Instead, Dr. Ortiz de Montellano testified that masking factors are not specific to ruxolitinib, but are applicable to any compound. *See* Appx5853(26:4-10); Appx5857(30:1-8).

c. That Incyte fails to substantiate its predictability arguments should come as no surprise: the Board itself recently found—on nearly identical evidence—that deuteration is notoriously unpredictable. In 2020, Incyte sought and the Board instituted a post-grant review to challenge a separate Concert patent claiming methods of using Concert's deuterated compounds to treat certain hair-loss disorders. Incyte largely relied on the same experts and evidence[4] as it did here. But the Board rejected Incyte's challenge, because "the evidence of record showed that . . . deuteration of compounds was not predictable." *Incyte Corp. v. Concert Pharms., Inc.*, No. PGR2021-00006, 2022 WL 11703590, at *4 (Oct. 11, 2022) (Paper 70, at 8-9).

[4] *See, e.g.*, Pet.'s Updated Exhibit List, *Incyte Corp. v. Concert Pharms., Inc.*, No. PGR2021-00006 (Jan. 12, 2022) (Paper 57), *available at* tinyurl.com/2ssz9sa7 (including Shilling, the Concert Backgrounder, and declarations from Drs. Shapiro, Guengerich, and Thisted as exhibits).

"[W]ithout the benefit of [Concert's discoveries]," the Board found, a skilled artisan "would not have been able to predict that [Concert's octa-deuterated compound] would have been successful"—and thus "would not have been motivated to arrive at the claimed method." *Id.*; *accord Incyte Corp. v. Concert Pharms., Inc.*, No. PGR2021-00006, 2022 WL 1613509, at *25 (May 11, 2022) (Paper 68, at 58) ("[I]f deuteration results were entirely predictable, the [supplemental data that Concert submitted during the '149 Patent's prosecution] would not have been necessary to generate to overcome obviousness or in general to assess the performance of the compounds.").

The difference in outcome between that PGR and this IPR does not stem from different evidentiary submissions or a different weighing of the evidence. It stems from the Board's failure in this case to put the evidence through the right legal test. Absent that legal error, the Board could not have found motivation.

4. Incyte fails to show that a skilled artisan would have deuterated ruxolitinib despite awareness of its dose-dependent side-effects.

Incyte's argument that deuteration would have a predictable effect on metabolism is also self-defeating. A skilled artisan would have believed that if deuteration increased ruxolitinib's metabolic stability, it would also increase the drug's dose-dependent side-effects—which limit the medical conditions that ruxolitinib can be

used to treat. Concert Br. 15-17, 43-44. The presence of that dose-dependent toxicity would have affirmatively discouraged a skilled artisan from deuterating the drug.[5]

a. Incyte tries to address this problem by repeating the Board's perplexing assertion that a skilled artisan would have thought that any side-effects could be managed by dose adjustment. Both Incyte and the Board insist that "the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug." Incyte Br. 48 (quoting Appx25-26). But that misunderstands the problem. Safe and effective treatment is possible only if ruxolitinib's concentration is high enough to treat AA but low enough to avoid its harmful side-effects for a sufficient period. *See* Concert Br. 21 (describing this therapeutic window). And a skilled artisan would have believed that ruxolitinib's beneficial properties and harmful side-effects were inextricably linked. *See* Concert Br. 44. Thus, a skilled artisan would have expected the lower-but-same-concentration dose of the deuterated drug that the Board posits to come with the same efficacy *and same unacceptable side-*

[5] Incyte claims (Br. 46) that this argument is "inconsisten[t]" with Concert's position that deuteration is fundamentally unpredictable. But the supposed "contradiction" (Incyte Br. 43) is illusory. As Concert has explained, a skilled artisan would not have expected deuteration to slow metabolism. But *if* the skilled artisan could have predicted slower metabolism, she would have expected that slowing effect to exacerbate the drug's side-effects, too. Concert Br. 43-44.

effects as the original, higher dose of ruxolitinib. Incyte offers no way around this problem.

Even on its own terms, moreover, Incyte's dose-adjustment theory ignores the real and substantial costs of dose adjustment. By definition, a patient must experience an adverse event *before* a treating physician attempts dose adjustment. And while those adverse events—and the subsequent trial-and-error of adjustment—may be tolerable for patients with life-threatening cancers, *see* Incyte Br. 47 (discussing dose adjustment in myelofibrosis patients), Incyte offers nothing to suggest that a skilled artisan would have considered them tolerable for an AA patient. For this reason, too, the Board erred in its assumption that the possibility of dose adjustment would have overcome a skilled artisan's expectation that deuteration would increase the risk of dose-dependent side-effects.

b. Incyte also attacks the prior art's teachings about these dose-dependent side-effects more directly. Relying on the testimony of its expert, Dr. Shapiro, Incyte argues (Br. 10) that a skilled artisan would not have found ruxolitinib's side-effects in myelofibrosis patients relevant in deciding how the drug would perform in AA patients. But that litigation-driven testimony contradicts Dr. Shapiro's own published work. Dr. Shapiro's article on AA treatment cites the experiences of myelofibrosis patients in explaining that "side effects of JAK inhibitors include (potentially serious) infections, viral reactivation, bone marrow disruption, transaminase

changes, and a theoretical—though unproven—risk for malignancy." Appx6686; Appx6688 (citing Appx9470-9480 as footnote 54).

Incyte also argues that these side-effects "rarely led to treatment discontinuation—even for myelofibrosis patients." Incyte Br. 47 (quotation marks omitted). But that is factually incorrect. As Concert has shown, ruxolitinib patients encountered "severe" or "life-threatening" adverse events, treatment interruption, and burdensome interventions (like blood transfusions) on a not-infrequent basis. *See* Concert Br. 16-17. And even if Incyte's claim were true, it glosses over the fact that side-effects that might be acceptable when treating myelofibrosis (a potentially fatal illness) are far less acceptable when treating AA (a non-life-threatening condition). *See* Concert Br. 17; *see also* Appx9382; Appx9580. Incyte has no response to that observation.

B. The PTAB failed to analyze a skilled artisan's motivation to pursue the specific claimed modifications.

In addition to its failure to consider deuteration's expected effect on pharmacokinetic properties, the Board's motivation inquiry is flawed for an independent reason: the Board failed to ask whether a skilled artisan would have pursued the "*specific molecular modifications* necessary to achieve the claimed invention." Concert Br. 45 (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). Incyte responds by reiterating (Br. 40) the Board's conclusion that a skilled artisan would have been motivated to deuterate

ruxolitinib at its known "hot spots," and so would have been motivated to create the '149 Patent's claimed "tetra-" and "octa-deuterated" compounds. But that statement—even if true—fails to address fatal deficiencies in the Board's analysis.

First, because nearly *all* FDA-approved drugs have known metabolic hot spots, the Board's reasoning supports nothing more than a generic motivation to deuterate every drug. *See* Concert Br. 47. The law demands more specificity than that. *See id.* This Court has set forth a rigorous framework for analyzing claims to novel pharmaceutical compounds. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-1292 (Fed. Cir. 2012). The PTAB applied that analysis here, *see* Appx20, and Incyte does not challenge that overarching standard. But the standard requires more than a general motivation to make changes—it requires identifying a lead compound and then a motivation to make specific modifications. *See Otsuka*, 678 F.3d at 1291-1292; Concert Br. 28, 36. Incyte's observation that ruxolitinib was FDA-approved and known to have "hot spots" is legally insufficient to make that showing. That is especially true in light of the affirmative reason *not* to deuterate ruxolitinib because of its known dose-dependent toxicities. *See supra*, pp. 13-16. Incyte argues (Br. 42) that Concert's objection to this deuterate-all-drugs error "goes nowhere," but it never explains why—it just repeats the observation that ruxolitinib had known hot spots.

Second, even focusing on the tetra- and octa-deuterated compounds, the Board still fails to identify a motivation for the specific claimed modifications. The Board concluded that a skilled artisan would have been motivated to create *both* the tetra-deuterated *and* the octa-deuterated compounds because there was a motivation to deuterate ruxolitinib along its cyclopentyl ring. Appx23. But the Board's logic does not hold up. If the relevant motivation is to deuterate at known hot spots, there is no reason why a skilled artisan would have stopped at four sites of deuteration (as necessary to create the tetra-deuterated compounds). *See* Concert Br. 47-48. For that matter, there is no reason why a skilled artisan would have stopped at eight sites of deuteration to create the octa-deuterated compound: why not deuterate all nine sites along the cyclopentyl ring? Neither the Board nor Incyte has any reason for focusing on the tetra- and octa-deuterated compounds other than pure hindsight.

C. The PTAB ignored whether a skilled artisan had a reasonable expectation of creating compounds with desired beneficial properties.

The Board also committed legal error at the reasonable-expectation stage of the obviousness inquiry: its decision failed to consider whether a skilled artisan would have expected the claimed modifications to ruxolitinib to result in beneficial changes. *See* Concert Br. 48-54. Incyte's defense of that analysis is wrong as a matter of both law and logic.

1. Doctrinally, Incyte maintains (Br. 51-52) that the reasonable-expectation inquiry cares only about claimed properties. But that has never been this Court's

approach to compound patents, as the decision in *Takeda* makes clear. There, the Court found that there was no reasonable expectation of success because a skilled artisan would not have expected the claimed modifications to result in relevant "beneficial changes"—even though the beneficial changes were not claimed in the compound-only patent. *See* Concert Br. 49-50.

Incyte's efforts to skirt *Takeda*'s holding are unconvincing. Incyte's main defense is to posit (Br. 52) that *Takeda*'s discussion of reasonable expectations was really a discussion of motivation in disguise. But both this Court and the district court were clear that they were talking about reasonable expectations of success. *See, e.g.*, *Takeda*, 492 F.3d at 1350 (discussing whether "homologation would bring about a reasonable expectation of success"); *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 385 (S.D.N.Y. 2006) (addressing whether there was a "reasonable expectation of success"). Incyte cannot get around these decisions by asserting that they simply did not mean what they said.

Incyte's citation of *Intelligent Bio-Systems v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016), does not aid its cause. That case did not consider a patent for a novel compound like those at issue in *Takeda* and this case. Indeed, Incyte identifies *no* compound case that has adopted its ignore-pertinent-properties approach. That is unsurprising: this Court has long recognized that "a compound and all of its properties are inseparable." *Honeywell Int'l Inc. v. Mexichem Amanco*

Holding, 865 F.3d 1348, 1355 (Fed. Cir. 2017) (quoting *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963)). The Court should apply *Takeda* and reject the Board's flawed reasonable-expectations analysis.

2. Not only is Incyte's approach doctrinally unsound, but it is also practically problematic. Adopting Incyte's approach and holding that the Board need not consider a compound's functional properties at the reasonable-expectations stage would effectively nullify that inquiry for most compound patents. That is because a skilled chemist will *often* be able to undertake the physical manipulations necessary to arrive at a new compound. *See* Concert Br. 55. As *Takeda* rightly recognized, it is an analysis of a claimed compound's properties that allows someone to distinguish the novel from the predictable.

3. Incyte also argues (Br. 53-57) that even if Concert is right about the legal standard, the Board *did* consider the claimed compounds' properties at the reasonable-expectation stage. But Incyte just reiterates arguments already refuted above—including, for example, that the claimed deuterated compounds would have had a similar selectivity and potency to ruxolitinib. *See supra*, pp. 4-6. And Incyte's argument (Br. 4, 30, 34, 44, 54-55) that it has shown a reasonable expectation of success because the deuterated compounds "may display" improved pharmacokinetic properties artificially lowers the legal standard. The question is what one skilled in

the art thought *would* occur—not what she thought *may* or *might* occur. *See* Concert Br. 52.

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Incyte combines a lax motivation inquiry (one that requires only a *potential* improvement in a compound's properties) with a crabbed reading of the reasonable-expectations test (one that asks only whether a chemist can *synthesize* the claimed compound). The result is a sweeping proposition: the Board need *never* consider—at *any* stage of the obviousness analysis—what a skilled artisan would have thought about the effect of deuteration on ruxolitinib's pharmacokinetic properties. In Incyte's view, it is enough that the modified compounds *might* display "better" pharmacokinetic properties (whatever "better" might mean), and that a skilled artisan could physically create those compounds.

That has never been the law of this circuit—just look at the Court's decision in *Sanofi-Synthelabo*. Apotex could plainly have shown that a single enantiomer *might* display superior properties to the racemic mixture. *See* 488 F. Supp. 2d 317, 337 (S.D.N.Y. 2006) (noting, as one possible outcome, that "one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole"). And it was certainly *physically possible* to isolate a single enantiomer. Under Incyte's watered-down analysis, therefore, the Court should have found the single enantiomer

obvious. But the Court reached the opposite result, *see* 470 F.3d at 1378-1379, because the law of obviousness is not so toothless. Incyte's arguments fail for the same reason.

II. The PTAB's analysis of objective indicia of nonobviousness rested on legal errors.

A. The PTAB misclassified CTP-543's unexpectedly flatter pharmacokinetic curve as a difference in degree.

The Board disregarded a meaningful and unexpected result—CTP-543's flatter pharmacokinetic curve—because it applied an overly expansive view of what constitutes a "difference in degree." Concert Br. 56-60. Incyte's efforts to justify that error are unavailing.

First, Concert's demonstration of an unexpectedly flatter pharmacokinetic curve does not depend on an "inapt comparison[]" to an "unnecessarily high dose of ruxolitinib" (Incyte Br. 23-24, 59-60). As Concert has explained, a 16 mg dose of CTP-543 inhibits the IFN-γ pathway (a key pathway relevant to treating AA) for 14.9 hours. Appx7661-7662(¶17). So Concert compared that dose to 27 mg of ruxolitinib—which would *also* inhibit the IFN-γ pathway for 14.9 hours. *Id.* It is unclear why Incyte thinks (Br. 24) this is an "apples-to-oranges comparison[]": the different pharmacokinetics of CTP-543 and ruxolitinib require comparing different doses that achieve similar efficacy. Concert compared the respective doses of CTP-543 and ruxolitinib needed to achieve the same duration of IFN-γ inhibition.

Second, Incyte is wrong to label the benefits of a flatter pharmacokinetic curve "entirely theoretical" (Br. 23, 60). Incyte bases that argument on the fact that "[t]here is no clinical data of record for CTP-543 in AA patients." But there is no rule that a patentee must demonstrate unexpected results by way of Phase 3 clinical studies. And such a rule would have little to recommend it. As a practical matter, "patents claiming innovative treatments are filed well before clinical testing begins." BGDL Amicus Br. 24. Thus, Incyte's rule would artificially restrict the consideration of unexpected results in cases involving patents on pharmaceutical compounds.

Third, CTP-543's flatter pharmacokinetic curve was not, as Incyte contends (Br. 22, 60-61) a "predictable effect of slowing ruxolitinib's metabolism via deuterium substitution." Incyte argues (Br. 60) that this flatter curve was "observed for deuterated versions of ivacaftor and venlafaxine." That is incorrect—and Incyte's own citations show as much. With respect to deuterated ivacaftor, Incyte relies on a poster[6] that shows that different deuterated ivacaftor compounds provided *different* pharmacokinetic results depending on the animal species involved:

[6] Incyte failed to establish that this poster—which presents Concert's own research—qualifies as prior art.

Figure 4: Metabolic stability in CYP3A4 supersomes

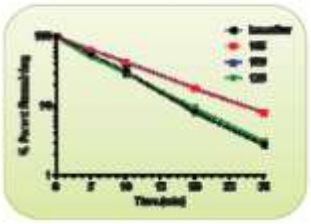


Figure 5: Oral PK in rats

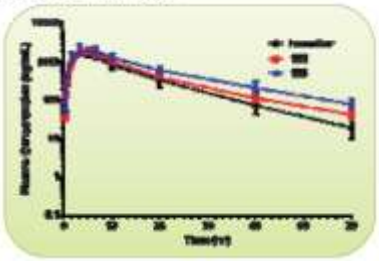
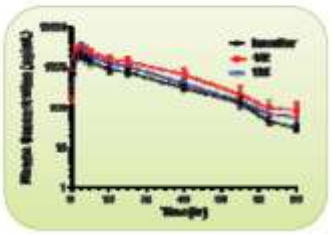
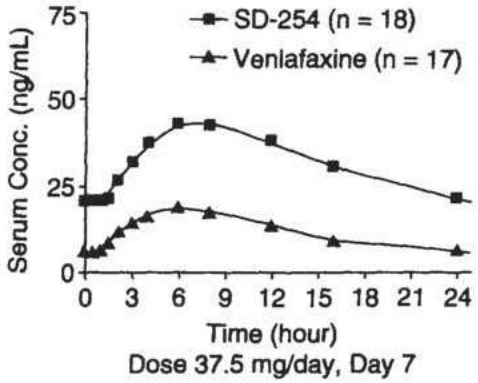


Figure 6: Oral PK in dogs



Appx2815 (deuterated curves in color). And with respect to deuterated venlafaxine, Incyte's reference shows that deuteration led to a curve that was *less flat*, with a markedly higher C_{max} value:



Appx1991 (deuterated curve on top). Incyte fails to explain how these entirely different results could have predicted CTP-543's flatter curve.

Finally, Incyte is wrong to argue (Br. 25, 58-59) that this flatter curve is clinically insignificant on the theory that, when dosed twice daily, both CTP-543 and an equivalently effective dose of ruxolitinib maintain plasma concentrations above 50 nanomoles per liter at all times. Incyte's argument ignores half the picture. The therapeutic window has an upper and lower bound: the plasma concentration must remain above 50 nanomoles per liter (below that, and the drug does not

effectively treat AA), but it must also remain *below 677 nanomoles per liter* (above that, and the risk of anemia-associated side-effects increases). *See* Concert Br. 21. Incyte does not dispute that ruxolitinib's plasma concentration exceeds the 677 nanomole-per-liter threshold for 35% longer than an equivalently effective dose of CTP-543. That is clinically significant: as Concert has explained, the presence of serious side-effects, while tolerable in the blood cancers that ruxolitinib treats, are not as tolerable in a non-life-threatening condition like AA. *See* Concert Br. 17; *supra*, p. 16.

In short, the Board improperly concluded that CTP-543's flatter pharmacokinetic curve is a "difference in degree," and improperly concluded that differences in degree are categorically irrelevant. *See* Concert Br. 56-60. The unexpectedly flatter pharmacokinetic curve objectively indicates the challenged claims' nonobviousness.

B. The PTAB misunderstood the unexpected inverse correlation that causes the fastest metabolizers of ruxolitinib to experience the greatest pharmacokinetic improvement on CTP-543.

Incyte also cannot justify the Board's failure to grasp an unexpected improvement experienced by the fastest metabolizers of ruxolitinib. *See* Concert Br. 61-62. Incyte argues (Br. 26, 61) that this inverse improvement is unremarkable because it just reflects "the same *absolute* increase" in half-life across all patients. But Incyte presents no biological reason why anyone would have expected the same absolute increase in half-life across all patients. A skilled artisan would have expected the

same *relative* change in half-life when patients are dosed with the deuterated drug. Appx9579-9580(¶51). The actual result—an inverse relationship—was totally unexpected.

This unexpected outcome means that, in the case of CTP-543, deuteration disproportionately benefits the patients least likely to be effectively treated with ruxolitinib, *i.e.*, patients with the shortest ruxolitinib half-life. *See* Concert Br. 22-23. That phenomenon, in turn, allows a greater percentage of the population to benefit from taking a given dose of the deuterated drug. *See id.* The Board misunderstood this clinically important advantage. *See* Concert Br. 61-62. Notably, Incyte's expert on this point, Dr. Thisted, is a biostatistician—he is not a person of ordinary skill in the art under either party's definition. *See* Appx11034-11036(9:9-11:3). And Incyte did not present any other competent evidence to rebut the testimony of Concert's experts that this inverse relationship would have been unexpected.[7]

C. The PTAB erroneously disregarded CTP-543's ability to satisfy a long-unmet need for a viable AA treatment.

As of the priority date, AA patients lacked a reliable treatment option for their condition. Concert Br. 18, 63; BGDL Amicus Br. 12-19. Concert's octa-deuterated

[7] Incyte observes (Br. 25, 61-62) that a Concert declarant, Dr. Harbeson, was aware of a similar inverse effect in a drug metabolized by a *different* enzyme. But that does nothing to rebut the essential point: the prior art did not teach—and no expert was aware of—this effect in a drug metabolized by the *same* enzyme as ruxolitinib. Concert Br. 22.

compound satisfied that unmet need—a fact the Board mistakenly ignored only because CTP-543 had not yet received FDA approval. *See* Concert Br. 62-65; BGDL Amicus Br. 19-22. None of Incyte's arguments salvages the Board's flawed analysis.

1. Incyte's suggestion (Br. 63-64) that there was not even an unmet need to begin with strains credulity. As of the priority date, "'[m]ost of the available therapeutic options' were known to be 'unsatisfactory' and there was 'no good trial evidence that any treatment provided long-term benefit to patients' with AA." BGDL Br. 16 (quoting M.J. Harries et al., *Management of Alopecia Areata*, 341 B.M.J. 3671, 3672 (2010)) (brackets omitted). The FDA obviously agreed: it granted CTP-543 a "Fast Track" designation reserved for drugs that will "fill an unmet medical need." Concert Br. 19, 63. Incyte's competing evidence—such as "successful use of ruxolitinib . . . in animal models" (Br. 9-10)—fails to overcome that clear showing of a long-unmet need.

In any event, Incyte's argument is not properly one this Court can consider. The PTAB did not dispute the existence of a long-felt need, *see* Appx35-37; Concert Br. 63, and this Court may not affirm the PTAB's decision on alternative grounds. If the Court disagrees with the Board's existing analysis, the Court must remand to the agency for further consideration of any alternative arguments. *INS v. Orlando Ventura*, 537 U.S. 12, 16-18 (2002) (per curiam) (reversing for failure to follow the

ordinary remand rule); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1586 (Fed. Cir. 1996) (remanding where "[t]he trial court made no decision on [an] issue" in the first instance and resolving the issue "would require" this Court to undertake the "impermissible exercise" of "weighing substantial but conflicting evidence").

2. On the question the Board actually decided—whether CTP-543 satisfied the long-felt need—Incyte's suggestion (Br. 64-65) that Concert invited the Board's error does not square with the record. Incyte alleges that, before the Board, Concert framed the unmet need as a need for an *FDA-approved* AA treatment. But Incyte is treating Concert's briefs the way it treats the prior art, plucking out scattered sentences while ignoring the totality. Concert explicitly argued that CTP-543 "satisfie[d]" the long-felt need, Appx465; Appx1085 (heading style omitted), which it could not have done if the need were for an already-FDA-approved drug. And in the body of its principal brief, Concert explained:

> There has been a long-felt need *for an effective AA treatment with a tolerable long-term side effect profile*. Concert's clinical studies have shown that CTP-543 is a promising drug to fill *this* unmet need.

Appx465 (citation and paragraph break omitted) (emphasis added); *see also id.* (explaining that "there has been a long-felt need for an evidence-based AA treatment that does not have unacceptable side effects"). Nothing about that description turns on FDA approval. *See* Appx1327 (Incyte's counsel agreeing that "[t]he FDA approval or not is . . . irrelevant to whether there was a long-felt need").

Finally, Incyte's argument (Br. 65-67) that Concert did not show it satisfied a long-felt need because it did not yet have "clinical data for CTP-543 in AA patients" is just the Board's FDA-approval requirement with a slightly earlier goalpost. Both the Board's rule and Incyte's corollary threaten to eviscerate the long-felt-need analysis in cases involving pharmaceutical products. That is because, as amicus explained, "[t]he grant of FDA approval to market an innovative treatment to patients almost always comes years after filing the patent application claiming the innovative treatment." BGDL Br. 24. The same is true of Phase 3 clinical testing—it almost never *precedes* the relevant patent application. *See id.* If patentees must have Phase 3 results or FDA approval in hand to show that they satisfied a long-felt need, the long-felt-need analysis is effectively dead letter in pharmaceutical cases.

This case points up the dangers of that rule. As BGDL has explained, Concert's subsequent Phase 3 data confirmed what Concert's evidence before the Board already indicated: CTP-543 is expected to provide a viable AA treatment.[8]

D. The Court should reject Incyte's argument that the objective indicia of nonobviousness are not commensurate with the claims.

Incyte concedes (Br. 30) that "[t]he Board did not reach" the commensurateness argument it now raises. This Court should not address the argument for the

[8] Incyte's observation (Br. 63) that the FDA has recently approved a different drug to treat AA is a non sequitur. The Court "look[s] to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *Procter & Gamble*, 566 F.3d at 998.

same reason: if the Court agrees with Concert that the Board erred, the Board should have the opportunity to consider any alternative arguments in the first instance. *See Orlando Ventura*, 537 U.S. at 16-18; *Vitronics*, 90 F.3d at 1586.

Regardless, Incyte's arguments fail. Incyte contends (Br. 21, 68) that CTP-543 is not commensurate with the claims because the '149 Patent claims "*hundreds* of deuterated analogs" of ruxolitinib, of which CTP-543 is just one. But Incyte's petition expressly limited its patentability arguments to the three compounds recited in claim 7—including the octa-deuterated compound—"[f]or the sake of efficiency." Appx130. Incyte cannot fault Concert for directing its objective evidence of nonobviousness to the compounds that Incyte's challenge singled out.

There is also no merit to Incyte's contention (Br. 21-22, 68-69) that CTP-543's isotopic purity affects whether Concert's evidence is commensurate with the claims. For one thing, Incyte's argument that "the unexpected results may not occur" for compounds with varying degrees of enrichment "is based solely on attorney argument," and so carries little weight. *Cephalon Inc. v. Mylan Pharms. Inc.*, 962 F. Supp. 2d 688, 720 (D. Del. 2013); *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1359 (Fed. Cir. 2018) ("[A]ttorney argument is not evidence and

cannot rebut other admitted evidence[.]" (quotation marks omitted)).[9] Moreover, Incyte's argument from the outset has been that deuteration is "eas[y] and predictab[le]." Appx157. The objective indicia of nonobviousness disprove that sweeping assertion.

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CTP-543's unexpected results and satisfaction of a long-unmet need for a viable AA treatment objectively confirm what a properly formulated structural obviousness inquiry already shows: a skilled artisan would not have been motivated to synthesize Concert's novel deuterated compounds and would not reasonably have expected to achieve their beneficial pharmacokinetic properties.

CONCLUSION

The Court should reverse the PTAB's decision.

[9] Testimony that "low enrichment" can "diminish[]" the KIE, Appx5802(82:22-25), does not support Incyte's argument: the '149 Patent requires at least 45% enrichment, Appx1429(3:41-4:3), so no claimed compound has "low enrichment."

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Respectfully submitted.

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CERTIFICATE OF SERVICE

I hereby certify that on November 10, 2022, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the Court's CM/ECF system. Counsel for all parties to the case are registered CM/ECF users and will be served by the CM/ECF system.

November 10, 2022

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because, excluding the parts of the document exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b), it contains 6,940 words.

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared using Microsoft Word for Office 365 in 14-point Times New Roman, a proportionally spaced typeface.

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