

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INARI AGRICULTURE, INC.,  
Petitioner,

v.

CORTEVA AGRISCIENCE LLC,  
Patent Owner.

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PGR2023-00022  
Patent 11,371,055

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**PATENT OWNER'S SUR-REPLY**

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## I. Introduction

The challenged claims cannot be shoehorned into the body of functionally defined genus caselaw (e.g., *Amgen*, *Baxalta*, *AbbVie*, and *PureCircle*) Petitioner relies upon. The '055 patent amply discloses to skilled artisans the *number* and *types* of amino-acid substitutions (e.g., 85+% sequence identity and conservative vs. non-conservative changes), and guides them on *where* to make or avoid such substitutions within SEQ ID NO: 2. Ex. 2011, ¶¶ 123-128, 44-57; Ex. 1001, 21:42-60, 11:1-14, 20:23-34, 28:57-60, Fig. 2. In his cursory reply declaration, Petitioner's declarant Dr. Silverstone—who has no enzymology expertise—did not dispute the specification's guidance to skilled artisans.

Instead, Petitioner pivoted to relying on the [REDACTED]  
[REDACTED]. Petitioner's arguments, however, incorrectly presume that the [REDACTED]  
[REDACTED]. Reply, 10. As detailed below, [REDACTED]  
[REDACTED]. As Dr. Bollinger testified, and Petitioner does not dispute, [REDACTED]  
[REDACTED]  
Ex. 2011, ¶¶ 123-128; Ex. 2025, 204-05 (“[C]hanges at ... highly conserved residues are generally deleterious.”). Petitioner's reliance on these AAD-12 variants is thus misplaced.

The Board should therefore hold that Petitioner has failed to prove lack of written description or enablement, and confirm the patentability of all challenged claims or terminate this proceeding for lack of jurisdiction because the '055 patent is entitled to its 2005-2006 filing dates and therefore is PGR-ineligible.

## **II. Petitioner Has Offered No Competent Expert Support for Its Written-Description and Enablement Challenges**

The Petition relied on a mathematical theory ( $10^{106}$  possible sequences) that improperly assumed that a *skilled* artisan would exercise *no skill* by randomly substituting all 19 alternative amino acids at every possible location within 85% sequence identity to SEQ ID NO: 2. *See* Pet. 10, 14, 24, 27, 30, 32, 38, 40, 45, 46, 59. Petitioner based its argument on the testimony of Dr. Silverstone, who has no training in enzymology, omitted knowledge of enzymology from his proposed level of skill, and failed to apply well-established structure-function principles. POR, 31-32, 47; Ex. 2011, ¶¶ 117-128.

Petitioner's numerosity theory was rebutted by Dr. Bollinger, who has over 20 years of experience working with  $\alpha$ KG-dependent dioxygenases. Ex. 2011, ¶¶ 2-4, 10-11. He explained that skilled artisans in 2005-2006 knew how to maintain function in enzyme variants. Ex. 2011, ¶¶ 44-57, 123-128, 160-161. They kept sequence identity high, maintained active site residues, and relied on sequence comparisons with related enzymes to identify residues that could be freely (or less

freely) substituted—i.e., precisely the type of structural guidance the '055 patent discloses. *Id.* In his reply declaration, Dr. Silverstone did not dispute the '055 patent's disclosures or any of these known principles for conserving enzyme function.

Instead, Petitioner revised its calculation downward to  $10^{45}$  or  $10^{66}$  possible sequences. Reply, 27. But Petitioner's theory remains purely mathematical. Petitioner nowhere establishes that following the '055 patent's guidance would have been insufficient to produce function-conserved AAD-12 variants. Thus, the Board should reject Petitioner's numerosity theory as failing to account for the specification's guidance or the perspective of a skilled enzymologist. *Lifescan*, PGR2019-00032, Paper 11 at 30 (rejecting similar numerosity argument (e.g.,  $5 \times 10^{76}$  sequences) as derived solely from the numerical size of the genus rather than the state of the art and the factors informing the written-description analysis).

Accordingly, Petitioner has failed to support its Section 112 challenges with any competent evidence from its declarant, Dr. Silverstone, and Petitioner's challenges should be rejected for this reason alone.

### **III. Petitioner Fails to Establish Lack of Written Description**

#### **A. The Common Structural Feature of at Least 85% Sequence Identity to SEQ ID NO: 2**

##### **1. The “At Least 85% Sequence Identity” Limitation Is Correlated to the Claimed Function**

The '055 patent discloses that enzyme variants having the “same or similar activity” as the exemplified proteins (e.g., AAD-12) typically have at least 60% sequence identity to SEQ ID NO: 2, including 85% or higher sequence identity, as claimed. POR, 72-73; Ex. 1001, 21:41-60. It also discloses that, among  $\alpha$ KG-dependent dioxygenases, variants with 85% sequence identity are “highly identical” and “would be expected to retain similar properties.” *Id.*, 32:1-6. Petitioner’s Reply does not address these disclosures. *See generally* Reply.

The at least 85% sequence-identity limitation is amply correlated to the claimed function. Petitioner originally speculated that broad structure-function diversity existed within 85% sequence identity to SEQ ID NO: 2, including enzymes that catalyze entirely different reactions or that fall into enzyme families other than  $\alpha$ KG-dependent dioxygenases. Ex. 1003, ¶¶ 48, 50; Pet. 46-47 (referencing dealkylation, desaturation, and other reactions). This argument, based on Dr. Silverstone’s testimony, has been discredited.

On a full trial record, Petitioner has failed to identify *any* enzyme within 85% sequence identity to SEQ ID NO: 2 that catalyzes a different reaction or that is in a

different enzyme family. Dr. Silverstone conceded he could not identify any such enzyme. Ex. 2009, 11:5-14:20, 17:5-9. Accordingly, unless one introduced substitutions that would destroy AAD-12 functionality—which skilled artisans knew how to avoid—it is undisputed that enzymes within 85% identity to SEQ ID NO: 2 presumably have the same function. POR, 37; Ex. 2011, ¶ 118; Ex. 1043, 168:14-20. This case is unlike *AbbVie*, *Amgen*, and *Baxalta*, where skilled artisans would have had to identify antibodies having the claimed properties out of the *entire universe* of possible antibody sequences and functions. See POR, 45-46, 79-80.

Petitioner has thus failed to establish that the narrow sequence space of at least 85% sequence identity to SEQ ID NO: 2 is uncorrelated to the dual herbicide-degrading function. Ex. 2011, ¶ 102 (“at least 85% sequence identity defines a narrow sequence space well within established ranges for conserving enzyme function”).

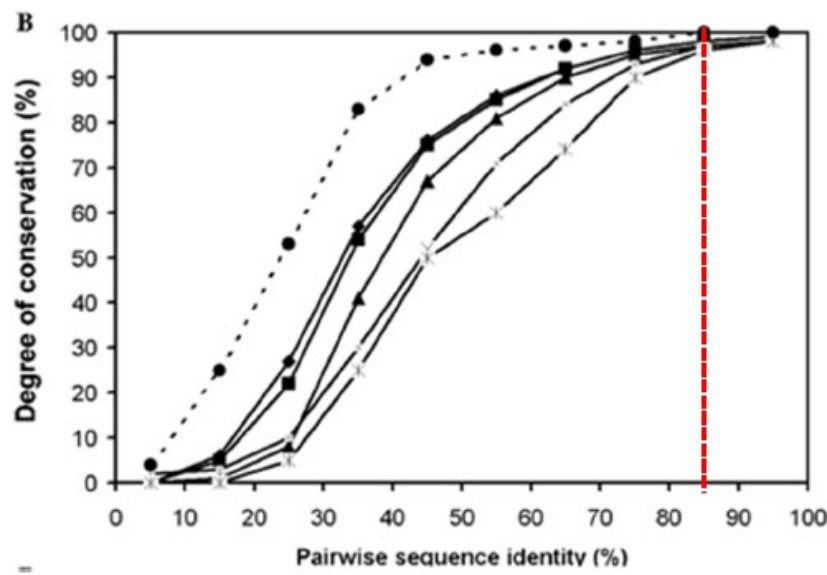
## **2. Skilled Artisans in 2005-2006 Had Extensive Knowledge of Enzyme Sequence-Function Relationships**

Dr. Bollinger also testified that a skilled artisan would have come to the '055 patent in 2005-2006 with significant background knowledge, including an expectation of retaining the same or similar function among enzymes having at least 85% sequence identity to SEQ ID NO: 2, *just as the '055 patent discloses*. Ex. 2011, ¶¶ 44-57, 160-161; Ex. 1001, 31:61-32:6, 21:41-60. That knowledge included

several studies using the best sequence/function databases in the field “to establish the threshold of sequence identity above which functional similarity can be affirmed.” Ex. 2019, 863-64; Ex. 2028, 595 (reporting “important benchmarks for everyday sequence analysis”); Exs. 2024, 2026, 2027. By 2005-2006, skilled artisans thus understood that sequence identities above 40-60% provide approximately 90% likelihood of retaining the same enzyme function, and the correlation with function at 85% identity was even higher. POR, 72-73.

Dr. Silverstone, who has no enzymology expertise, did not address these studies, thus ignoring well-established structure-function principles. Petitioner instead only presented unsupported attorney argument, which fails to disturb Dr. Bollinger’s testimony and the well-established principles these studies illustrate. *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) (attorney argument “is not evidence” and cannot rebut other admitted evidence).

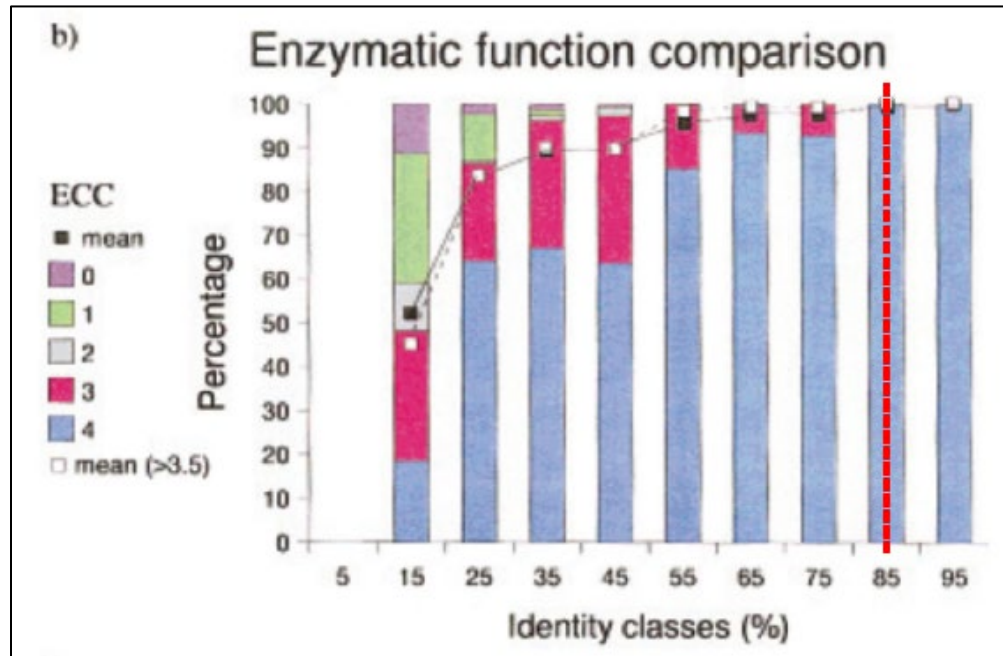
First, Petitioner incorrectly criticizes the studies using the SWISSPROT database, notwithstanding that it was recognized as the “gold standard” database for functional assignments (e.g., EC numbers) to amino acid sequences. Ex. 2019, 864; Reply, 13-14. Petitioner suggests that the studies were biased by *excluding non-enzyme proteins* (Reply 14 n.5) and analyzing only functional enzyme sequences (Reply, 13-14). To the contrary, Dr. Bollinger’s annotated Figure 1(B) from Tian 2003 came from a broader analysis of both enzyme and non-enzyme sequences:



Ex. 2011, ¶ 99; Ex. 2019, 866 (Figure 1(B) “includes both enzyme–enzyme and enzyme–non-enzyme sequence pairs”).

Second, Petitioner argues that the sequence-function relationship studies excluded multi-functional enzymes. Reply, 15. As Dr. Bollinger testified, such enzymes are referred to as multi-domain enzymes, which generally have two domains (i.e., active sites) and “do two different reactions at [their] different domains.” Ex. 1043, 104:8-105:2 (citing Ex. 2028, 605). But Petitioner presents no evidence that multidomain proteins having 85+% lack the same enzymatic function. Petitioner’s argument is also misplaced because AAD-12 is not a multi-domain enzyme—AAD-12 and other  $\alpha$ KG-dependent dioxygenases have a single active site characterized by each enzyme’s motif residues and spacing. Ex. 1001, FIG. 2, 20:23-34 (directing skilled artisans to Figure 2 of the ’055 patent regarding the active site of AAD-12 and related enzymes); *see also* Ex. 2002, 1358; Ex. 2001, 24316

(Fig. 11). Nor did all studies exclude multi-function enzymes as Petitioner contends. Devos 2000 did not exclude such proteins and its results showed that function was consistently retained at high levels of sequence identity, including at 85% and above:



Ex. 2026, 99-101 (Fig. 1(b) (red annotation at 85% added); Ex. 2011, ¶¶ 31-39.

Third, Petitioner incorrectly criticizes the sequence-function relationship studies on the basis that most (but not all) of the enzymes in the SWISSPROT database are natural enzymes rather than variants. Reply, 14-15. Petitioner ignores Dr. Bollinger's undisputed testimony that skilled artisans widely used such natural sequences when making variants, aligning them to identify important residues to conserve and which residues could be more broadly mutated to produce function-conserved enzymes. Ex. 2011, ¶¶ 44-57, 160-161, Ex. 1043, 57:24-58:11. Indeed, that is precisely the type of information the '055 patent discloses in Figure 2. *Id.*,

¶¶ 123-128; Ex. 1043, 162:2-12 (Figure 2 provides a “ton of information” to skilled artisans), 117:5-22. The pre-2006 literature further confirms Dr. Bollinger’s testimony, which again stands undisputed by Dr. Silverstone. Ex. 2025, 203 (sequences of related proteins are “a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function”); Ex. 2044, 3812 (aligning sequences of “related proteins” identifies residues presumably important to function that should not be changed); *see also* Ex. 2035, 180 (“a wide variety of tools” can be used to create variants, including “sequence alignments”).

Accordingly, at least 85% sequence identity to SEQ ID NO: 2 was a narrow sequence space in which skilled artisans would have expected to produce function-conserved AAD-12 variants. That is more than ample correlation under the written-description requirement. *Ex parte Campbell*, No. 2021-000865, Decision on Appeal at 15 (PTAB July 20, 2021) (reversing written-description rejection where sequence comparisons provided guidance on where to make amino-acid substitutions).

### **3. Petitioner Incorrectly Relies on Corteva’s AAD-12 Variants**

Petitioner’s reliance on [REDACTED]  
[REDACTED]. Reply, 8-12. Petitioner misconstrues Dr. Bollinger’s testimony as indicating that any amino-acid substitution was “chosen well” if it did not place a proline or glycine at a secondary-structure location. *Id.*, 10. To the

contrary, Dr. Bollinger detailed the principles skilled artisans used in making function-conserved variants in his declaration:

1. Maintain high sequence identity in view of the known sequence-function correlations for enzymes;
2. Maintain the active-site motif;
3. Retain other non-motif residues that are highly conserved across related enzymes (e.g., as shown in Figure 2 of the '055 patent); and
4. Retain surface charge distribution and steric bulk.

Ex. 2011, ¶¶ 56, 123-128. Dr. Bollinger had to repeatedly correct and remind counsel of these principles during questioning, which Petitioner omitted from its Reply. *E.g.*, Ex. 1043, 147:3-9 (proline and glycine substitutions are “not two principles. The principles are mapped in my declaration”), 146:14-147:2 (“I think the declaration illustrates well how the patent provides the guidance to [make AAD-12 variants].”). Moreover, these principles are undisputed, as Dr. Silverstone nowhere addressed them. *See* Ex. 1045.

As shown

[REDACTED]. Dr. Bollinger testified without rebuttal that such strictly conserved residues are “presumptively structurally and functionally important” and skilled artisans would “generally avoid making substitutions to those strictly conserved residues.” Ex. 2011, ¶ 125; Ex. 1043, 151:6-17. [REDACTED]

[REDACTED]

[REDACTED] Ex. 2025, 204-05; Ex. 2044, 3812 (changing highly conserved residues is generally “deleterious to protein function”); Ex. 1045, ¶ 15.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

|                           |  |
|---------------------------|--|
| '055 Pat. Fig. 2 position |  |
| TauD                      |  |
| Elkins sec. structures    |  |
| AAD-12 position           |  |
| AAD-12 (SEQ ID NO:2)      |  |
|                           |  |

[REDACTED] Dr. Bollinger testified without rebuttal that such conserved residues may tolerate conservative changes to similar amino acids but are “preferentially left unsubstituted.” Ex. 1043, 123:5-124:4, 139:12-140:18, 150:11-19, 153:16-154:14; Ex. 2011, ¶ 126. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (written description requires evaluating the *specification’s* guidance); *Allergan, Inc. v. Sandoz*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (similarly holding that enablement turns on whether a skilled artisan, “after reading the *specification*, would be able to make and use the claimed invention”).

[REDACTED]

[REDACTED] The specification provides guidance on *where* and *what types* of substitutions to make to conserve function. Ex. 2011, ¶¶ 123-128 (citing Ex. 1001, Fig. 2), ¶¶ 44-57;

Ex. 1043, 168:14-20. Such guidance, lacking in the *AbbVie* and *PureCircle* cases Petitioner cites, strongly supports written description. *See Lifescan*, PGR2019-00032, Paper 11 at 26, 30 (crediting testimony that a skilled artisan could make a “fair guess” about conserving or not conserving enzyme function based on sequence modifications).

Petitioner also misconstrues Dr. Bollinger’s positions regarding 75% of AAD-12 variants having the dual herbicide-degrading activity. Reply, 10, 1. Petitioner omits that its question asked Dr. Bollinger to focus on changing amino acids that are *not shaded*—i.e., not conserved—in Figure 2 of the ’055 patent. Ex. 1043, 142:18-143:5 (“Q. So take a hypothetical where a POSA focuses almost exclusively on changing amino acids here that are not shaded....”). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Ex. 2011, ¶¶ 123-128, 44-57; Ex. 1043, 142:5-17.

Petitioner further overreaches with its [REDACTED]

[REDACTED]

[REDACTED] an issue Petitioner could have addressed by asking Dr. Bollinger during his deposition. But Petitioner never did so.

Petitioner's arguments about the AAD-12 variants, which lack any support from Dr. Silverstone and inaccurately characterize Dr. Bollinger's testimony, thus boil down to bare attorney argument that cannot support Petitioner's written-description challenge. *Icon Health*, 849 F.3d at 1043 (attorney argument "is not evidence").

**B. The AAD-12 Motif Is Correlated to the Claimed Function**

Petitioner's written-description challenge also fails for the independent reason that the AAD-12 motif is a disclosed function-correlated structure. Each of Petitioner's arguments regarding the motif is incorrect.

Involvement in herbicide degradation: Contrary to Petitioner's position, there is ample, undisputed evidence that the AAD-12 motif is "involved in degrading" both classes of herbicides. Reply, 3. The specification expressly describes the motif as the enzyme's "active site." Ex. 1001, 11:1-6, 14:8-13, 20:23-34 (changes to the "active site" affect functionality). As Dr. Bollinger explained without rebuttal, the AAD-12 motif residues and spacing determine the contours of the enzyme's active site, which accommodates the herbicide substrate, the Fe<sup>2+</sup> co-factor, and the  $\alpha$ KG and O<sub>2</sub> co-substrates required for the dual herbicide-degrading oxidation reaction to occur. Ex. 1043, 203:2-19, 177:8-178:2, 20:1-10; Ex. 1001, 6:46-55, Fig. 1 (reaction diagram depicting oxidation of the herbicide into a phenol and a glyoxylate).

Herbicide binding: Petitioner criticizes the motif residues for not directly binding herbicide substrates (Reply, 3), but fails to address the *degrading* activity recited in the claims. Petitioner does not dispute that the active site defined by the AAD-12 motif residues accommodates the required reactants for the herbicide-*degrading* activity. Further, Dr. Bollinger testified that AAD-12's active site motif is unique and correlated to function, as the "location and spacing of the motif residues differ from those in other  $\alpha$ KG-dependent dioxygenases having different substrate specificities." Ex. 2011, ¶¶ 154-156 ("skilled artisans understood that *active site* residues are, as their name reflects, correlated to an enzyme's *activity*"); Ex. 1043, 211:21-212:22, 22:18-22 (a "motif" is a stretch of amino acids that "relates to a function"). Indeed, Petitioner identifies *no enzyme* having different spacing that retains the AAD-12 dual herbicide-degrading function. Dr. Bollinger's testimony that the claimed function is quite sensitive to the amino acid spacers required by the claims is undisputed. Ex. 1043, 177:8-181:4; Ex. 2011, ¶ 112.

Unclaimed features: Petitioner asserts that the spacing of motif residues in various enzymes is not correlated to their *relative magnitude of 2,4-D degrading activity*. Reply, 5-8; *see also id.*, 16-17 (advancing similar arguments regarding *magnitude* of triclopyr degrading activity). But the claims do not require any relative magnitude of activity compared to other enzymes—they only require "enzymatically degrad[ing] a phenoxy auxin herbicide and a pyridyloxy auxin herbicide." Ex. 1001,

claim 1; Ex. 1044, 70:5-18; Ex. 2098, 25:20-30:20.<sup>1</sup> Petitioner cites no authority requiring correlation to unclaimed activity levels. *See Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014) (rejecting similar arguments for nonenablement where the claims did “not require a particular level ... or a particular magnitude of increase”); *cf. Ajinomoto*, 932 F.3d at 1360 (requiring correlation to “stronger” promoter activity where the claims required stronger activity).

Petitioner’s reliance on Dr. Bollinger’s testimony that the different motif spacing of TfdA and AAD-2 (i.e., two *unclaimed* enzymes) had a “lame correlation” to *magnitude* (also *unclaimed*) of 2,4-D degrading activity is thus misplaced and fails to support its case. Ex. 1043, 81:11-18.

[REDACTED]

[REDACTED], just as Dr. Bollinger testified a skilled artisan would have expected. Ex. 2011, ¶ 56; Ex. 2025, 204-05 (“changes at key active site residues ... are generally deleterious”); Ex. 2098, 43:7-45:13. [REDACTED]

[REDACTED]

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<sup>1</sup> As Dr. Bollinger repeatedly explained during cross-examination, but Petitioner omitted from its Reply, mixing-and-matching of data from different *in vitro* experimental conditions to calculate and compare efficiency constants is also unreliable. Ex. 1043, 74:17-75:16, 76:6-15, 78:4-10.

[REDACTED]

[REDACTED]

[REDACTED]

Ex. 1043, 171:4-12; Reply, 10-11.

Petitioner thus fails to establish that the AAD-12 motif is uncorrelated to the claimed function. POR, 77-78; *Ajinomoto*, 932 F.3d at 1360-61.

**C. Petitioner Applies an Incorrect Legal Standard for Function-Related Common Structure**

As Corteva's Response explained, the law requires only a *relationship* between structure and function—i.e., a reasonable correlation—rather than the higher standard Petitioner seeks to impose by demanding that the common structures must be *necessary* or *sufficient* for that function. POR, 76-80. Petitioner did not respond to Corteva's argument and incorrectly continues to advance positions inconsistent with controlling law.

For example, Petitioner challenges the correlation of function and the AAD-12 motif—HX<sub>109</sub>D(X)<sub>111-134</sub>T(X)<sub>136-261</sub>H(X)<sub>263-272</sub>R—by arguing that

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] the law is to the contrary. *Lifescan*, PGR2019-00032, Paper 11 at 29

(finding adequate written description where a motif “or some close variation thereof” supported the claimed function); *Ajinomoto*, 932 F.3d at 1360 (finding adequate written description where a sequence generally—*but not always*—closer to a consensus sequence was more likely to exhibit the claimed function).

Petitioner also argues that the specification must explain [REDACTED]. Here again, the law is to the contrary. *Lifescan*, PGR2019-00032, Paper 11 at 23 (“Nor does the law require that the POSA be able to predict each species encompassed within a claim that would have the required characteristics.” (citing *In re Angstadt*, 537 F.2d 498, 503 (CCPA 1976))); *PureCircle*, No. 22-1946, 2024 WL 20567, \*4 n.10 (Fed. Cir. 2024) (for common structure, perfect correspondence is not required and reasonable testing is allowed). Petitioner’s focus on [REDACTED] reflects its legally deficient attempt to impose a “perfect correspondence” standard for common structure. *Ajinomoto*, 932 F.3d at 1360.

Petitioner also fails to distinguish Corteva’s supporting case law. Petitioner does not identify any meaningful difference between its purely mathematical numerosity theory and the similar theory rejected in *Lifescan*. PGR2019-00032, Paper 11 at 30 (rejecting petitioner’s conclusory argument that it would be impossible to “predict the behavior” of  $5 \times 10^{76}$  sequences). Petitioner also incorrectly

seeks to distinguish *Ajinomoto* by asserting that the '055 patent “discloses no methodology” for measuring whether variants have the dual herbicide-degrading activity. Reply, 12. Petitioner overlooks the routine assays the '055 patent discloses, which had been used in the field since as early as 1993, as well as available *in vivo* techniques. Ex. 2011, ¶¶ 86, 143-144; Ex. 1043, 199:22-200:1; Ex. 2012, ¶ 69.

Petitioner's reliance on *PureCircle* is also misplaced. Reply, 3-4. The claims in that case lacked any structural limitations and thus would have required sifting through an *unlimited* sequence space to locate functional enzymes—a far cry from the narrow, *highly identical* space of at least 85% identity to SEQ ID NO: 2 and the active-site motif present here. Ex. 2011, ¶¶ 149-154, 93-104; *PureCircle*, 2024 WL 20567 at \*4 (explaining that the functionally defined claims encompassed enzymes lacking common structures). Petitioner's argument that the AAD-12 motif is not involved in the claimed herbicide degradation is incorrect as discussed above. *Supra* Section III.B.

#### **D. Petitioner's Representative-Species Challenge Fails**

Corteva's Response explained that the claimed genus of AAD-12 enzymes is essentially the opposite of a structurally or functionally diverse genus—it is a group of *highly identical* enzymes with a conserved active-site motif. POR, 82-83. The disclosed AAD-12 species are thus amply representative of the genus of AAD-12 enzymes, which are all of a similar type. *Idenix Pharms. LLC v. Gilead Scis. Inc.*,

941 F.3d 1149, 1165 (Fed. Cir. 2019) (the law “allow[s] relatively few representative examples or formulas to support a claim on a structurally similar genus”).

As detailed above, Petitioner fails to establish that any structure-function diversity exists within 85% identity to SEQ ID NO: 2. *Supra* Section III.A.1. Instead, Petitioner repeats its incorrect arguments about the AAD-12 variants and unclaimed *magnitudes* of herbicide-degrading activity. Reply, 15-17. Petitioner thus fails to establish that the disclosed AAD-12 variants are not representative of the claimed genus.

#### **IV. Petitioner Fails to Establish Lack of Enablement**

##### **A. The '055 Patent Discloses and Claims Qualities Common to the AAD-12 Enzymes of the Challenged Claims**

For qualities common to the claimed AAD-12 enzyme genus, Petitioner presents no unique arguments compared to its written-description positions. Instead, Petitioner repeats its incorrect arguments about the sequence-function enzymology studies (*see supra* Section III.A.2), the AAD-12 motif (*see supra* Section III.B) and the AAD-12 variants (*see supra* Section III.A.3). For the reasons detailed above, Petitioner’s arguments are legally and factually incorrect and fail to demonstrate that the disclosed and claimed requirements of at least 85% sequence identity to SEQ ID NO: 2 and the AAD-12 motif lack correlation to the claimed dual-herbicide degrading activity. Ex. 1001, 31:61-32:6, 21:41-60 (disclosing making enzymes having “the same or similar activity” at identities of 85% and higher); POR, 35-36.

Petitioner does not dispute that once a general quality common to AAD-12 enzymes was established, nothing further would be required to satisfy the enablement requirement. *See* Reply, 17-18; *Amgen Inc. v. Sanofi*, 598 U.S. 594, 611 (2023) (“it may suffice to give *an example* ... if the specification also discloses ‘some general quality ... running through’ the class” (citation omitted)). Indeed, Dr. Silverstone does not dispute that it was routine to make enzyme variants using known techniques, as Dr. Bollinger testified. Ex. 2011, ¶ 129. Nor did he rebut Dr. Christou’s testimony that as of 2005-2006, using AAD-12 genes to produce transgenic plants (e.g., via biolistics) would have been routine and that none of the commercial-development activities Dr. Silverstone relied upon were necessary. Ex. 2012, ¶¶ 113-128; POR, 19, 64-70.

Accordingly, the at least 85% sequence identity and AAD-12 motif are structural qualities correlated to the claimed function and common to the genus of AAD-12 enzymes, satisfying the enablement requirement.

**B. Petitioner’s *Wands* Analysis Is Factually and Legally Deficient**

**1. Level of Skill and Claim Scope (Factors 4, 6, 8)**

Corteva’s Response detailed how Petitioner legally erred by ignoring a skilled artisan’s knowledge of enzymology. POR, 47; 35 U.S.C. § 112 (enablement is assessed from the perspective of one “skilled in the art”). Petitioner provided no response. *See* Reply, 27.

Instead, Petitioner continues pursuing its mathematical numerosity theory, arguing that practicing the full scope of the claims would require “the testing of all proteins” satisfying the claims’ structural requirements. Reply, 19, 22, 25. That is legal error. *Amgen*, 598 U.S. at 615 (“enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim”).

The deficiencies of Petitioner’s enablement challenge are exacerbated by its legally incorrect gap-filling argument, which seeks to avoid consideration of known techniques for making enzymes. Reply, 26-27. From the perspective of a skilled enzymologist—which Dr. Silverstone is unqualified to address—it would have been routine to produce large numbers of AAD-12 variants that maintain function using the guidance of the specification and known techniques, such as directed evolution. POR, 61-62; Ex. 2011, ¶¶ 55; Ex. 1043, 161:11-17 (“It’s not a difficult exercise”), 136:12-138:1, 44:11-45:10, 206:2-209:18. Directed evolution is one of the techniques disclosed in the specification, and Dr. Bollinger explained how computer programs (e.g., SIFT) could further assist skilled artisans, which Petitioner describes as showing that over half of the residues in SEQ ID NO: 2 are amenable to substitution to 17 or more different amino acids. Ex. 1001, 28:54-30:9, Fig. 2; Ex. 1045, ¶ 17; Ex. 1043, 156:11-20, 163:5-20; Ex. 2098, 35:21-36:7, 37:9-40:6. Petitioner thus fails to establish that any gap-filling would have been necessary, particularly where those techniques could be used to routinely produce AAD-12

variants but *are not themselves the invention claimed*. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (enablement requires disclosure of only one mode of making and using the invention).

## **2. The Specification's Guidance and Examples (Factors 2, 3, 5)**

Contrary to Petitioner's arguments, the '055 patent's guidance is far greater than in *Baxalta* and *Amgen*. Reply, 24-26. As detailed above, the '055 patent amply discloses to skilled artisans the *number* and *types* of amino-acid substitutions to make, and guides them on *where* to make or avoid such mutations within SEQ ID NO: 2. Ex. 2011, ¶¶ 123-128; Ex. 1001, 21:42-60, 11:1-14, 20:23-34, 28:57-60, Fig. 2. Indeed, as Dr. Bollinger testified without rebuttal, Figure 2 identifies residues that will likely tolerate a broad range of substitutions as well as highly conserved residues where substitutions should be restricted or avoided. Ex. 2011, ¶¶ 123-128. Neither *Baxalta* nor *Amgen* involved such detailed guidance, instead leaving it to skilled artisans to broadly explore an *unlimited* antibody sequence space without any identified residues analogous to the AAD-12 motif here. *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1366 (Fed. Cir. 2023) (concluding, as in *Amgen*, that requiring artisans to immunize mice, generate hybridomas, and screen the resulting antibodies for desired results without structural guidance was insufficient).

**3. The Amount of Experimentation Would Not Have Been Undue (Factors 1, 7)**

Petitioner fails to identify any aspect of making and using the claimed invention that was beyond the exercise of routine skill. *Cephalon Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338 (Fed. Cir. 2013) (mere “repetition of known or commonly used techniques” fails to establish nonenablement).

Petitioner repeats its [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Ex. 2011,

¶ 101; Ex. 1043, 142:1-17, 149:5-15.

Petitioner also incorrectly alleges that the '055 patent's *in planta* visual-injury analyses could not detect herbicide-degrading activity for variants having 1-2% *in vitro* activity on triclopyr compared to wild-type AAD-12. Reply, 22-23. Even Dr. Silverstone does not support Petitioner's argument. *See* Ex. 1045. Petitioner presents no evidence that 1-2% of the activity of a strong, commercial-level

herbicide-tolerance enzyme like AAD-12 would fail to demonstrate herbicide resistance, particularly when used with a suitable promoter to drive expression. Ex. 2012, ¶¶ 30-45, 103-104, 138-139 (skilled artisans routinely selected appropriate promoters to increase expression in plants); Ex. 1044, 125:12-18.

Accordingly, either under a common-quality analysis or under the *Wands* factors, Petitioner has failed to establish lack of enablement.

#### **V. Petitioner Failed to Address the Issues the Board Raised at Institution**

In its Response, Corteva replied to the issues the Board raised in its Institution Decision. POR, 29-30. Petitioner did not. With a full trial record, all of those issues weigh in Corteva’s favor and support upholding patentability.

*First*, the Board invited testing the strength of Dr. Silverstone’s testimony. ID, 37. Dr. Silverstone has now been shown to have *no expertise* regarding enzymology—i.e., the focus of Petitioner’s written-description and enablement challenges. POR, 31-33. In his reply declaration, he failed to address his lack of enzymology experience and his omission of enzymology from the level of skill he relied upon. *See* Ex. 1045.

*Second*, the Board questioned whether a skilled artisan would have been “able to predict” whether an AAD-12 enzyme at about 85% identity to SEQ ID NO: 2 would retain the function of degrading the recited herbicides. ID, 52, 55; *see id.*, 39, 36 (stating, on a preliminary record, that it was “unclear” how far AAD-12 enzymes

can deviate in sequence from SEQ ID NO: 2). Dr. Bollinger, the only enzymologist to testify in this proceeding, confirmed that skilled artisans would have reliably been able to make AAD-12 variants having 85% or higher identity to SEQ ID NO: 2, just as the '055 patent discloses. Ex. 2011, ¶¶ 44-57, 123-128, 160-161; Ex. 1001, 21:41-60, 32:1-6, Fig. 2; Ex. 2019, 863 (disclosing that only “60% sequence identity is needed to have at least 90% accuracy” in conserving function); Ex. 1044, 147:17-149:18. [REDACTED]

[REDACTED]

[REDACTED]

*Third*, the Board questioned whether the location and spacing of the AAD-12 motif residues differed compared to other  $\alpha$ KG-dependent dioxygenases. ID, 37. On a full record, it is now undisputed that the AAD-12 motif is indeed different compared to the motif in other  $\alpha$ KG-dependent dioxygenases, which lack the dual herbicide-degrading activity. POR, 41-45; *supra* Section III.B. That is ample evidence of structure-function correlation. *Ajinomoto*, 932 F.3d at 1360-61; Ex. 1043, 211:21-212:22, 22:18-22, 177:8-179:10.

## **VI. Conclusion**

Corteva respectfully requests that the Board terminate this proceeding for lack of jurisdiction or confirm the patentability of all challenged claims of the '055 patent.

Respectfully submitted,

Dated: June 10, 2024

/Pier D. DeRoo/

Pier D. DeRoo

Reg. No. 69,340

**CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24(d), I, Pier D. DeRoo, certify that **Patent Owner's Sur-Reply** contains 5,418 words, excluding those portions identified in 37 C.F.R. § 42.24(c), as measured by the word-processing system used to prepare this paper.

Dated: June 10, 2024

/Pier D. DeRoo/  
Pier D. DeRoo  
Reg. No. 69,340

**CERTIFICATE OF SERVICE**

The undersigned certifies that a copy of the foregoing **Patent Owner's Sur-Reply** was served electronically via email on June 10, 2024, in its entirety on the following:

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