UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INARI AGRICULTURE, INC.,
Petitioner,

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

Case No. PGR2023-00022
Patent No. 11,371,055

**PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE**

## TABLE OF CONTENTS


I. GROUND 1: CLAIMS 1-33 LACK WRITTEN DESCRIPTION SUPPORT ..... 2

A. The '055 Patent Fails to Disclose a Structure-Function Correlation. ..... 2

1. Corteva Fails to Identify Any Evidence That the So-Called "AAD-12 Motif" Is Correlated with the Claimed Dual Herbicide-Degrading Functionality. ..... 2

a. The AAD-12 Motif Residues Are Not Correlated to Functionality. ..... 3

b. The AAD-12 Motif Is Not Necessary to Functionality. ..... 4

c. The AAD-12 Motif's Fixed Spacing Is Not Correlated to Functionality. ..... 5

2. [redacted], Confirming the Lack of a Structure-Function Correlation. ..... 8

3. Corteva's Enzyme Literature Is Inapposite ..... 13

B. The Two Near-Identical Embodiments Disclosed in the '055 Patent Are Not Representative of the $10^{106}$ Claimed Species. ..... 15

II. GROUND 2: THE FULL SCOPE OF CLAIMS 1-33 IS NOT ENABLED ..... 17

A. The '055 Patent Fails to Disclose Qualities Common to the Claimed AAD-12 Enzymes. ..... 17

B. The *Wands* Factors Confirm the Challenged Claims Are Not Enabled. ..... 19

1. Factors 4 and 8: The Scope of the Claims Is Undisputedly "Astronomical" ..... 19

2. Factors 1 and 7 ..... 20

a. The Incorrect Predictions of Corteva's Experts Demonstrate Undue Experimentation and Unpredictability. ..... 20

b. [redacted] Contribute to Undue Experimentation. ..... 22

3. Factors 2, 3, and 5 .....24
a. Insufficient Guidance and Working Examples in the Specification.....24
b. Corteva Improperly Relies on the Purported Knowledge of a POSA To Fill Gaps. .....26
4. Factor 6: Level of Skill in the Art .....27
III. CONCLUSION.....27

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*Ajinomoto Co. v. Int'l Trade Comm'n*,
932 F.3d 1342 (Fed. Cir. 2019) ..... 12, 16

*ALZA Corp. v. Andrx Pharms., LLC*,
603 F.3d 935 (Fed. Cir. 2010) .....20

*Amgen Inc. v. Sanofi*,
598 U.S. 594 (2023)..... 21, 25

*Amgen Inc. v. Sanofi*,
872 F.3d 1367 (Fed. Cir. 2017) ..... 4, 20

*Ariad Pharm., Inc. v. Eli Lilly & Co.*,
598 F.3d 1336 (Fed. Cir. 2010) (en banc) .....4

*Baxalta Inc. v. Genentech, Inc.*,
81 F.4th 1362 (Fed. Cir. 2023) ..... 20, 21, 24

*Idenix Pharms. LLC v. Gilead Sciences Inc.*,
941 F.3d 1149 (Fed. Cir. 2019) ..... 19, 20, 22, 26

*Lifescan Glob. Corp. v. Ikeda Food Rsch., Ltd.*,
PGR2019-00032, Paper 11 (PTAB Aug. 15, 2019) ..... 11, 12

*Pacific Biosciences of California, Inc. v. Oxford Nanopore Techs., Inc.*,
996 F.3d 1342 (Fed. Cir. 2021) .....21

*PureCircle USA Inc. v. SweeGen, Inc.*,
No. 2022-1946, 2024 WL 20567 (Fed. Cir. Jan. 2, 2024)..... 3, 16

## APPENDIX LISTING OF EXHIBITS

| Exhibit | Description |
|---|---|
| 1001 | U.S. Patent No. 11,371,055 ("'055") |
| 1002 | File History of U.S. Patent No. 11,371,055 |
| 1003 | Declaration of Dr. Aron Silverstone ("Silverstone Decl.") |
| 1004 | Corteva Agriscience – Technology Use Agreement (8/2022) (https://www.corteva.us/content/dam/dpagco/corteva/na/us/en/files/ trait-stewardship/DOC-Corteva-Technology-Use-Agreement-WATERMARK-NONEXECUTABLE-COPY.pdf) |
| 1005 | Wright, T.R. et al., Robust crop resistance to broadleaf and grass herbicides provided by aryloxyalkanoate dioxygenase transgenes, PNAS 107 (47) 20240-20245 (11/23/2010) (https://doi.org/10.1073/pnas.1013154107) |
| 1006 | *Enlist™ Herbicide Tolerance and Soybean Symptomology - Get the Facts* (https://www.enlist.com/en/News/enlist-tolerance-soybean-symptomology.html) (7/13/2021) |
| 1007 | *Director's Blog: the latest from USPTO leadership: Increasing transparency, boosting competition, and supporting innovation can deliver better choices for farmers in the seed marketplace* (https://www.uspto.gov/blog/director/entry/increasing- transparency-boosting-competition-and) (3/7/2023) |
| 1008 | *Executive Order on Promoting Competition in the American Economy* (https://www.whitehouse.gov/briefing-room/presidential-actions/2021/07/09/executive-order-on-promoting-competition-in- the-american-economy/) (7/9/2021) |
| 1009 | U.S. Department of Agriculture: *More and Better Choices for Farmers: Promoting Fair Competition and Innovation in Seeds and Other Agricultural Inputs, A report directed by President Biden'sExecutive Order Number 14036: "Promoting Competition in America's Economy"* (https://www.ams.usda.gov/sites/default/files/media/SeedsReport.p df) (3/2023) |
| 1010 | Declaration Under 37 C.F.R. §1.132 of Dr. Terry R. Wright (7/29/2021) |
| 1011 | Corteva Agriscience: Enlist 1 Herbicide Label (https://www.corteva.ca/content/dam/dpagco/corteva/na/ca/en/files/ products/label/DF-Enlist-1-Herbicide-Label-English.pdf) |

| Exhibit | Description |
|---|---|
| 1012 | Corteva Agriscience: Enlist Duo Herbicide Label (https://www.corteva.ca/content/dam/dpagco/corteva/na/ca/en/files/products/label/DF-Enlist-Duo-Herbicide-Label-English.pdf) |
| 1013 | Anjanappa, R.B. and Gruissem, W., 2021. Current progress and challenges in crop genetic transformation. Journal of Plant Physiology, 261, 153411. |
| 1014 | Herman, P.L., Behrens, M., Chakraborty, S., Chrastil, B.M., Barycki, J. and Weeks, D.P., 2005. A three-component dicamba O- demethylase from Pseudomonas maltophilia, strain DI-6: gene isolation, characterization, and heterologous expression. *Journal of Biological Chemistry*, *280*(26), pp.24759-24767 |
| 1015 | Chekan, Jonathan R, et al. "Molecular basis for enantioselective herbicide degradation imparted by aryloxyalkanoate dioxygenases in transgenic plants." Proceedings of the National Academy of Sciences 116.27 (2019): 13299-13304. |
| 1016 | Englander, S.W. and Mayne, L., 2014. The nature of protein folding pathways. Proceedings of the National Academy of Sciences, 111(45), pp.15873-15880. |
| 1017 | Gao SS, Naowarojna N, Cheng R, Liu X, Liu P. Recent Examples of α-Ketoglutarate-Dependent Mononuclear Non-Haem Iron Enzymes in Natural Product Biosyntheses. Nat Prod Rep. 2018 Aug. 15; 35(8): 792–837. |
| 1018 | Peach C, Velten J. Transgene expression variability (position effect) of CAT and GUS reporter genes driven by linked divergent T-DNA promoters. Plant Mol Biol. 1991;17(1):49-60. |
| 1019 | Hogan, D.A., Smith, S.R., Saari, E.A., McCracken, J. and Hausinger, R.P., 2000. Site-directed Mutagenesis of 2, 4- Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase: IDENTIFICATION OF RESIDUES INVOLVED IN METALLOCENTER FORMATION AND SUBSTRATE BINDING. Journal of Biological Chemistry, 275(17), pp.12400- 12409. |
| 1020 | Müller, T.A., Zavodszky, M.I., Feig, M., Kuhn, L.A. and Hausinger, R.P., 2006. Structural basis for the enantiospecificities of R- and S-specific phenoxypropionate/α-ketoglutarate dioxygenases. Protein Science, 15(6), pp.1356-1368. |

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| 1021 | Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, Tunyasuvunakool K, Bates R, Žídek A, Potapenko A, Bridgland A, Meyer C, Kohl SAA, Ballard AJ, Cowie A, Romera-Paredes B, Nikolov S, Jain R, Adler J, Back T, Petersen S, Reiman D, Clancy E, Zielinski M, Steinegger M, Pacholska M, Berghammer T, Bodenstein S, Silver D, Vinyals O, Senior AW, Kavukcuoglu K, Kohli P, Hassabis D. Highly accurate protein structure prediction with AlphaFold. Nature. 2021 Aug.;596(7873):583-589. |
| 1022 | Bagdonas, H., Fogarty, C.A., Fadda, E. and Agirre, J., 2021. The case for post-predictional modifications in the AlphaFold Protein Structure Database. Nature Structural & Molecular Biology, 28(11), pp.869-870. |
| 1023 | Müller, TA, Fleischmann, T, van der Meer, JR and Kohler, HPE, Purification and characterization of two enantioselective α-ketoglutarate-dependent dioxygenases, RdpA and SdpA, from Sphingomonas herbicidovorans MH. Applied and environmental microbiology, 2006. 72(7), pp.4853-4861. |
| 1024 | Prabakaran, S., Lippens, G., Steen, H. and Gunawardena, J., 2012. Post-translational modification: nature's escape from genetic imprisonment and the basis for dynamic information encoding. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 4(6), pp.565-583. |
| 1025 | Streber, W.R., Timmis, K.N. and Zenk, M.H., 1987. Analysis, cloning, and high-level expression of 2, 4-dichlorophenoxyacetate monooxygenase gene tfdA of Alcaligenes eutrophus JMP134. Journal of Bacteriology, 169(7), pp.2950-2955. |
| 1026 | Brannigan, J.A. and Wilkinson, A.J., 2002. Protein engineering 20 years on. Nature Reviews Molecular Cell Biology, 3(12), pp.964- 970. |
| 1027 | Westendorf, A, Müller, RH, Babel, W, Purification and characterisation of the enantiospecific dioxygenases from Delftia acidovorans MC1 initiating the degradation of phenoxypropionate and phenoxyacetate herbicides. Acta biotechnologica, 2003. 23(1), pp.3-17. |
| 1028 | Levels of Protein Organization (https://comis.med.uvm.edu/VIC/coursefiles/MD540/MD540-Protein_Organization_10400_574581210/Protein-org/index.html) |
| 1029 | Corteva Agriscience Enlist Weed Control System 2020 Product Use Guide (https://www.enlist.com/content/dam/hdas/enlist/pdfs/Enlist_Product_Use_Guide_2020.pdf) |

| Exhibit | Description |
|---|---|
| 1030 | NASA JPL, Genesis – Search for Origins, A Public Outreach Module: Atoms, Elements, and Isotopes (https://solarsystem.nasa.gov/genesismission/science/mod2_aei/index.html) |
| 1031 | Oxford University Press, Oxford Education Blog, Number of Atoms in the Universe (https://educationblog.oup.com/secondary/maths/numbers-of- atoms-in-the-universe) |
| 1032 | Declaration of Jonathan Bradford |
| 1033 | Nelson, D.L, and Cox, M.M., 2005. Lehninger Principles of Biochemistry, 4th edition, pp.116-156. |
| 1034 | Mall, T., Gupta, M., Dhadialla, T.S. and Rodrigo, S., 2019. Overview of biotechnology-derived herbicide tolerance and insect resistance traits in plant agriculture. Transgenic plants: methods and protocols, pp.313-342. |
| 1035 | Scan of Physical Copy of Exhibit 1034 [**SUPPLEMENTAL EVIDENCE – NOT FILED**] |
| 1036 | Scan of Physical Copy of Exhibit 1033 [**SUPPLEMENTAL EVIDENCE – NOT FILED**] |
| 1037 | [Reserved] |
| 1038 | Declaration of Eric J. Rutt in support of motion for *pro hac vice* |
| 1039 | [Reserved] |
| 1040 | [Reserved] |
| 1041 | [Reserved] |
| 1042 | Todd et al., *Evolution of Function in Protein Superfamilies, from a Structural Perspective*, 307 J. MOL. BIOL. 1113-43 (2001) ("Todd"). |
| 1043 | Transcript from Deposition of Dr. Bollinger (Feb. 29, 2024) |
| 1044 | Transcript from Deposition of Dr. Christou (Mar. 5, 2024) |
| 1045 | Reply Declaration of Dr. Aron Silverstone ("Reply-Silverstone") |

The experimental evidence Corteva submitted with its POR and its experts' deposition testimony confirms that Claims 1-33 of the '055 patent ("the Challenged Claims") are unpatentable for lack of written description and enablement.

Corteva's experts based their declaration testimony on the incorrect assumption that the claimed structural limitations (i.e., the AAD-12 motif and at least 85% sequence identity) are correlated to the claimed dual herbicide-degrading functionality. The evidence shows no such correlation exists. Dr. Bollinger admitted the AAD-12 motif's five conserved residues do not bind to the claimed herbicides. He also called any connection between motif spacing and herbicide-degrading ability "a pretty lame correlation." Ex. 1043 ("Bollinger Dep."), 81:11-17.

Corteva's experimental evidence (Exs. 2084-2095) emphasizes the absence of a structure-function correlation. . Ex. 2092 at 8. Dr. Bollinger nevertheless testified to the opposite, i.e., that at least 75% of AAD-12 variants would ***have*** the claimed functionality;

More troubling is that the entire premise of Corteva's structure-function argument is baseless. Its argument has nothing to do with the claimed genus of transgenic AAD-12 enzyme variants. Rather, Corteva attempts a sleight of hand by focusing on studies of unrelated enzymes. The studies exclude enzymes that perform multiple functions and are limited to enzymes produced by natural evolution that

have a known function. By contrast, the claimed AAD-12 variants are multi-functional, transgenic (i.e., not produced by natural evolution), and mostly nonfunctional.

Without a structure-function correlation to identify functional AAD-12 variants, a POSA could not have recognized the claimed genus without undue experimentation. Instead, a POSA would have had to make and test each variant to assess relevant functionality. Moreover, the two AAD-12 enzymes disclosed in the '055 patent are 99.3% identical; they are not representative of the broad claim scope, which undisputedly encompasses $10^{106}$ variants having the claimed structure.

Accordingly, claims 1-33 should be cancelled as lacking written description and enablement.

## I. GROUND 1: CLAIMS 1-33 LACK WRITTEN DESCRIPTION SUPPORT

### A. The '055 Patent Fails to Disclose a Structure-Function Correlation.

#### 1. Corteva Fails to Identify Any Evidence That the So-Called "AAD-12 Motif" Is Correlated with the Claimed Dual Herbicide-Degrading Functionality.

Corteva's written description theory rests on its assumption that "the structural AAD-12 motif and 85% sequence identity features of the claims are each common structures correlated to the claimed function." POR, 76. This argument fails.

[redacted]

### a. The AAD-12 Motif Residues Are Not Correlated to Functionality.

Corteva and its experts offer no evidence the AAD-12 motif's five conserved residues are involved in degrading either class of herbicides (i.e., phenoxy and pyridyloxy) recited in the Challenged Claims. Corteva's expert, Dr. Bollinger, admitted that even today (let alone in 2005) it is not known which of AAD-12's 292 residues bind to 2,4-D or triclopyr (Bollinger Dep., 37:22-24, 38:21-23, 39:8-14), which are phenoxy and pyridyloxy herbicides, respectively, described in the '055 patent (Ex. 1001, 2:45-54, Tables 10, 11, 13, 18, 19, 28). Dr. Bollinger admitted that rather than binding to herbicides the AAD-12 motif's five residues bind to alpha-ketoglutarate ("αKG") and to iron. Bollinger Dep., 32:16-33:2, 33:16-34:1.

Dr. Bollinger's testimony suffers the same infirmities the Federal Circuit identified in *PureCircle*, where he also served as the patent owner's expert on written description. Analogous to the patent in *PureCircle*, the '055 patent discloses a "motif" but "does not identify which part of the amino acid sequence is necessary for the [claimed] function of the enzyme" because, as Dr. Bollinger admits, the amino acids that bind to phenoxy and pyridyloxy herbicides remain unknown. *PureCircle USA Inc. v. SweeGen, Inc.*, 2024 WL 20567, at *4 (Fed. Cir. Jan. 2, 2024). Corteva attempts to distinguish *PureCircle* on the ground that the claims "contained no sequence limitations and a skilled artisan would need to empirically determine the active site's location." POR, 78. Of course the same is true here: the '055 patent

does not identify the active site residues involved in the claimed herbicide degradation.

**b. The AAD-12 Motif Is Not Necessary to Functionality.**

Experimental data submitted by Corteva show the AAD-12 motif is not even "necessary" to the claimed dual herbicide-degrading functionality, as Corteva suggests.[1] POR, 74. . Ex. 2085 at 2, 5-7; Ex. 2089; 2095 at 3. . Ex. 2089 at 1. . Ex. 2089 at 1; Ex. 2095 at 3.

[1] Corteva's experimental data regarding AAD-12 variants, dated 2020 (Ex. 2092 at 1), is relevant to showing ***lack*** of written description. "[P]ost-priority-date evidence of a particular species can reasonably bear on whether a patent 'fails to disclose a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus.'" *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017) (*quoting Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)).

[redacted]. Ex. 2089 at 1; Ex. 2095 at 3. [redacted] (Ex. 2092 at 6) [redacted] (Ex. 2092 at 8).

Dr. Bollinger had not reviewed Corteva's experimental data. Bollinger Dep., 179:3-10 ("I have yet to see any protein that doesn't conform to that motif … and has activity"). [redacted]

In sum, the so-called "AAD-12 motif" is not necessary to the claimed dual herbicide-degrading functionality, and Corteva's data contradicts Dr. Bollinger's predictions to the contrary.

**c. The AAD-12 Motif's Fixed Spacing Is Not Correlated to Functionality.**

Data regarding the ability of αKG enzymes to degrade 2,4-D, a phenoxy herbicide, contradicts Dr. Bollinger's assertion that "the conserved residues and fixed spacing of the AAD-12 motif represent the active site and correlate to the

claimed dual activity." Bollinger Decl., ¶ 154; *see also* POR, 74 (citing Bollinger Decl., ¶ 154). Figure 2 of the '055 patent "shows an amino acid sequence alignment of AAD-12 and other αKG-dependent enzymes." Bollinger Decl., ¶ 83. Dr. Bollinger explained that "none of these other Group II αKG-dependent dioxygenases have the exact, specified spacer lengths recited in the AAD-12 motif of the '055 patent (*see* table below)." Bollinger Decl., ¶ 112.

| Enzyme | Active-Site Motif | % Seq Identity to AAD-12 |
|---|---|---|
| AAD-12 | $HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$ | 100% |
| tfdA | $HX_{115}D(X)_{117\text{-}140}T(X)_{142\text{-}262}H(X)_{264\text{-}273}R$ | 37% |
| AAD-2 | $HX_{116}D(X)_{118\text{-}141}T(X)_{143\text{-}263}H(X)_{265\text{-}274}R$ | 35% |
| AAD-1 | $HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R$ | 30% |
| TauD | $HX_{100}D(X)_{102\text{-}125}T(X)_{127\text{-}254}H(X)_{256\text{-}265}R$ | 26% |

Bollinger Decl., ¶ 112.

At his deposition, Dr. Bollinger agreed the fixed spacing of the motif residues (i.e., H, D, T, H, R) of the five αKG enzymes shown in Figure 2 is identical except for the residues between T and H (highlighted yellow below).[2] Bollinger Dep., 67:13-68:7.

[2] The five motif residues are identified with Dr. Bollinger's color-coding scheme. Citations to Dr. Bollinger's deposition (Ex. 1043) are provided in the bottom row.

[redacted]

| αKG Enzyme | Residues between H and D | Residues between D and T | Residues between T and H | Residues between H and R | Ability to Degrade 2,4-D (Efficiency Constant) |
|---|---|---|---|---|---|
| AAD-12 | 1 | 24 | 126 | 10 | 500,000 |
| tfdA | 1 | 24 | 121 | 10 | 125,000,000[3] |
| AAD-2 | 1 | 24 | 121 | 10 | 2,200 |
| AAD-1 | 1 | 24 | 131 | 10 | 27,000 |
| TauD | 1 | 24 | 128 | 10 | N/A |
| Bollinger Dep. Cites | 65:13-16 | 65:21-66:18 | 68:11-69:16 | 66:19-67:7 | 78:4-10; 79:12-80:6 |

An enzyme's ability to degrade 2,4-D is measured with an "efficiency constant," where a greater number indicates a greater ability to degrade 2,4-D. Bollinger Dep., 74:8-75:16. Based on Dr. Bollinger's testimony, the relative ability of the five αKG enzymes to degrade 2,4-D is: tfdA > AAD-12 > AAD-1 > AAD-2 > TauD.[4] Despite having identical spacing, AAD-2 and tfdA have the greatest difference in ability to degrade 2,4-D. Confronted with this evidence, Dr. Bollinger admitted that if there were any correlation between motif spacing and ability to degrade 2,4-D, "that would be a pretty lame correlation." Bollinger Dep., 81:11-17.

TauD also illustrates the absence of a correlation. TauD's motif spacing is identical to the other enzymes except for the spacing between T and H (highlighted

[3] Dr. Bollinger agreed that Ex. 1015, which he co-authored, reports that "TfdA is about 250 times greater in its efficiency against 2,4-D than is AAD-12." Bollinger Dep., 80:2-5 (referring to Ex. 1015, p. 13300). 250 x 500,000 = 125,000,000.

[4] TauD does not degrade 2,4-D. Bollinger Dep., 83:9-18.

yellow in above table), which contains 128 residues. This is midway between the spacing of AAD-12 (126 residues) and AAD-1 (131 residues). However, TauD's ability to degrade 2,4-D is ***not*** midway between that of AAD-12 and AAD-1; indeed, TauD cannot degrade 2,4-D at all. Bollinger Dep., 83:9-18.

**2. Confirming the Lack of a Structure-Function Correlation.**

. Ex. 2092 at 8. undermines Corteva's contention that "those structural features are correlated to the claimed function." POR, 3.

. *See* Section I.A.1.b *supra* (citing Exs. 2085, 2089, and 2095). . Ex. 1045 ("Reply-Silverstone"), ¶¶ 3-5; Ex 2089.

. Ex. 2092 at 2. As detailed in Table A below,

[redacted]. Reply-Silverstone, ¶¶ 6-9 (citing Ex 2092 at 6 and 8). [redacted]. Ex. 2092 at 5-11.

| Table A | | | |
|---|---|---|---|
| Variant | % Seq. Identity | % Activity | |
| | | 2,4-D | Triclopyr |
| AAD-12 wt | 100.0% | 100% | 100% |

[redacted]. Thus, Corteva's experimental data contradict the assumption underpinning its core written description arguments, i.e., that the '055 patent discloses "function-correlated structure." POR, 72-80 (passim).

Corteva's experimental data likewise contradict the fundamental assumption underpinning its experts' opinions – namely, their assumption that most AAD-12

variants that satisfy the claimed "structural" requirements would have the claimed dual herbicide-degrading activity.

Dr. Bollinger testified he "certainly would expect" 75% of AAD-12 variants to have the claimed dual functionality if the residue changes are "chosen well." Bollinger Dep., 142:18-143:5. According to Dr. Bollinger, well-chosen changes mean not putting proline or glycine in positions where there are secondary structures that Elkins identified. Bollinger Dep., 143:16-144:8 (citing Elkins [Ex. 2022], Fig. 5).

Under Dr. Bollinger's criteria, Reply-Silverstone, ¶ 11. Thus, Dr. Bollinger based his written description opinion on the incorrect assumption that most AAD-12 variants having the claimed structure would also have the claimed dual functionality.

Dr. Bollinger also incorrectly assumed Bollinger Dep., 170:7-171:3

[redacted]. Ex. 2092 at 8. [redacted]. Reply-Silverstone, ¶ 12; see Table A *supra*.

In sum, Dr. Bollinger incorrectly predicted certain residue changes would preserve dual functionality and others would destroy it. His incorrect predictions, in both directions, flowed from his unfounded assumption that there exists a structure-function relationship between the AAD-12 motif and the claimed dual herbicide-degrading functionality.

Dr. Christou based his opinions on a similar assumption. He incorrectly assumed that "the variants of AAD-12 would all have similar activity." Ex. 1044, Christou Dep. 135:10-19; *see also id.*, 81:15-82:18, 134:19-136:8. As detailed above, [redacted] Ex. 2092, at 8.

The incorrect assumptions and predictions of Corteva's experts demonstrate the need for trial-and-error testing to determine which AAD-12 variants are functional.

Corteva's reliance on *Lifescan* is misplaced. POR, 46, 58, 63, 74, 79-81. There, the inventors tested nine examples and found the claimed activity occurred only in examples that contained a critical amino acid sequence and did not occur in

[redacted]

examples without it. PGR2019-00032, Paper 11 at 16. Moreover, "substitution of amino acid residues other than those in the [critical] sequence did not affect" the claimed activity. *Id.* By contrast, the '055 patent describes testing a single example (Christou Dep., 80:19-22) instead of the nine examples in *Lifescan*. Moreover, [redacted]. See Sections I.A.2 and I.A.1.b *supra*. In short, the *Lifescan* patent disclosed evidence of a structure-function correlation whereas Corteva's '055 patent does not.

*Ajinomoto*, cited by Corteva (POR, 72, 74-80), is similarly inapposite. There, the challenged claims recited a single protein sequence (the *yddG* gene) in which a native promoter was replaced by a "more potent promoter." *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1347 (Fed. Cir. 2019). The specification disclosed four examples of "potent promoters" and cited an article that "describes a general methodology for determining promoter strength," and thus showed a POSA would have been able to identify more potent promoters using common tools. *Id.*, at 1359. By contrast, the '055 patent claims $10^{106}$ different protein sequences and discloses no methodology to identify which variants have the claimed dual herbicide-degrading functionality.

### 3. Corteva's Enzyme Literature Is Inapposite

Corteva relies on several articles that analyze an enzyme database called SWISSPROT as evidence that "a skilled artisan would have viewed an enzyme that was 85% (or more) identical to AAD-12 as essentially the same enzyme having the same function." POR, 73 (citing Bollinger Decl., ¶¶ 152-153). Corteva primarily relies on graphs from Exhibits 2019 and 2028 that compare degree of function conservation with percent sequence identity. POR, 2, 9, 10, 37, 73 (citing Ex. 2019, Fig. 1(B) and Ex. 2028, Fig. 5); *see also* Bollinger Decl., ¶¶ 20-39, 99, 102, 151, 167 (citing same). Corteva and its expert also cite Exhibits 2027 and 2029, which are also studies of the SWISSPROT database. Corteva's enzyme articles are inapposite to the claimed AAD-12 genus for three reasons.

***First***, Corteva's articles analyzed SWISSPROT, which is "a curated database" that "only include enzymes of known function." Bollinger Dep., 101:8-18. Indeed, "that's the whole point." Id. See also Ex. 2019, at 876 ("we retrieved 33,024 sequences … [from] the newest version of the SWISSPROT database-sprot40.dat"); Ex. 2028, at 605 ("The data set of enzymes of known function were taken from the current merger of SWISS-PROT + SWISS-PROT_new."); Ex. 2029, at 94-95 ("We prepared datasets derived from the PDB and Swiss-Prot," and noting that PDB is a

[redacted]

"subset of Swiss-Prot"); Ex. 2027[5], at 1139 ("Every protein chain in the PDB was matched to its corresponding SWISS-PROT sequence entry"). In contrast to the functional enzymes from SWISSPROT, [redacted]

***Second***, most of the enzymes in SWISSPROT "come from a natural source" (Bollinger Dep., 101:19-102:3) and therefore "are generally subjected to evolutionary pressure for functionality" (id., 104:2-7). By contrast, the Challenged Claims are directed to a "transgenic plant cell" or a "recombinant polynucleotide," in which genetic material is "introduced by a scientist into a plant cell," and therefore not subject to evolutionary pressure. Bollinger Dep., 17:21-18:11, 19:3-22.

Dr. Bollinger highlighted the difference between artificial and evolutionary changes. When changing a natural AAD enzyme, he "would feel a lot more confident that if one identified natural sequences and aligned them that" such changes would produce a functional enzyme because "[n]ature solves those things." Bollinger Dep., 57:24-58:23. Neither Corteva nor its expert offered any evidence that the purported correlation between sequence identity and conserved function in SWISS-PROT's

[5] Ex. 1042 is a clearer copy of Ex. 2027. To the extent these databases included non-enzymes, the authors excluded them. Ex. 2027, at 1039 (describing exclusion of certain SWISS-PROT entries as non-enzymes).

naturally evolved enzymes would apply to the $10^{106}$ non-evolutionary AAD-12 variants encompassed by the Challenged Claims.

***Third***, the Challenged Claims require dual functionality whereas the studies cited by Corteva expressly excluded multi-functional enzymes, i.e., enzymes having two or more EC numbers. Bollinger Dep., 99:1-100:18 (referring to Exs. 2027/1042 at 1139); 104:8-22 (referring to Ex. 2028 at 605); 105:21-106:5 (referring to Ex. 2019 at 876); 111:22-112:4 (referring to Ex. 2029 at 95); Ex. 2029 at 95 ("A few entries have more than one EC number, for example, multifunctional and multidomain enzymes. We have excluded all these cases from the final dataset…"). Neither Corteva nor its expert address this issue, much less explain why purported correlations from studies that expressly exclude multi-functional enzymes would be applicable to the claimed dual-function enzymes.

### B. The Two Near-Identical Embodiments Disclosed in the '055 Patent Are Not Representative of the $10^{106}$ Claimed Species.

The '055 patent discloses just two embodiments: the native AAD-12 enzyme (SEQ ID NO:2) and a "plant-optimized" version, dubbed "AAD-12 (v1)," which has an extra alanine at the second position (SEQ ID NO:4). '055 patent, 35:2-13.[6] The

[6] The '055 patent also describes an *E. Coli*-optimized (v2) with different nucleic acids, but it encodes the same amino acid sequence (SEQ ID NO:4) as the plant-optimized (v1). '055 patent, 37:3-17.

[redacted]

two embodiments "are 99.3% identical, differing only at amino acid number 2." *Id.*, 35:20-22. The '055 patent only discloses test results for the AAD-12(v1) embodiment. Christou Dep., 80:19-22; *see also id.*, 71:14-80:18 (admitting that examples 7-12, 14, 16, 17, and 19-24 only disclose test results for AAD-12(v1)).

The two near-identical embodiments are not representative of the claimed genus because they have "not been shown to be typical of the entire genus of [AAD-12 variants] claimed." *PureCircle*, 2024 WL 20567, at *4. Unlike "the genus of more potent promoters" in *Ajinomoto*, which "was already well explored" at the time of invention, the '055 patent provides no guidance as to which of the $10^{106}$ AAD-12 variants have the claimed dual functionality or how to identify them other than by testing each one. 932 F.3d at 1359.

[redacted]. The '055 patent sheds no light on [redacted]. Percent sequence identity does not explain it. [redacted].

Corteva's experimental data also suggest there is no correlation between percent sequence identity and herbicide-degrading activity. For example, although

[redacted] See Table A *supra*. Likewise, [redacted] See Table A *supra*. Far from explaining such discrepancies, Dr. Bollinger expected the opposite, i.e., that with decreasing sequence identity "it's more likely [2,4-D activity] would go down." Bollinger Dep., 173:17-174:10.

## II. GROUND 2: THE FULL SCOPE OF CLAIMS 1-33 IS NOT ENABLED

### A. The '055 Patent Fails to Disclose Qualities Common to the Claimed AAD-12 Enzymes.

Corteva's enablement arguments turn on its contention that the '055 patent discloses "function-correlated structural features [that] provide a 'common quality' to AAD-12 enzymes." POR, 34. Corteva's contention rests on the same two unfounded assumptions regarding structure-function correlation that underpin its written description arguments – namely:

- That studies of naturally-evolved, single-function enzymes (Exs. 2019, 2027-2029) support the inference that transgenic AAD-12 variants with 85% sequence identity to the native AAD-12 enzyme would have the claimed dual functionality (POR, 36-40); and

- "The AAD-12 motif of conserved residues with fixed spacing, representing the active site of AAD-12, is thus also unique and correlated to the claimed dual herbicide-degrading activity." POR, 45; *see also* POR, 41-45.

Both assumptions are incorrect. First, the enzyme studies cited by Corteva are inapposite. Section I.A.3 *supra*. Second, the '055 patent, Corteva's experts, and Corteva's experimental data confirm there is no correlation between the structural and functional requirements of the Challenged Claims. For one, the AAD-12 motif residues undisputedly bind to αKG and iron rather than to the herbicides recited in the Challenged Claims. Section I.A.1.a *supra*. Additionally, (see Section I.A.2 *supra*).

upon which Drs. Bollinger and Christou base their enablement opinions. Dr. Bollinger incorrectly assumed most AAD-12 variants would have the claimed dual functionality (Bollinger Dep., 142:18-143:5), (Ex. 2092 at 8). Dr. Christou assumed "the variants of AAD-12 would all have similar activity" to the native enzyme (Christou Dep., 135:10-12), (Ex. 2092 at 8). See Section I.A.2 *supra*.

[redacted]

### B. The *Wands* Factors Confirm the Challenged Claims Are Not Enabled.

#### 1. Factors 4 and 8: The Scope of the Claims Is Undisputedly "Astronomical"

Corteva's analysis of *Wands* factors 4 and 8 (POR, 47-49) incorrectly assumes the claimed structural features "are correlated to function." POR, 48. Based on this assumption, Corteva erroneously concludes the claim scope "is narrow." Id.

Corteva and its expert do not dispute that $10^{106}$ AAD-12 variants have the claimed structure. Bollinger Dep., 160:21-24. Indeed, Dr. Bollinger admitted "the calculations may be right, and that number is astronomical." Id., 161:11-12. Unable to dispute the math, he argued the number is "not relevant because given a functional sequence, a [POSA] can make variants in huge numbers … and maintain function. It's not a difficult exercise." Id., 161:11-17. [redacted]"

Because functionality cannot be presumed from structure, practicing "the full scope of the claims would require the testing of all proteins" that satisfy the structural features. Petition, 39; see also Ex. 1003, ¶¶ 79, 86. Even if such testing were routine, the scale of testing would be far more than the "tens of thousands of candidate compounds" found to be excessive in *Idenix Pharms. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019).

[redacted]

### 2. Factors 1 and 7

#### a. The Incorrect Predictions of Corteva's Experts Demonstrate Undue Experimentation and Unpredictability.

Corteva contends the '055 patent is distinguishable from the non-enabled patents in *Amgen* and *Baxalta* because, there, "the specification disclosed no structural features that would guide skilled artisans towards additional antibodies having the claimed functions." POR, 58. However, Corteva likewise fails to show the AAD-12 motif and ≥85% sequence identity are correlated to the claimed functionality. See Section I.A *supra*. Having failed to identify a quality common to functional AAD-12 variants, undue experimentation is unavoidable because the '055 patent provides "only a starting point, a direction for further research." *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010); *see also Idenix*, 941 F.3d at 1161 (specification requiring "trial-and-error process" is not enabling).

Corteva's failure to identify a quality common to functional AAD-12 variants is compounded by the art's unpredictability. **The unpredictability is evidenced by Corteva's experts' incorrect predictions and assumptions.** Dr. Bollinger predicted that most AAD-12 variants that satisfy the structural requirements would also satisfy the claimed functionality; [redacted]. See Section I.A.2 *supra*. He also predicted that replacing the AAD-12 motif residues $T_{135}$ or $R_{273}$ would

[redacted]

destroy dual functionality; [redacted]. See Section I.A.1.b *supra*.

Dr. Christou incorrectly assumed all AAD-12 variants satisfying the structural requirements would have similar activity levels; [redacted] See Table A *supra*.

Corteva's experimental data illustrate the unpredictability of the claimed AAD-12 genus. [redacted]. Reply-Silverstone, ¶ 13. [redacted] (Bollinger Decl., ¶¶ 125-126), [redacted] (Bollinger Dep., 153:16-155:8); [redacted] Reply-Silverstone, ¶ 13. The '055 patent fails to disclose "a quality common to every functional embodiment," *Amgen*, 598 U.S. at 614, that would allow a POSA to predict [redacted]. *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1366 (Fed. Cir. 2023).

[redacted] fully 15 years after the 2005 priority date supports non-enablement. *See Pacific Biosciences of California, Inc. v. Oxford Nanopore Techs., Inc.*, 996 F.3d 1342, 1352 (Fed. Cir. 2021) (affirming non-enablement where

[redacted]

"nobody was able to use" claimed invention until two or three years after priority date).

The unpredictability and lack of a quality common to the claimed AAD-12 genus confirms Dr. Silverstone's testimony that a POSA would have needed to make and test every AAD-12 variant to determine the full scope of the claimed invention. Ex. 1003, ¶¶ 79, 84-86. [redacted] (Ex. 2092 at 8; see Table A *supra*), a POSA would have needed "to determine which of the 'large number' of [AAD-12 variants] falls into the 'small' group of candidates that [are functional]. The size disparity between those two groups requires significant experimentation, which weighs against enablement." *Idenix*, 941 F.3d at 1162.

**b. [redacted] Contribute to Undue Experimentation.**

Corteva and its experts argue "a skilled artisan's task in making and using AAD-12 variants would be comparatively simpler because the claims do not require any particular level of dual herbicide-degrading activity." POR, 60; see also Ex. 2011, ¶ 135; Ex. 2012, ¶ 144. However, they overlook the difficulty of distinguishing between AAD-12 variants with 0% activity (outside the claims) and those with 1-2% activity (within the claims).

The '055 patent's *in planta* experiments cannot distinguish between AAD-12 variants having 0% and 1-2% activity because herbicide-degrading activity is

[redacted]

evaluated "in terms of % visual injury."'055 patent, 51:47-52 (broadly categorizing "little or no injury (<20%)"). [redacted] (Ex. 2092 at 8).

[redacted]

Ex. 2092 at 8.

Dr. Christou never considered the enablement difficulties due to low activity levels (Christou Dep., 70:15-18, 82:2-18) because he assumed AAD-12 variants "all have the same enzymatic activity," which would avoid the "need to actually do this testing" (id., 69:4-70:3).

### 3. Factors 2, 3, and 5

#### a. Insufficient Guidance and Working Examples in the Specification

Corteva contends "[t]he '055 patent provides extensive structural guidance to skilled artisans making AAD-12 enzymes to maintain the claimed dual herbicide-degrading function." POR, 50. The so-called guidance, however, is insufficient because it "does not disclose any common structural (or other) feature delineating which [AAD-12 variants] will [have the claimed herbicide-degrading] activity from those that will not." *Baxalta*, 81 F.4th at 1366.

As the Board noted, the '055 patent provides only two embodiments, which are over 99% identical. Institution Decision, 56; see Section I.B *supra*. The '055 patent provides no examples having between 85% and 99% sequence identity. Moreover, the specification's only experimental data concerns a single embodiment. Christou Dep., 80:19-22.

Corteva asserts "the '055 patent calls out 85% as a threshold" and "also discloses where to locate the active site motif in AAD-12." POR, 51. These are simply the "structural" limitations of the Challenged Claims; they do not delineate which of the $10^{106}$ AAD-12 variants have the claimed functionality. And what Corteva calls the "active site motif" does not include the residues that bind to herbicides; indeed, those residues remain unknown. Section I.A.1.a *supra*.

Corteva contends the ’055 patent “discloses known conservative mutations” and provides “significant guidance” on “the types of amino acid substitutions that should or should not be made.” POR, 52. As the Board noted, however, the Supreme Court previously rejected the same “conservative substitution” proposal. Institution Decision, 53 (citing *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023)). While “conservative substitution” might suffice to enable claims if “the inventor identifies a quality common to every functional embodiment” such that “painstaking experimentation” can be avoided (*Amgen*, 598 U.S. at 614), Corteva fails to identify a common quality (see Section I.A *supra*).

Corteva also contends the alignment of five αKG sequences in Figure 2 “provides significant guidance to avoid making changes (or at least use conservative substitutions) at those positions” that are “highly conserved residues.” POR, 51-52 (citing Bollinger Decl., ¶¶ 125-126)). However, this “guidance” would not avoid a genus with an astronomical number of variants. Dr. Bollinger identified 57 “conserved” amino acids in the Figure 2 alignment. Bollinger Dep., 119:19-120:11 (referring to Bollinger Decl., ¶¶ 125-126). Even if a POSA would have avoided changing these 57 “conserved” amino acids – doubtful given his admission that “the patent doesn’t say one shouldn’t change those” (Bollinger Dep., 117:12-19) – there would be about $10^{78}$ possible AAD-12 variants. Reply-Silverstone, ¶ 14. Still astronomical.

There is another problem with Dr. Bollinger's proposal to avoid changing certain residues: . Reply-Silverstone, ¶ 15 (quoting Bollinger Decl., ¶ 125).

**b. Corteva Improperly Relies on the Purported Knowledge of a POSA To Fill Gaps.**

Corteva relies on the purported knowledge of a POSA to fill gaps in the specification by invoking "basic principles for making enzyme variants that maintain function." POR, 12 (citing Bollinger Decl., ¶¶ 56-57); *see also* POR, 52. This is improper. *Idenix*, 941 F.3d at 1159 ("[I]t would be improper to rely on a POSA's knowledge … to fill the gaps in the specification.").

***First***, Corteva and Dr. Bollinger identify SIFT, a program that "predicts whether an amino acid substitution affects protein function." POR, 13 (citing Ex. 2044, which describes SIFT); see also Bollinger Decl., ¶¶ 54, 56. They contend a POSA using SIFT would have "had no need to randomly pick" amino acid substitutions "when making enzyme variants." POR, 12; see also Bollinger Decl., ¶ 51. Despite never having used SIFT himself (Bollinger Dep., 157:8-15, 162:23), Dr. Bollinger assumed SIFT "could exclude some number" of possible variants but did not "know what number" (id., 162:2-163:20). Dr. Silverstone applied the SIFT protocol Dr. Bollinger said a POSA would have used (Bollinger Dep., 159:22-160:7) and found that SIFT predicted "tolerated" substitutions that would yield between at

least $10^{45}$ and $10^{66}$ possible variants (Reply-Silverstone, ¶¶ 16-17). Thus, this so-called "protein engineering principle" would not avoid an astronomical genus.

***Second***, Corteva and Dr. Bollinger contend a POSA in 2005-2006 "would have been routinely able to make AAD-12 variants" with "directed evolution techniques." POR, 61; Bollinger Decl., ¶¶ 55, 82, 116, 129, 137, 139. When doing "targeted protein evolution," Dr. Bollinger acknowledged "it's helpful to know which portions of a protein are most likely to impact the property of interest." Bollinger Dep., 202:22-203:11. He admitted the AAD-12 residues that bind 2,4-D and triclopyr were not known in 2005/2006 (Bollinger Dep., 39:8-14) and even today remain unknown (id., 37:22-24, 38:21-23). A POSA could not use targeted protein evolution to make AAD-12 variants without a target.

#### 4. Factor 6: Level of Skill in the Art

Though not disputing Dr. Silverstone's math, Corteva contends his calculation of $10^{106}$ variants "assumes a *skilled* artisan would use *no skill* in making AAD-12 variants." POR, 47 (emphasis Corteva's). However, the purported "guidance" would still produce an astronomical number of variants. See Section II.B.3 *supra*.

## III. CONCLUSION

The Challenged Claims are unpatentable.

Date: April 29, 2024

/Scott A. McKeown/
Scott A. McKeown, Reg. No. 42,866

**CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (e)(4)**

I certify that on April 29, 2024, I will cause a copy of the foregoing document, including any exhibits filed therewith, to be served via electronic mail, as previously consented to by Patent Owner, upon the following:

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Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing **PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE** contains words excluding; a table of contents, a table of authorities, Mandatory Notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Petitioner has relied on the word count feature of the word processing system used to create this paper in making this certification.

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