

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INARI AGRICULTURE, INC.,
Petitioner,

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

PGR2023-00022
U.S. Patent No. 11,371,055

PATENT OWNER'S SECOND UNOPPOSED MOTION TO SEAL

I. Introduction

Patent Owner Corteva Agriscience LLC requests that the confidential versions of Petitioner's Reply to Patent Owner's Response ("Reply," Paper 27) and Exhibit 1045 (Dr. Silverstone's Supplemental Declaration) be sealed under 37 C.F.R. § 42.54. Redacted copies of the Reply and Ex. 1045 are enclosed as Appendices A and B to this motion. Good cause to seal exists because (i) Petitioner has agreed to publicly file the enclosed redacted versions of the Reply and Exhibit 1045 if the Board grants this motion, and (ii) the redacted portions of the Reply and Exhibit 1045 quote, discuss, and/or refer to confidential information in previously sealed Exhibits 2084-2095, which reflect Patent Owner's proprietary protein research information that is not publicly available. The Board previously entered the parties' agreed-upon Protective Order and granted Patent Owner's motion to seal Exhibits 2084-2095 in their entireties. *See* Paper 22; Paper 18.

Counsel for Patent Owner asked Petitioner's counsel whether Petitioner consents to this motion to seal documents. In response, counsel for Petitioner stated that Petitioner does not oppose. Petitioner has confirmed that it will publicly file the enclosed redacted versions of the Reply (Appendix A) and Exhibit 1045 (Appendix B) if the Board grants this motion.

II. Governing Rules and PTAB Guidance

Under 35 U.S.C. § 316(a)(1), the default rule is that all papers filed in an *inter partes* review are open and available for access by the public, but a party may file a concurrent motion to seal and the information at issue shall be sealed pending the outcome of the motion.

Similarly, 37 C.F.R. § 42.14 provides:

The record of a proceeding, including documents and things, shall be made available to the public, except as otherwise ordered. A party intending a document or thing to be sealed shall file a motion to seal concurrent with the filing of the document or thing to be sealed. The document or thing shall be provisionally sealed on receipt of the motion and remain so pending the outcome of the decision on the motion.

It is, however, only “confidential information” that is protected from disclosure. 35 U.S.C. § 316(a)(7) (“The Director shall prescribe regulations -- . . . providing for protective orders governing the exchange and submission of confidential information”). In that regard, the *Office Trial Practice Guide*, 77 *Fed. Reg.* 48756, 48760 (Aug. 14, 2012) provides:

The rules aim to strike a balance between the public’s interest in maintaining a complete and understandable file history and the parties’ interest in protecting truly sensitive information.

* * *

Confidential Information: The rules identify confidential information in a manner consistent with Federal Rule of Civil Procedure 26(c)(1)(G), which provides for protective orders for trade secret or other confidential research, development, or commercial information. § 42.54.

III. Identification of Confidential Information

The confidential information consists of Patent Owner's proprietary protein research information that is not publicly available. This information is contained in the following documents:

- Petitioner's Reply in pages i, 1, 4, 5, 8-12, 14, 16-23, and 26.
- Exhibit 1045 in pages 1-6, 8, and A-1 through A-3.

IV. Good Cause Exists for Sealing the Confidential Information

The Board's rules identify confidential information in a manner consistent with Federal Rule of Civil Procedure 26(c)(1)(G), which provides for protective orders for trade secret or other confidential research, development, or commercial information. Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012) ("The rules identify confidential information in a manner consistent with Federal Rule of Civil Procedure 26(c)(1)(G), which provides for protective orders for trade secret or other confidential research, development, or commercial information."). Here, the confidential information that Patent Owner seeks to seal pertains to proprietary protein research information that is not publicly available.

The Board has found good cause to seal proprietary scientific research information under similar circumstances and should find the same here. For example, in *Bayer CropScience LP v. Corteva Agriscience LLC*, the Board found good cause to grant a motion to seal documents regarding “proprietary protein research and analysis.” IPR2023-01036, Paper 15 at 3-6 (PTAB January 8, 2024); *see also* IPR2023-01037, Paper 16 at 3-6 (PTAB January 8, 2024); IPR2023-01038, Paper 16 at 3-6 (PTAB January 8, 2024). Similarly, in *Illumina, Inc. v. Cornell Research Foundation, Inc.*, the Board found good cause to grant a patent owner’s motion to seal a document containing non-public research data. IPR2016-00549, Paper 20 at 4-6 (PTAB May 26, 2017); *see also* IPR2016-00553, Paper 21 at 4-6 (PTAB May 26, 2017); IPR2016-00557, Paper 52 at 4-6 (PTAB May 26, 2017); IPR2016-00559, Paper 21 at 4-6 (PTAB May 26, 2017). The Board also found good cause to seal portions of a declaration and the Patent Owner’s Response that cited such non-public data. IPR2016-00549, Paper 20 at 4-6 (PTAB May 26, 2017). In *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, the Board similarly found good cause to grant a patent owner’s motion to seal copies of documents that contained “proprietary technical and product development information,” as well as declarations and papers discussing that confidential information. IPR2013-00517, Paper 83 at 4-5 (PTAB Jan. 29, 2015).

Here, the confidential information quoted, discussed, and/or referred to in the Reply and Exhibit 1045 is the content from the already sealed Exhibits 2084-2095, which is confidential information reflecting Patent Owner's non-public research. Appendix A at i, 1, 4, 5, 8-12, 14, 16-23, and 26; Appendix B at 1-6, 8, A-1 to A-3. Patent Owner has maintained Exhibits 2084-2095 and the information they contain as confidential and proprietary. If such non-public research data is made public, it would create a competitive disadvantage for Patent Owner. Accordingly, there is good cause to grant this second motion to seal.

V. Proposed Protective Order

On February 5, 2024, the Board entered the parties' agreed-upon Protective Order that was attached as Appendix A to the first unopposed Motion to Seal (Paper 18). *See* Paper 22. This previously entered Protective Order will also govern the treatment of the Reply and Exhibit 1045 and the confidential information therein.

VI. Conclusion

For the reasons set forth above, Patent Owner respectfully requests that the Board grant this second unopposed motion to seal. If the Board grants this motion, Petitioner has confirmed that it will publicly file the enclosed redacted versions of the Reply and Exhibit 1045.

Respectfully submitted,

Dated: May 6, 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 Second Unopposed Motion to Seal** was served electronically via email on May 6, 2024, in its entirety on the following:

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Appendix A



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INARI AGRICULTURE, INC.,
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Case No. PGR2023-00022
Patent No. 11,371,055

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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TABLE OF AUTHORITIES

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<i>ALZA Corp. v. Andrx Pharms., LLC</i> , 603 F.3d 935 (Fed. Cir. 2010)	20
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023).....	21, 25
<i>Amgen Inc. v. Sanofi</i> , 872 F.3d 1367 (Fed. Cir. 2017)	4, 20
<i>Ariad Pharm., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010) (en banc)	4
<i>Baxalta Inc. v. Genentech, Inc.</i> , 81 F.4th 1362 (Fed. Cir. 2023)	20, 21, 24
<i>Idenix Pharms. LLC v. Gilead Sciences Inc.</i> , 941 F.3d 1149 (Fed. Cir. 2019)	19, 20, 22, 26
<i>Lifescan Glob. Corp. v. Ikeda Food Rsch., Ltd.</i> , PGR2019-00032, Paper 11 (PTAB Aug. 15, 2019)	11, 12
<i>Pacific Biosciences of California, Inc. v. Oxford Nanopore Techs., Inc.</i> , 996 F.3d 1342 (Fed. Cir. 2021)	21
<i>PureCircle USA Inc. v. SweeGen, Inc.</i> , 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	<i>Enlist™ Herbicide Tolerance and Soybean Symptomology - Get the Facts</i> (https://www.enlist.com/en/News/enlist-tolerance-soybean-symptomology.html) (7/13/2021)
1007	<i>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</i> (https://www.uspto.gov/blog/director/entry/increasing-transparency-boosting-competition-and) (3/7/2023)
1008	<i>Executive Order on Promoting Competition in the American Economy</i> (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: <i>More and Better Choices for Farmers: Promoting Fair Competition and Innovation in Seeds and Other Agricultural Inputs, A report directed by President Biden’s Executive Order Number 14036: “Promoting Competition in America’s Economy”</i> (https://www.ams.usda.gov/sites/default/files/media/SeedsReport.pdf) (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. <i>Journal of Plant Physiology</i> , 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 <i>Pseudomonas maltophilia</i> , strain DI-6: gene isolation, characterization, and heterologous expression. <i>Journal of Biological Chemistry</i> , 280(26), pp.24759-24767
1015	Chekan, Jonathan R, et al. "Molecular basis for enantioselective herbicide degradation imparted by aryloxyalkanoate dioxygenases in transgenic plants." <i>Proceedings of the National Academy of Sciences</i> 116.27 (2019): 13299-13304.
1016	Englander, S.W. and Mayne, L., 2014. The nature of protein folding pathways. <i>Proceedings of the National Academy of Sciences</i> , 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. <i>Nat Prod Rep</i> . 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. <i>Plant Mol Biol</i> . 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. <i>Journal of Biological Chemistry</i> , 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. <i>Protein Science</i> , 15(6), pp.1356-1368.

Exhibit	Description
1021	Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, Tunyasuvunakool K, Bates R, Židek 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. <i>Nature</i> . 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. <i>Nature Structural & Molecular Biology</i> , 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 <i>Sphingomonas herbicidovorans</i> MH. <i>Applied and environmental microbiology</i> , 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. <i>Wiley Interdisciplinary Reviews: Systems Biology and Medicine</i> , 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 <i>tfdA</i> of <i>Alcaligenes eutrophus</i> JMP134. <i>Journal of Bacteriology</i> , 169(7), pp.2950-2955.
1026	Brannigan, J.A. and Wilkinson, A.J., 2002. Protein engineering 20 years on. <i>Nature Reviews Molecular Cell Biology</i> , 3(12), pp.964- 970.
1027	Westendorf, A, Müller, RH, Babel, W, Purification and characterisation of the enantiospecific dioxygenases from <i>Delftia acidovorans</i> MC1 initiating the degradation of phenoxypropionate and phenoxyacetate herbicides. <i>Acta biotechnologica</i> , 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 <i>pro hac vice</i>
1039	[Reserved]
1040	[Reserved]
1041	[Reserved]
1042	Todd et al., <i>Evolution of Function in Protein Superfamilies, from a Structural Perspective</i> , 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”)

[REDACTED]

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. [REDACTED]

[REDACTED]. 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; [REDACTED]

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

[REDACTED]

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.

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

[REDACTED]

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. [REDACTED]. Ex.

2085 at 2, 5-7; Ex. 2089; 2095 at 3. [REDACTED]

[REDACTED]. Ex. 2089 at 1. [REDACTED]

[REDACTED]. Ex. 2089 at 1; Ex. 2095 at 3. [REDACTED]

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]

[REDACTED]. Ex. 2089 at 1; Ex. 2095 at 3. [REDACTED]

[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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 α KG 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 α KG-dependent enzymes.” Bollinger Decl., ¶ 83. Dr. Bollinger explained that “none of these other Group II α KG-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) ₁₁₁₋₁₃₄ T(X) ₁₃₆₋₂₆₁ H(X) ₂₆₃₋₂₇₂ R	100%
tfdA	HX ₁₁₅ D(X) ₁₁₇₋₁₄₀ T(X) ₁₄₂₋₂₆₂ H(X) ₂₆₄₋₂₇₃ R	37%
AAD-2	HX ₁₁₆ D(X) ₁₁₈₋₁₄₁ T(X) ₁₄₃₋₂₆₃ H(X) ₂₆₅₋₂₇₄ R	35%
AAD-1	HX ₁₁₂ D(X) ₁₁₄₋₁₃₇ T(X) ₁₃₉₋₂₆₉ H(X) ₂₇₁₋₂₈₀ R	30%
TauD	HX ₁₀₀ D(X) ₁₀₂₋₁₂₅ T(X) ₁₂₇₋₂₅₄ H(X) ₂₅₆₋₂₆₅ 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 α KG 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.

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.

[REDACTED]

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.

[REDACTED] **Confirming the Lack of a Structure-Function Correlation.**

[REDACTED]

[REDACTED] Ex. 2092 at 8. [REDACTED]

[REDACTED]

[REDACTED] undermines Corteva’s contention that “those structural features are correlated to the claimed function.” POR, 3.

[REDACTED]. See Section I.A.1.b *supra* (citing Exs. 2085, 2089, and 2095). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Ex. 1045 (“Reply-Silverstone”), ¶¶ 3-5; Ex 2089.

[REDACTED]

[REDACTED]

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

[REDACTED]

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

[REDACTED]

[REDACTED]. Ex. 2092 at 5-11.

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

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

[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

[REDACTED]

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, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] 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 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Bollinger Dep., 170:7-171:3 [REDACTED]

[REDACTED]

[REDACTED]. Ex. 2092
at 8. [REDACTED]

[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]

[REDACTED]

[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]

[REDACTED]

[REDACTED]

[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. 2027⁵, 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]

[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).

[REDACTED]

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 10¹⁰⁶ 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]

[REDACTED]. The ’055 patent sheds no light on [REDACTED]

[REDACTED]

[REDACTED]. Percent sequence identity does not explain it. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

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

[REDACTED]

[REDACTED]

[REDACTED] See Table A *supra*. Likewise, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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

- [REDACTED]
- “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 α KG and iron rather than to the herbicides recited in the Challenged Claims. Section I.A.1.a *supra*. Additionally, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (see Section I.A.2 *supra*).

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED] 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), [REDACTED] (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), [REDACTED] (Ex. 2092 at 8). See Section I.A.2 *supra*.

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).

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 $\geq 85\%$ 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 T₁₃₅ or R₂₇₃ would

[REDACTED]

destroy dual functionality; [REDACTED]

[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]

[REDACTED] See Table
A supra.

Corteva’s experimental data illustrate the unpredictability of the claimed AAD-12 genus. [REDACTED]

[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]

[REDACTED]. *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1366 (Fed. Cir. 2023).

[REDACTED]
[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]

[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]

[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 10¹⁰⁶ 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*.

[REDACTED]

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 α KG 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.

[REDACTED]

There is another problem with Dr. Bollinger’s proposal to avoid changing certain residues: [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]. 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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Date: April 29, 2024

//
MacAulay Rush
Paralegal
WOLF, GREENFIELD & SACKS, P.C.

CERTIFICATE OF WORD COUNT

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.

Date: April 29, 2024

/MacAulay Rush/
MacAulay Rush
Paralegal
WOLF, GREENFIELD & SACKS, P.C.

Appendix B

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

REPLY DECLARATION OF DR. ARON SILVERSTONE, Ph.D.

Inari Exhibit 1045 Inari v. Corteva PGR2023-00022

I, Aron Silverstone, Ph.D., hereby declare under penalty of perjury:

1. My name is Aron Silverstone, and I have been retained by counsel for Petitioner Inari Agriculture, Inc. (“Inari” or “Petitioner”) as an expert witness to provide assistance regarding U.S. Patent No. 11,371,055 (the “’055 Patent”). I previously submitted a declaration (Ex. 1003) in support of Inari’s Petition. I have personal knowledge of the facts and opinions set forth in this declaration and believe them to be true. If called upon to do so, I would testify competently thereto.

2. My opinions set forth in this declaration are based on my consideration of the following exhibits and papers:

Exhibit No.	Material Considered
Ex. 2011	Paragraphs 125-126 from the Declaration of Dr. Bollinger
Ex. 2085	Slide 2 from Protein presentation (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
Ex. 2089	Protein sequences (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
Ex. 2092	Protein presentation (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
Ex. 2095	Protein sequences and analysis (CONFIDENTIAL – PROTECTIVE ORDER MATERIAL)
Ex. 1043	The portions of the transcript of the deposition of Dr. Bollinger (Feb. 29, 2024) cited in this declaration

3. Exhibits 2085, 2089, and 2095 describe [REDACTED]

[REDACTED]. [REDACTED]

[REDACTED], [REDACTED]

[REDACTED]

[REDACTED]. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. '055 patent, 11:29.

4. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

Week 1		Week 2		Week 3		Week 4		Week 5		Week 6				
Day	Activity	Day	Activity	Day	Activity	Day	Activity	Day	Activity	Day	Activity	Day	Activity	
1	Math	1	Math	1	Math	1	Math	1	Math	1	Math	1	Math	
2	Science	2	Science	2	Science	2	Science	2	Science	2	Science	2	Science	
3	History	3	History	3	History	3	History	3	History	3	History	3	History	
4	Art	4	Art	4	Art	4	Art	4	Art	4	Art	4	Art	
5	Physical Education	5	Physical Education	5	Physical Education	5	Physical Education	5	Physical Education	5	Physical Education	5	Physical Education	
6	Music	6	Music	6	Music	6	Music	6	Music	6	Music	6	Music	
7	Language Arts	7	Language Arts	7	Language Arts	7	Language Arts	7	Language Arts	7	Language Arts	7	Language Arts	
8	Math	8	Math	8	Math	8	Math	8	Math	8	Math	8	Math	
9	Science	9	Science	9	Science	9	Science	9	Science	9	Science	9	Science	
10	History	10	History	10	History	10	History	10	History	10	History	10	History	
11	Art	11	Art	11	Art	11	Art	11	Art	11	Art	11	Art	
12	Physical Education	12	Physical Education	12	Physical Education	12	Physical Education	12	Physical Education	12	Physical Education	12	Physical Education	
13	Music	13	Music	13	Music	13	Music	13	Music	13	Music	13	Music	
14	Language Arts	14	Language Arts	14	Language Arts	14	Language Arts	14	Language Arts	14	Language Arts	14	Language Arts	
15	Math	15	Math	15	Math	15	Math	15	Math	15	Math	15	Math	
16	Science	16	Science	16	Science	16	Science	16	Science	16	Science	16	Science	
17	History	17	History	17	History	17	History	17	History	17	History	17	History	
18	Art	18	Art	18	Art	18	Art	18	Art	18	Art	18	Art	
19	Physical Education	19	Physical Education	19	Physical Education	19	Physical Education	19	Physical Education	19	Physical Education	19	Physical Education	
20	Music	20	Music	20	Music	20	Music	20	Music	20	Music	20	Music	
21	Language Arts	21	Language Arts	21	Language Arts	21	Language Arts	21	Language Arts	21	Language Arts	21	Language Arts	
22	Math	22	Math	22	Math	22	Math	22	Math	22	Math	22	Math	
23	Science	23	Science	23	Science	23	Science	23	Science	23	Science	23	Science	
24	History	24	History	24	History	24	History	24	History	24	History	24	History	
25	Art	25	Art	25	Art	25	Art	25	Art	25	Art	25	Art	
26	Physical Education	26	Physical Education	26	Physical Education	26	Physical Education	26	Physical Education	26	Physical Education	26	Physical Education	
27	Music	27	Music	27	Music	27	Music	27	Music	27	Music	27	Music	
28	Language Arts	28	Language Arts	28	Language Arts	28	Language Arts	28	Language Arts	28	Language Arts	28	Language Arts	
29	Math	29	Math	29	Math	29	Math	29	Math	29	Math	29	Math	
30	Science	30	Science	30	Science	30	Science	30	Science	30	Science	30	Science	
31	History	31	History	31	History	31	History	31	History	31	History	31	History	
32	Art	32	Art	32	Art	32	Art	32	Art	32	Art	32	Art	
33	Physical Education	33	Physical Education	33	Physical Education	33	Physical Education	33	Physical Education	33	Physical Education	33	Physical Education	
34	Music	34	Music	34	Music	34	Music	34	Music	34	Music	34	Music	
35	Language Arts	35	Language Arts	35	Language Arts	35	Language Arts	35	Language Arts	35	Language Arts	35	Language Arts	
36	Math	36	Math	36	Math	36	Math	36	Math	36	Math	36	Math	
37	Science	37	Science	37	Science	37	Science	37	Science	37	Science	37	Science	
38	History	38	History	38	History	38	History	38	History	38	History	38	History	
39	Art	39	Art	39	Art	39	Art	39	Art	39	Art	39	Art	
40	Physical Education	40	Physical Education	40	Physical Education	40	Physical Education	40	Physical Education	40	Physical Education	40	Physical Education	
41	Music	41	Music	41	Music	41	Music	41	Music	41	Music	41	Music	
42	Language Arts	42	Language Arts	42	Language Arts	42	Language Arts	42	Language Arts	42	Language Arts	42	Language Arts	
43	Math	43	Math	43	Math	43	Math	43	Math	43	Math	43	Math	
44	Science	44	Science	44	Science	44	Science	44	Science	44	Science	44	Science	
45	History	45	History	45	History	45	History	45	History	45	History	45	History	
46	Art	46	Art	46	Art	46	Art	46	Art	46	Art	46	Art	
47	Physical Education	47	Physical Education	47	Physical Education	47	Physical Education	47	Physical Education	47	Physical Education	47	Physical Education	
48	Music	48	Music	48	Music	48	Music	48	Music	48	Music	48	Music	
49	Language Arts	49	Language Arts	49	Language Arts	49	Language Arts	49	Language Arts	49	Language Arts	49	Language Arts	
50	Math	50	Math	50	Math	50	Math	50	Math	50	Math	50	Math	
51	Science	51	Science	51	Science	51	Science	51	Science	51	Science	51	Science	
52	History	52	History	52	History	52	History	52	History	52	History	52	History	
53	Art	53	Art	53	Art	53	Art	53	Art	53	Art	53	Art	
54	Physical Education	54	Physical Education	54	Physical Education	54	Physical Education	54	Physical Education	54	Physical Education	54	Physical Education	
55	Music	55	Music	55	Music	55	Music	55	Music	55	Music	55	Music	
56	Language Arts	56	Language Arts	56	Language Arts	56	Language Arts	56	Language Arts	56	Language Arts	56	Language Arts	

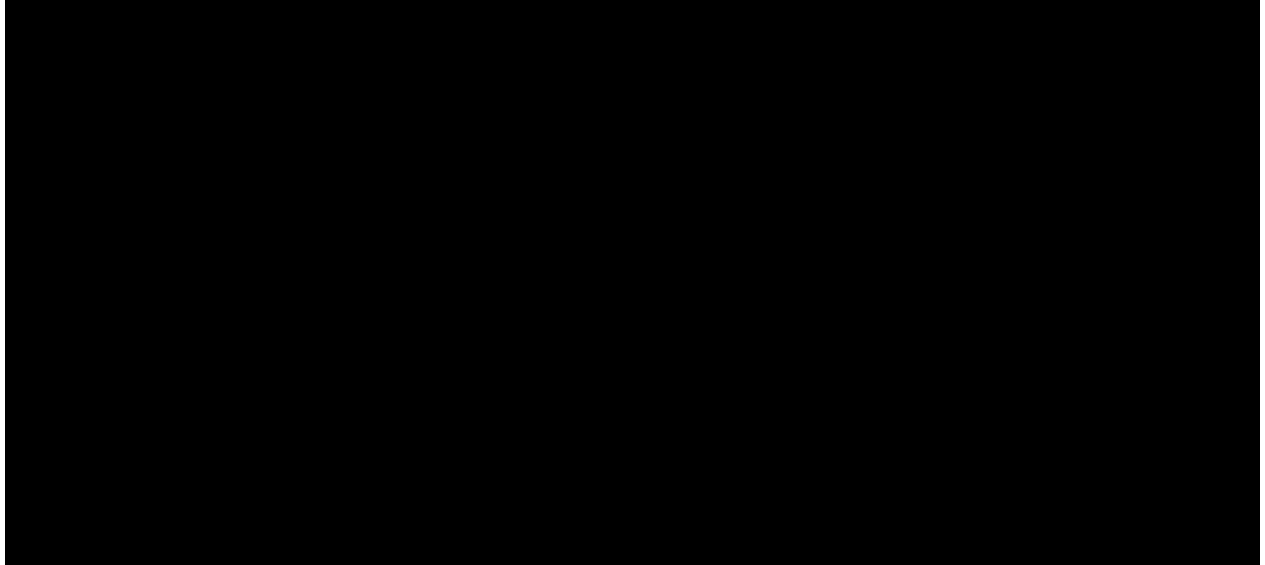
[REDACTED]. In Appendix A, I have [REDACTED]

[REDACTED]. Appendix A includes the positions of the alignment in Figure 2 of the '055 patent and the 292 positions of the amino acids in SEQ ID NO:2 (AAD-12). I have highlighted in green [REDACTED]

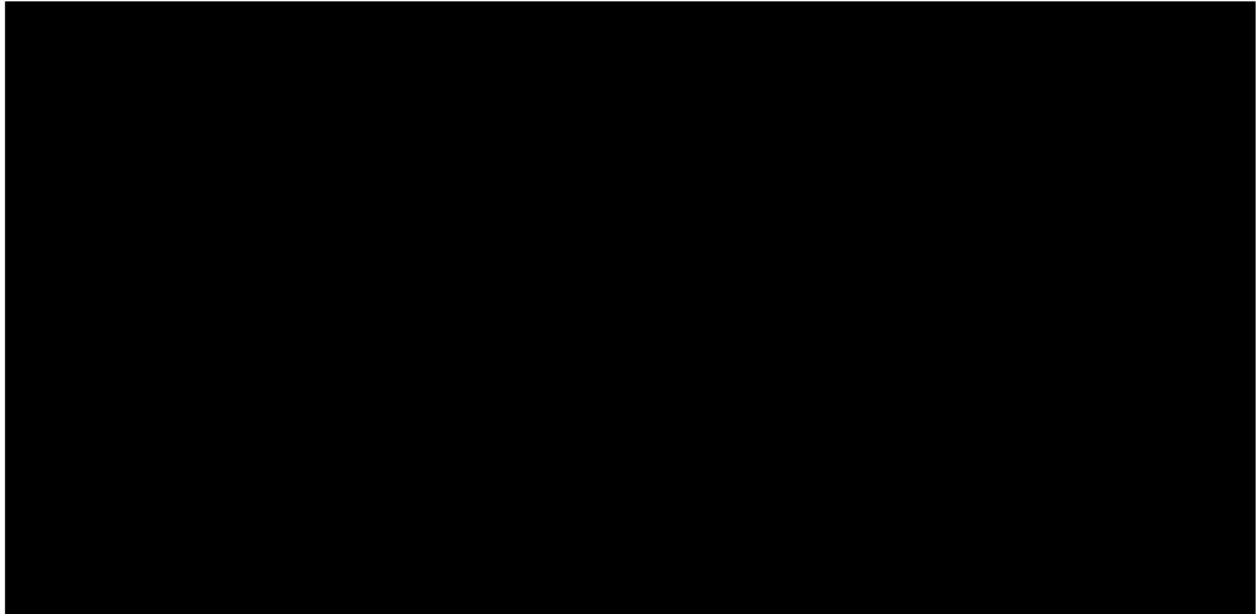
[REDACTED]

[REDACTED] ([REDACTED]). Using the positions of TauD, I have also identified the secondary structures (i.e., α -helixes and β -strands) identified in Elkins (Ex. 2022), Figure 5, which I have highlighted in yellow.

7. Exhibit 2092, [REDACTED]:



8. Exhibit 2092, [REDACTED] :



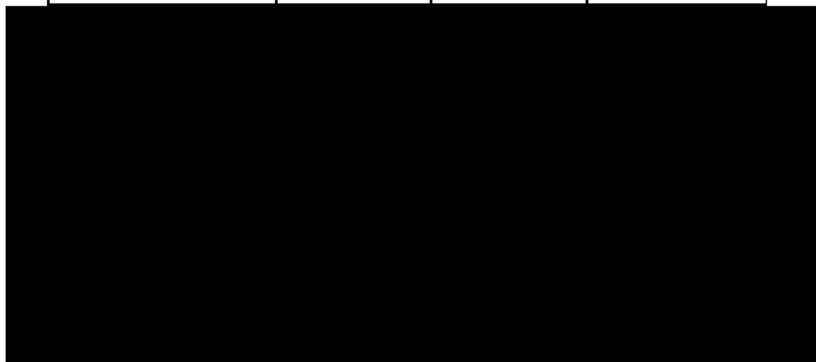
9. [REDACTED]

[REDACTED]. [REDACTED]

[REDACTED], are highlighted in

green:

Table A			
Variant No.	% Seq. Identity	% Activity	
		2,4-D	Triclopyr
AAD-12 wt	100.0%	100%	100%



[REDACTED]

10. As depicted in the table in Appendix A to this declaration, [REDACTED]

[REDACTED]

[REDACTED].

11. As depicted in Appendix A, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. [REDACTED] Elkins identified as

having a secondary structure, which are highlighted in yellow.

12. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

13. As depicted in Appendix A, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. [REDACTED]

[REDACTED] 57 positions that Dr. Bollinger identified as “strictly conserved” or
“somewhat conserved” in Figure 2 of the ’055 patent (Ex. 2011, ¶¶ 125-126),

which 57 positions are identified in red highlighting in the '055 patent Figure 2 position in Appendix A.

14. Dr. Bollinger identified 57 amino acids as “conserved” in Figure 2 of the '055 patent: he identified 28 as “strictly conserved” and he identified 29 as “somewhat conserved.” Ex. 2011, ¶¶ 125-126. This leaves 235 amino acids, i.e., $292 - 28 - 29 = 235$. Varying these 235 amino acids results in about 10^{78} possible AAD-12 variants. To get an estimate of a minimum number of variants a POSA would have had to choose from if they assume that both the “conserved” and “strictly conserved” are invariant from the AAD-12 (SEQ ID NO:2), they would have assumed that only 235 amino acids could change, and that up to 43 changes would be tolerated for an 85% homology. The equation I used to determine the number of different proteins is: $43^{19} * (235! / ((235-43)! * 43!))$. The solution for this is 2.69×10^{78} . Even if we were to assume that the 235 amino acids could only be substituted by one different amino acid (instead of 19), the total possible AAD-12 variants would still be on the order of 10^{50} . This is based on the following equation: $43^1 * (235! / ((235-43)! * 43!))$.

15. In his declaration, Dr. Bollinger stated: “Skilled artisans would readily identify in Figure 2 the residues that are identical across all five enzymes and generally avoid making substitutions to those strictly conserved residues.” Ex. 2011, ¶ 125. In his annotation of Figure 2, Dr. Bollinger identified position 71 as

one of the “strictly conserved” amino acids that a POSA would have generally avoided changing. Ex. 2011, ¶ 125. [REDACTED]

[REDACTED], as depicted in Appendix A.

16. I understand that Dr. Bollinger testified that, when using SIFT, “a POSA would have used the first four [of the sequences shown in Figure 2 of the ’055 patent], and I think it has been established since then that these alignments of functionally related but not strictly orthologous proteins helps in this, so inclusion of TauD is not a bad choice.” TauD is the fifth sequence shown in Figure 2 of the ’055 patent. Ex. 1043 (Bollinger Dep.), 159:22-160:7. I submitted to the SIFT website (<https://sift.bii.a-star.edu.sg/>) the five sequences in Figure 2 of the ’055 patent. SIFT generated the table attached as Appendix B to this declaration. For each of the 292 positions in AAD-12 (SEQ ID NO:2), SIFT predicted how many of the 20 natural amino acids would be tolerated if substituted. The table below summarizes SIFT’s results. SIFT predicts that over half of the amino acids would tolerate substitutions by 17 or more amino acids, as summarized in Table B below. Even assuming that 43 of the amino acids (i.e., 15% of 292) could tolerate substitutions by only four different amino acids (far fewer than the amount indicated by SIFT), the number of possible variants would be at least 10⁴⁵.

17. Using the output of the SIFT analysis in Table B below, the positions that can tolerate virtually any amino acid substitution (i.e., 17-19 amino acids) represents over half the amino acids in the protein sequence (153 amino acids). SIFT analysis indicated 37 amino acids are absolutely conserved and would not tolerate a substitution. If a POSA only examines the potential substitutions among the 153 positions that can tolerate the most changes, 17-19 amino acids, for 85% homology (that is up to 43 changes), there are still at least 1.23×10^{66} different proteins that fit these criteria. This is calculated by assuming the smallest number of amino acid substitutions (17) for a sequence that is 153 amino acids long that can tolerate up to 43 changes. The equation I used to determine the number of different proteins is: $43^{17} * (153! / ((153-43)! * 43!))$. The solution for this is 1.23×10^{66} . I streamlined this analysis by focusing on only the 153 amino acids that tolerate 17 or more substitutions, which simplifies the calculations. This approach does not take into account the other 102 amino acids (i.e., $292 - 153 - 37 = 102$) that can tolerate between 2 and 16 substitutions.

Table B			
# of Amino Acid Substitutions Tolerated	Positions	% of Total positions	Cumulative %
19	69	23.6%	23.6%
18	63	21.6%	45.2%
17	21	7.2%	52.4%
16	8	2.7%	55.1%
15	13	4.5%	59.6%
14	7	2.4%	62.0%
13	7	2.4%	64.4%
12	8	2.7%	67.1%
11	8	2.7%	69.9%
10	3	1.0%	70.9%
9	1	0.3%	71.2%
8	4	1.4%	72.6%
7	2	0.7%	73.3%
6	11	3.8%	77.1%
5	8	2.7%	79.8%
4	8	2.7%	82.5%
3	5	1.7%	84.2%
2	9	3.1%	87.3%
1	0	0.0%	87.3%
0	37	12.7%	100.0%
	292		

18. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: April 28, 2024



Dr. Aron Silverstone
Durham, NC

APPENDIX A

'055 Pat. Fig. 2 position	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
TauD	M	S	E	R	L	S	I	T	P	L	G	P	Y	I	G	A	Q	I	S	G	A	D	L	T	R	P	L	S	D	N	Q	F	E	Q	L
Elkins sec. structures						β1	β1	β1	β1	β1					β2	β2	β2	β2	β2	β2									α1	α1	α1	α1	α1	α1	α1
AAD-12 position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		26	27	28	29	30	31	32	33	34
AAD-12 (SEQ ID NO:2)	M	Q	T	T	L	Q	I	T	P	T	G	A	T	L	G	A	T	V	T	G	V	H	L	A	T		L	D	D	A	G	F	A	A	L

'055 Pat. Fig. 2 position	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85
TauD	Y	H	A	V	L	R	H	Q	V	V	F	L	R	D	Q	A	I	T	P	Q	Q	Q	R	A	L	A	Q	R	F	G					
Elkins sec. structures	α1	α1	α1	α1	α1	α1	α1		β3	β3	β3	β3	β3							α2	α2	α2	α2	α2	α2	α2	α2	α2	α2						
AAD-12 position	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64					
AAD-12 (SEQ ID NO:2)	H	A	A	W	L	Q	H	A	L	L	I	F	P	G	Q	H	L	S	N	D	Q	Q	I	T	F	A	K	R	F	G					

'055 Pat. Fig. 2 position	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120			
TauD					E	L	H	I	H	P	V	Y	P	H	A	E	G	V	D	E	I	I	V	L	D	T	H	N	D	N	P	P						
Elkins sec. structures					β4	β4	β4													β5	β5	β5	β5	β5														
AAD-12 position					65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95			
AAD-12 (SEQ ID NO:2)					A	I	E	R	I	G	G	G	D	I	V	A	I	S	N	V	K	A	D	G	T	V	R	Q	H	S	P	A	E	W	D			

APPENDIX A

'055 Pat. Fig. 2 position	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155
TauD								D	N	D	N	W	H	T	D	V	T	F	I	E	T	P	P	A	G	A	I	L	A	A	K	E	L	P	S
Elkins sec. structures													β6	β6	β6									β7	β7	β7	β7	β7	β7	β7	β7				
AAD-12 position	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130
AAD-12 (SEQ ID NO:2)	D	M	M	K	V	I	V	G	N	M	A	W	H	A	D	S	T	Y	M	P	V	M	A	Q	G	A	V	F	S	A	E	V	V	P	A

'055 Pat. Fig. 2 position	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190
TauD	T	G	G	D	T	L	W	T	S	G	I	A	A	Y	E	A	L	S	V	P	F	R	Q	L	L	S	G	L	R	A	E	H	D	F	R
Elkins sec. structures				β8	β8	β8	β8	β8	β8			α3	α3	α3	α3	α3		α4	α4	α4	α4	α4	α4	α4			β9	β9	β9	β9	β9	β9			
AAD-12 position	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165
AAD-12 (SEQ ID NO:2)	V	G	G	R	T	C	F	A	D	M	R	A	A	Y	D	A	L	D	E	A	T	R	A	L	V	H	Q	R	S	A	R	H	S	L	V

'055 Pat. Fig. 2 position	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225
TauD	K	S	F	P				E	Y	K	Y	R	K	T	E	E	E	H	Q	R	W	R	E	A	V	A	K	N	P	P	L	L	H	P	V
Elkins sec. structures																						α5	α5	α5	α5	α5	α5				β10	β10	β10		
AAD-12 position	166	167	168	169					170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196
AAD-12 (SEQ ID NO:2)	Y	S	Q	S					K	L	G	H	V	Q	Q	A	G	S	A	Y	I	G	Y	G	M	D	T	T	A	T	P	L	R	P	L

APPENDIX A

'055 Pat. Fig. 2 position	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260
TauD	V	R	T	H	P	V	S	G	K	Q	A	L	F	V	N	E	G	F	T	T	R	I	V	D	V	S	E	K	E	S	E	A	L	L	S
Elkins sec. structures	β11	β11	β11	β11					β12	β12	β12	β12	β12					β13	β13	β13	β13	β13	β13				α6	α6	α6	α6	α6	α6	α6	α6	α6
AAD-12 position	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212		213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230
AAD-12 (SEQ ID NO:2)	V	K	V	H	P	E	T	G	R	P	S	L	L	I	G	R		H	A	H	A	I	P	G	M	D	A	A	E	S	E	R	F	L	E

'055 Pat. Fig. 2 position	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295
TauD	F	L	F	A	H	I	T	K	P	E	F	Q	V	R	W	R	W	Q	P	N	D	I	A	I	W	D	N	R	V	T	Q	H	Y	A	N
Elkins sec. structures	α6	α6	α6	α6	α6	α6					β14	β14	β14	β14	β14					β15	β15	β15	β15	β15	β15	β15	β15				β16	β16	β16	β16	β16
AAD-12 position	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265
AAD-12 (SEQ ID NO:2)	G	L	V	D	W	A	C	Q	A	P	R	V	H	A	H	Q	W	A	A	G	D	V	V	V	W	D	N	R	C	L	L	H	R	A	E

'055 Pat. Fig. 2 position	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322
TauD	A	D	Y	L	P	Q	R	R	I	M	H	R	A	T	I	L	G	D	K	P	F	Y	R	A	G		
Elkins sec. structures								β17	β17	β17	β17	β17	β17	β17	β17	β17											
AAD-12 position	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292
AAD-12 (SEQ ID NO:2)	P	W	D	F	K	L	P	R	V	M	W	H	S	R	L	A	G	R	P	E	T	E	G	A	A	L	V

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																					
																		1M	0.6	w	c	p	d	h	f	g	y	n	i	s	t	v	q	e	M	a	l	R	k		
																		2Q	0.6	w	c	m	p	i	g	h	d	n	Q	v	r	F	t	l	k	e	S	y	a		
																	w	3T	1	c	f	M	y	h	i	p	g	l	n	v	r	q	d	T	s	a	k	E			
																	w	4T	1	c	f	m	y	h	i	l	p	v	g	d	q	n	R	e	a	k	S	T			
							h	w	d	q	n	p	e	c	r	g	s	k	y	5L	1	t	a	f	m	V	L	l													
																		w	6Q	1	c	f	m	y	h	i	p	l	g	n	r	d	V	t	Q	k	e	S	A		
							w	h	g	d	n	r	q	y	e	k	c	s	p	f	7I	1	m	t	l	A	V	l													
																		w	8T	1	c	f	y	m	h	i	p	v	l	g	N	d	Q	R	a	T	s	e	k		
													w	c	m	f	y	i	h	9P	1	v	l	n	g	t	s	r	d	a	k	e	Q	P							
								w	h	c	d	g	n	y	p	q	e	r	10T	1	k	s	f	m	a	i	v	T	L												
																			11G	1	w	c	m	i	p	f	v	H	y	l	r	Q	n	d	G	T	a	s	e	k	
																		w	12A	1	f	m	y	h	c	i	l	v	r	n	q	d	k	e	P	T	G	s	A		
																			13T	1	c	w	p	d	m	e	q	k	n	g	r	i	T	s	V	a	H	L	f	Y	
							d	c	g	n	e	h	w	k	s	r	p	q	t	14L	1	y	a	m	v	F	l	L													
																		w	15G	1	h	m	f	y	i	c	n	q	r	d	l	k	e	t	p	V	s	G	A		
		w	h	y	f	m	i	q	r	c	l	n	d	k	e	v	t	p	16A	1	s	G	A																		
																		w	17T	1	c	f	y	m	h	i	p	v	l	G	n	r	T	Q	d	s	a	k	E		
		h	w	q	d	n	p	r	e	g	c	k	s	y	f	m	t	a	18V	1	l	l	V																		
													w	f	y	c	m	19T	1	h	i	l	p	v	g	r	q	n	d	k	a	E	S	T							
							w	m	i	f	c	v	l	y	r	h	p	q	20G	1	t	k	a	e	s	n	D	G													
							w	h	g	d	n	r	q	y	e	k	s	c	p	21V	1	f	m	t	A	L	l	V													
												w	m	c	i	f	v	l	22H	1	y	r	p	t	q	a	k	s	g	H	e	n	D								
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	23L	1	L																				
																		w	24A	1	c	f	m	y	h	i	p	l	v	g	n	d	q	e	s	T	A	R	k		
																		w	25T	1	f	y	m	h	i	p	v	l	g	n	d	q	s	T	a	R	E	K			
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	26L	1	L																				
																		w	27D	1	c	f	m	y	i	h	v	l	p	r	q	G	a	k	n	T	e	S	D		

APPENDIX B

Predict Not Tolerated																Position	Seq Rep	Predict Tolerated																						
															w	c	f	m	28D	1	y	i	h	l	v	r	q	t	g	P	k	a	n	e	S	D				
																		w	29A	1	c	f	y	m	h	i	p	v	l	G	r	q	N	d	T	k	A	S	e	
																	w	c	30G	1	y	f	m	h	i	v	p	l	G	n	r	T	Q	d	s	a	k	E		
																			31F	1	c	d	p	m	e	q	k	n	g	r	W	s	t	i	h	A	V	l	y	F
																	w		32A	1	c	f	y	m	h	i	p	v	l	g	t	N	q	d	R	s	A	k	E	
															w	c	f	y	m	33A	1	h	i	v	l	p	g	n	r	t	s	k	Q	d	A	E				
							h	w	d	q	n	p	e	c	r	g	s	k	y	34L	1	t	a	f	m	V	L	l												
																			35H	1	c	w	p	m	d	q	n	E	g	k	r	i	t	s	v	a	H	L	f	Y
																		w	36A	1	c	m	f	y	H	i	p	v	l	g	n	R	q	t	D	S	A	k	e	
																	w	h	37A	1	c	y	n	d	q	r	f	m	e	p	k	g	t	s	i	v	L	A		
																			38W	1	c	d	p	e	k	n	q	g	W	r	s	t	h	M	a	i	V	F	y	l
																			39L	1	w	c	m	p	i	H	r	v	g	q	f	t	n	k	D	s	L	a	y	e
																w	c	y	f	40Q	1	m	h	i	p	v	l	g	n	d	s	T	a	Q	R	E	K			
																			41H	1	c	w	m	p	d	e	g	i	n	q	t	s	v	a	r	l	f	K	H	Y
																		w	42A	1	c	f	y	m	h	i	l	v	p	n	r	g	d	t	k	Q	e	S	A	
		h	w	d	n	g	q	r	e	c	p	k	s	y	f	t	m	a	43L	1	i	L	V																	
					h	d	w	n	g	q	e	p	c	r	s	k	y	t	44L	1	a	f	m	V	l	L														
																			45I	1	c	p	d	w	e	q	n	k	g	r	m	s	t	h	a	F	Y	l	l	V
						d	n	c	g	e	h	k	r	p	q	s	t	w	a	46F	1	m	v	i	y	L	F													
																			47P	1	c	w	m	i	f	P	v	d	H	g	y	l	n	t	s	a	e	q	R	k
													w	m	i	f	c	v	l	48G	1	y	r	h	p	q	t	k	a	e	s	n	D	G						
y	w	v	t	s	r	p	n	m	l	k	i	h	g	f	e	d	c	a	49Q	1	Q																			
																			50H	1	w	c	m	f	i	H	y	P	v	l	g	r	t	q	n	s	D	A	k	e
				h	d	w	n	g	c	e	r	p	s	q	k	y	t	a	51L	1	f	m	v	L	l															
			w	f	y	h	m	c	i	l	r	q	e	g	k	v	d	p	52S	1	n	a	S	T																
																		w	53N	1	c	f	m	y	i	h	v	l	P	r	t	g	a	Q	s	k	D	e	N	
									c	w	f	y	m	i	h	v	l	54D	1	r	g	p	n	t	s	a	k	Q	D	E										

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																					
y	w	v	t	s	r	p	n	m	l	k	i	h	g	f	e	d	c	a	55Q	1	Q																				
											w	c	m	i	f	v	p	y	56Q	1	l	g	t	s	a	n	d	e	r	k	H	Q									
																		w	57I	1	c	d	p	g	h	n	q	e	s	y	t	k	f	a	R	M	v	l	l		
								w	h	y	f	m	c	r	q	d	n	i	58T	1	l	k	e	p	g	v	s	T	A												
					d	n	c	g	e	h	k	r	p	q	s	t	w	a	59F	1	m	v	i	y	L	F															
			w	h	y	f	m	i	c	r	q	l	n	d	k	e	v	p	60A	1	t	g	S	A																	
																w	c	f	61K	1	m	y	i	h	v	p	g	d	n	t	s	L	a	e	Q	R	K				
															w	c	m	f	62R	1	i	y	v	p	h	l	t	a	g	s	d	e	q	k	N	R					
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	e	d	c	a	63F	1	F																				
y	w	v	t	s	r	q	p	n	m	l	k	i	h	f	e	d	c	a	64G	1	G																				
																w	c	f	y	65A	1	m	h	i	v	l	g	n	r	t	s	P	d	Q	k	A	E				
												w	d	c	h	p	n	g	66I	1	q	e	s	k	y	R	t	m	f	a	L	V	I								
										w	c	m	f	y	i	v	l	67E	1	r	p	t	g	s	n	a	q	k	H	D	E										
																	w	68R	1	c	f	m	y	h	l	P	v	l	G	n	R	t	q	D	s	a	k	e			
																		69I	1	w	c	m	p	d	n	G	l	q	r	e	k	t	H	V	s	f	A	l	y		
																		70G	1	w	c	m	P	i	d	n	q	G	h	v	t	R	e	F	s	l	k	a	y		
												w	c	p	d	q	h	71G	1	n	r	e	G	k	s	t	m	a	y	f	L	V	I								
																		72G	1	c	w	m	p	d	n	G	q	i	e	t	s	r	v	K	h	a	f	L	Y		
																	w	73D	1	c	y	f	m	h	i	P	V	l	g	n	r	q	T	D	s	a	K	e			
								w	d	p	c	q	e	n	k	r	g	74I	1	h	s	t	a	m	f	Y	L	V	I												
																	w	75V	1	c	f	y	m	h	i	P	V	l	g	N	r	q	t	D	s	A	k	e			
												w	c	f	y	m	i	76A	1	h	v	l	r	g	p	n	t	s	q	k	A	D	E								
		h	w	q	d	n	p	e	r	g	c	k	s	y	f	m	t	a	77I	1	l	V	l																		
																		78S	1	w	c	m	f	h	y	p	l	g	v	l	n	r	d	Q	a	k	e	t	S		
																		79N	1	w	c	p	h	M	g	d	q	N	r	f	y	e	k	s	t	a	i	l	V		
				h	w	d	q	n	p	e	r	g	c	s	k	y	t	a	80V	1	f	m	L	l	V																
																	w	81K	1	y	c	f	m	h	i	p	v	l	G	n	R	t	q	D	a	S	K	e			

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																					
																		82A	0.6	w	c	m	f	y	h	p	i	g	n	v	L	d	q	t	r	s	A	e	K		
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	c	a	83D	0.6	D																				
y	w	v	t	s	r	q	p	n	m	l	k	i	h	f	e	d	c	a	84G	0.6	G																				
																w	c	f	85T	1	m	y	i	h	v	p	g	l	d	n	s	a	T	q	e	R	K				
																			86V	1	w	c	m	P	i	H	f	g	n	V	y	r	l	q	d	t	s	a	k	E	
																			87R	0.8	w	c	m	f	h	p	y	i	g	n	d	v	q	t	L	s	R	e	A	k	
																	w		88Q	0.6	c	m	f	y	h	i	p	l	v	n	g	r	t	d	s	k	Q	A	e		
																c	w		89H	0.6	m	f	i	y	v	p	d	g	l	n	H	t	s	a	e	q	R	K			
													w	c	m	f	y	i	90S	0.6	h	v	l	p	r	q	g	t	k	a	n	e	S	D							
															w	f	m	y	91P	0.6	h	c	i	l	v	r	n	q	d	k	e	t	g	P	S	A					
																	w		92A	0.6	c	m	f	y	h	i	p	v	l	n	d	g	t	q	s	e	A	R	k		
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	d	c	a	93E	0.2	E																				
y	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	94W	0.2	W																				
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	c	a	95D	0.2	D																				
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	c	a	96D	0.2	D																				
																	w		97M	0.8	c	f	M	y	h	i	p	v	l	g	N	r	q	d	T	s	a	k	E		
																			98M	1	w	c	M	p	i	H	g	f	V	N	d	r	q	l	t	y	s	k	a	E	
																	w		99K	1	c	f	y	m	h	i	p	V	L	g	n	r	t	q	D	S	a	K	e		
																			100V	1	w	c	m	p	d	q	N	G	r	e	k	i	t	h	s	V	a	F	l	y	
																			101I	1	w	c	m	f	h	l	y	P	v	g	l	N	d	q	t	R	s	a	e	k	
																			102V	1	w	d	c	n	g	e	q	k	P	r	s	h	m	t	a	y	F	i	V	L	
																	w		103G	1	c	m	f	h	y	l	p	v	l	r	n	G	q	t	D	s	k	A	e		
											w	m	i	f	c	v	l	y	104N	1	r	p	h	q	t	a	k	e	s	d	G	N									
																			105M	1	w	C	M	f	h	i	p	y	v	g	l	n	r	Q	D	t	s	a	k	e	
																	w		106A	1	c	m	f	y	h	i	p	v	L	g	r	N	q	t	D	s	A	k	e		
y	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	107W	1	W																				
y	w	v	t	s	r	q	p	n	m	l	k	i	g	f	e	d	c	a	108H	1	H																				

APPENDIX B

Predict Not Tolerated																			Position	Seq Rep	Predict Tolerated																				
												w	f	y	h	m	c	i	109A	1	l	r	q	p	v	d	g	e	k	n	A	S	T								
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	c	a	110D	1	D																				
																		w	111S	1	h	m	y	f	c	r	q	d	n	e	p	k	l	i	g	V	t	a	S		
			w	f	y	h	m	c	i	l	r	q	e	g	k	d	v	p	112T	1	n	a	S	T																	
		q	k	n	d	r	g	e	p	h	c	t	s	m	a	v	i	w	113Y	1	l	Y	F																		
																			114M	1	w	c	p	g	h	d	n	M	t	f	s	y	Q	e	v	R	k	a	l	L	
													w	c	f	y	m		115P	1	i	h	v	l	g	r	n	t	P	s	a	Q	k	D	E						
																	w		116V	1	h	g	y	f	c	d	n	m	r	q	P	k	s	e	l	T	I	A	V		
																	w		117M	1	h	c	y	f	n	d	q	r	M	i	k	e	t	l	g	P	v	s	A		
													w	h	y	f			118A	1	m	c	i	n	r	q	d	l	k	e	t	v	P	g	s	A					
																w	c		119Q	1	f	y	m	h	i	v	p	l	g	n	d	t	s	Q	A	R	e	K			
																			120G	1	c	w	p	d	m	e	q	k	n	r	G	i	t	s	v	h	A	I	F	Y	
												w	h	f	y	m	c		121A	1	r	n	q	d	i	l	p	k	e	g	t	V	S	A							
				h	w	d	n	q	e	p	g	c	r	s	k	y	t		122V	1	a	f	M	L	I	V															
			d	g	c	n	e	h	w	s	k	r	p	q	t	y	a		123F	1	v	i	M	F	L																
																	w		124S	1	c	f	m	y	h	i	l	v	p	n	q	d	g	t	e	k	R	A	S		
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	125A	1	A																				
																	w		126E	1	c	f	y	m	h	l	p	V	l	g	n	t	R	d	q	s	a	E	K		
																	w	c	127V	1	f	m	y	h	i	l	p	g	V	r	n	t	s	q	a	k	D	E			
		h	w	d	n	g	q	r	e	c	p	k	s	y	f	m	t	a	128V	1	i	L	V																		
													w	m	c	f	i		129P	1	y	l	v	h	q	r	k	t	e	a	g	s	d	N	P						
													w	y	c	f			130A	1	m	h	i	l	v	g	n	r	q	t	d	k	P	S	A	E					
																			131V	1	w	c	m	p	i	g	H	f	d	q	r	n	l	y	V	e	k	a	S	T	
y	w	v	t	s	r	q	p	n	m	l	k	i	h	f	e	d	c	a	132G	1	G																				
y	w	v	t	s	r	q	p	n	m	l	k	i	h	f	e	d	c	a	133G	1	G																				
														w	c	m	f		134R	1	i	y	v	l	h	p	q	t	a	R	g	k	s	e	N	D					
y	w	v	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	135T	1	T																				

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																					
																		136C	1	w	C	m	i	p	h	f	v	y	G	n	L	r	q	d	t	s	k	E	a		
			q	n	k	d	r	g	h	e	p	c	t	s	m	a	v	i	137F	1	l	y	W	F																	
																		138A	1	w	m	h	C	d	n	p	r	f	g	q	y	k	e	s	i	L	T	A	v		
											w	m	f	c	i	y	l	v	139D	1	h	r	p	q	k	a	t	g	e	n	S	D									
																		140M	1	w	c	h	y	q	f	d	r	n	e	i	p	k	t	v	M	s	l	G	a		
																		141R	1	c	w	d	p	m	n	g	e	q	s	t	l	h	a	v	f	k	R	l	Y		
				w	h	y	f	m	c	r	q	d	n	i	k	l	e	p	142A	1	g	v	s	T	A																
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	143A	1	A																				
			d	q	n	k	p	r	c	e	g	h	m	t	s	a	i	v	144Y	1	l	f	W	Y																	
						c	w	f	m	y	i	l	v	h	r	t	g	p	145D	1	s	n	a	k	q	E	D														
				w	h	y	f	m	c	r	q	d	n	i	k	l	e	p	146A	1	g	v	s	T	A																
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	147L	1	L																				
																	w	148D	1	f	c	m	y	i	h	l	v	r	P	q	g	k	t	a	n	e	S	D			
																	w	149E	1	c	y	f	m	h	i	P	V	l	g	n	R	t	q	D	s	a	k	E			
																w	y	c	150A	1	f	m	h	i	v	P	l	g	n	r	T	q	D	s	A	k	E				
																		151T	1	c	w	d	p	g	n	e	k	q	r	s	h	T	a	M	y	F	v	i	L		
											c	w	f	m	y	i	d	v	152R	1	h	p	g	l	n	s	t	a	e	Q	K	R									
												w	f	c	y	m	h	153A	1	i	l	v	p	n	r	d	g	t	k	e	Q	S	A								
																	w	154L	1	c	m	f	h	y	p	i	g	n	r	v	L	q	d	T	s	a	k	E			
						h	w	d	q	n	p	e	r	c	g	s	k	y	155V	1	t	a	f	m	L	V	l														
																	w	c	156H	1	m	f	i	y	v	p	l	g	r	t	H	q	n	a	k	d	S	E			
																w	c	m	157Q	1	f	i	y	v	l	h	p	r	t	a	k	s	Q	n	e	D	G				
																	w	c	158R	1	d	p	h	g	n	y	s	e	t	q	f	m	a	v	i	k	R	L			
																	w	159S	1	c	m	f	y	h	i	p	V	l	g	N	q	d	R	t	a	S	e	k			
													w	h	d	y	n	160A	1	r	f	q	m	e	k	p	g	s	l	t	C	i	V	A							
																	w	161R	1	c	f	m	y	h	i	p	l	g	V	n	t	d	q	s	a	R	k	E			
y	w	v	t	s	r	q	p	n	m	l	k	i	g	f	e	d	c	a	162H	1	H																				

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																					
																		163S	1	w	c	m	i	p	v	f	r	l	h	q	Y	k	a	e	t	g	D	S	n		
																		164L	1	c	d	w	p	n	e	g	k	q	r	h	s	t	m	y	A	v	F	i	L		
																		165V	1	w	c	p	M	g	h	d	n	q	f	R	s	y	e	k	T	i	a	L	V		
																		166Y	1	c	w	m	p	i	d	g	v	f	h	N	t	s	e	l	a	q	Y	R	K		
																	w	167S	1	h	m	y	f	c	r	q	d	n	e	p	k	l	i	g	V	t	a	S			
																		168Q	1	c	w	m	p	d	i	g	n	v	h	t	s	F	e	Q	a	l	y	R	k		
																		169S	1	w	c	m	i	h	P	q	r	d	F	v	n	k	l	e	t	y	G	S	a		
																	w	170K	1	c	f	y	m	h	i	p	v	L	g	n	r	t	q	d	S	a	K	E			
							d	c	p	n	e	g	q	k	r	h	s	t	w	171L	1	a	m	v	i	f	Y	L													
																		172G	1	w	c	m	p	i	v	f	h	t	q	l	e	d	s	a	r	n	Y	G	K		
																		173H	1	c	w	p	m	D	e	k	n	g	r	Q	i	t	s	v	a	H	I	F	Y		
																w	h	174V	0.8	y	f	c	g	m	d	r	n	q	p	k	e	s	l	i	A	T	V				
													w	c	f	y	m	i	175Q	0.8	h	v	l	g	p	r	n	t	s	a	k	D	Q	E							
																		176Q	0.8	w	c	m	p	i	Q	v	t	e	g	d	r	h	s	k	a	f	l	N	Y		
																w		177A	1	c	f	y	m	h	i	p	l	v	g	n	q	d	R	T	A	k	e	S			
																w	c	178G	0.6	f	m	y	i	h	v	p	l	G	d	n	t	s	a	q	e	R	K				
																		179S	0.6	w	c	m	i	p	f	v	l	H	y	q	r	g	e	k	a	d	t	n	S		
																	w	180A	0.6	c	m	f	h	y	p	g	n	i	r	d	l	Q	t	s	k	e	V	A			
																		181Y	0.6	c	w	m	d	p	i	g	f	v	n	h	s	t	l	a	Y	e	q	R	K		
																d	c	p	182I	0.6	q	n	e	g	r	k	h	s	W	m	t	a	y	f	l	V	I				
																	w	183G	1	c	f	y	M	h	i	p	v	l	G	n	R	t	q	D	s	a	k	E			
																	w	184Y	1	m	i	f	h	v	p	Y	l	g	r	n	t	s	q	k	A	D	E				
																		185G	1	c	f	y	m	h	i	p	V	l	G	n	r	t	Q	d	s	A	k	E			
																		186M	1	c	f	M	y	h	i	p	V	l	g	n	R	t	q	D	s	a	K	e			
																		187D	1	c	f	y	m	h	i	v	p	l	g	r	t	Q	N	A	s	D	k	e			
																		188T	1	c	f	y	M	h	i	p	v	l	G	n	r	q	d	T	s	A	K	e			
																		189T	1	w	c	M	p	i	g	h	D	N	v	q	r	F	l	T	k	s	e	y	a		

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																						
																	w	c	190A	1	f	y	m	h	i	v	l	g	n	d	t	q	P	s	e	A	R	K				
																	w	c	191T	1	f	y	m	h	i	l	v	g	r	n	q	d	a	s	k	T	P	E				
																		w	192P	1	g	h	c	d	n	y	r	f	m	q	P	e	k	s	T	L	i	a	V			
																		w	193L	1	c	d	p	g	h	q	r	e	N	s	k	y	m	t	f	a	i	V	L			
																			194R	1	c	W	m	d	p	g	i	n	e	t	s	v	Q	a	f	H	l	y	R	k		
																w	c	m	f	195P	1	y	i	h	v	d	l	n	t	g	s	q	e	a	k	R	P					
				d	h	w	g	n	c	e	r	s	q	p	k	y	t	a	196L	1	f	m	i	V	L																	
y	w	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	197V	1	V																					
																	w	c	198K	1	f	m	y	i	d	h	p	g	l	n	V	s	t	a	e	q	R	K				
					w	h	y	g	f	d	r	c	q	m	n	e	p	k	199V	1	l	s	i	a	V	T																
y	w	v	t	s	r	q	p	n	m	l	k	i	g	f	e	d	c	a	200H	1	H																					
					w	h	y	f	m	c	i	n	r	q	l	d	k	e	201P	1	v	t	g	s	A	P																
																	w	202E	1	c	m	f	h	y	i	p	l	V	n	r	G	t	q	d	s	k	a	E				
																	w	203T	1	c	m	f	i	y	p	l	v	r	q	g	e	d	H	k	n	a	T	S				
																w	m	c	f	204G	1	i	y	h	v	l	p	t	q	e	d	n	s	a	k	R	G					
		c	w	f	m	d	i	y	v	g	p	h	s	l	n	t	a	e	205R	1	q	K	R																			
																	w	c	f	206P	1	m	y	i	h	v	l	g	n	d	t	P	s	a	Q	e	r	K				
																			207S	1	w	m	c	i	h	q	d	r	p	n	F	v	l	k	e	y	t	G	S	A		
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	208L	1	L																					
										d	c	p	k	q	n	e	g	r	209L	1	m	t	s	h	a	i	w	v	L	Y	F											
		h	w	q	d	p	n	e	r	c	g	s	k	y	t	a	f	m	210I	1	L	V	l																			
															w	m	i	f	c	211G	1	v	l	y	p	h	r	q	t	k	a	e	d	S	G	N						
																	w	y	212R	1	c	f	m	h	i	p	v	l	g	n	t	R	d	Q	S	A	k	E				
																			213H	1	c	w	p	d	m	e	q	k	n	g	r	t	i	s	v	a	l	F	Y	H		
															w	h	m	f	214A	1	y	r	d	q	n	e	k	p	l	i	g	C	s	v	T	A						
																			215H	1	w	c	m	f	H	i	y	p	v	l	G	r	n	Q	d	T	a	S	k	e		
																	w	c	216A	1	m	f	i	y	p	v	g	d	l	H	n	t	s	q	e	A	R	K				

APPENDIX B

Predict Not Tolerated																	Position	Seq Rep	Predict Tolerated																					
		h	w	q	d	n	p	e	r	g	c	k	s	y	f	m	t	a	217I	1	l	V	l																	
																	w	218P	1	c	f	y	m	h	i	P	l	g	n	r	V	q	t	d	s	k	A	E		
											w	m	f	c	i	y	v	l	219G	1	h	p	r	q	t	k	e	a	n	S	D	G								
						d	h	g	w	n	c	e	r	s	k	p	q	y	220M	1	t	a	f	i	V	L	M													
																	w	221D	1	f	y	c	m	h	i	l	v	P	g	r	q	n	D	a	k	e	T	S		
																	w	222A	1	f	y	m	h	i	p	l	V	g	n	r	t	q	s	D	A	k	E			
																	w	223A	1	f	c	y	m	h	i	l	v	n	q	d	P	t	r	g	s	e	K	A		
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	d	c	a	224E	1	E																			
																	w	225S	1	m	f	i	y	h	c	l	r	q	v	e	k	p	t	d	n	G	a	S		
																w	c	f	226E	1	y	m	i	h	v	p	l	g	n	d	t	s	a	q	E	R	K			
																			227R	1	w	c	M	P	h	f	i	y	g	v	n	d	q	L	R	t	s	A	e	k
						d	g	c	n	h	e	k	r	s	p	q	w	t	a	228F	1	y	m	v	i	F	L													
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	229L	1	L																			
																	w	y	c	230E	1	f	m	h	i	p	v	l	g	n	t	R	d	Q	S	A	k	E		
																			231G	1	w	c	m	i	p	F	h	v	l	r	y	t	G	q	n	s	k	a	D	E
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	232L	1	L																			
																			233V	1	c	w	p	d	m	e	k	q	N	g	r	t	s	i	a	V	h	L	F	Y
											w	c	f	y	m	i	h		234D	1	v	l	r	g	p	n	t	s	q	k	A	D	E							
																			235W	1	c	m	p	W	d	q	e	i	g	t	n	s	v	r	k	a	f	l	y	H
																	w	h	236A	1	y	d	n	c	r	q	f	m	e	k	p	g	s	t	l	l	v	A		
													w	h	f	m	y		237C	1	r	q	e	d	k	p	g	l	n	i	C	v	a	s	T					
												c	w	f	m	y	i		238Q	1	v	d	h	p	g	l	n	s	t	a	e	R	K	Q						
																			239A	1	w	c	m	P	i	d	n	h	g	q	v	t	R	F	e	l	s	k	y	A
											w	c	f	m	y	i	h		240P	1	v	l	r	g	t	n	s	P	a	k	q	D	E							
																			241R	1	w	c	d	p	m	n	g	e	q	t	s	h	i	v	a	y	k	R	l	F
																	w		242V	1	c	h	f	y	m	g	p	n	d	r	e	k	Q	s	l	i	a	T	V	
																			243H	1	w	C	p	d	m	e	k	q	n	g	r	t	i	s	a	V	H	l	f	Y

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																														
																		244A	1	w	c	m	f	h	y	p	n	d	g	i	q	l	t	s	e	R	V	k	A											
																		245H	1	c	W	p	d	m	e	q	n	g	k	r	t	s	i	a	V	H	f	l	y											
																	c	w	f	m	y	i	d	v	p	h	g	246Q	1	l	n	s	t	a	e	Q	K	R												
y	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	247W	1	W																													
																		w	c	248A	1	f	y	m	h	i	p	v	l	g	t	N	r	d	s	Q	A	e	K											
																				249A	1	w	c	m	f	h	y	P	i	g	n	L	r	d	q	V	t	s	K	A	e									
																		w	m	i	c	250G	1	f	v	l	y	p	r	q	t	a	H	k	e	s	G	D	N											
																	w	c	m	f	i	y	v	l	h	r	p	251D	1	t	g	s	a	k	n	e	Q	D												
																				252V	1	f	m	L	l	V																								
																	w	h	d	g	n	y	r	q	c	e	k	p	s	253V	1	f	m	t	i	A	L	V												
																		h	w	d	n	q	g	r	e	p	c	s	k	y	254V	1	f	t	a	l	M	l	V											
y	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	255W	1	W																													
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	c	a	256D	1	D																													
y	w	v	t	s	r	q	p	m	l	k	i	h	g	f	e	d	c	a	257N	1	N																													
																		w	c	258R	1	d	y	f	m	p	h	g	n	s	t	i	v	e	a	q	L	k	R											
																				259C	1	w	d	m	h	n	p	g	r	f	e	k	y	Q	s	t	C	i	l	a	V									
																			w	260L	1	g	h	d	n	y	r	c	q	p	e	k	f	m	s	a	T	L	i	V										
																		c	w	d	g	h	n	p	s	261L	1	e	y	r	t	k	a	Q	f	v	i	M	L											
y	w	v	t	s	r	q	p	n	m	l	k	i	g	f	e	d	c	a	262H	1	H																													
																		c	w	263R	1	m	d	p	i	f	v	g	h	n	s	t	e	a	l	q	Y	k	R											
																		w	h	m	f	y	i	c	n	264A	1	q	r	d	l	k	e	t	p	s	V	G	A											
																			w	265E	1	c	f	y	m	h	i	p	V	l	g	N	t	q	d	R	s	a	k	E										
																			w	266P	1	c	m	f	y	h	i	l	v	n	d	P	q	g	t	e	s	R	k	A										
																				267W	1	c	m	W	p	q	k	D	r	e	i	g	t	n	s	v	a	h	l	f	Y									
																				268D	1	w	m	c	i	v	p	r	l	h	f	q	t	k	a	Y	s	g	e	n	D									
																				269F	1	w	c	p	d	n	g	m	Q	e	k	r	s	t	h	A	l	v	F	y	L									
																		w	270K	1	c	f	y	m	h	i	v	l	P	r	G	n	q	t	d	S	a	K	e											

APPENDIX B

Predict Not Tolerated																		Position	Seq Rep	Predict Tolerated																				
																	w	271L	1	c	f	m	y	h	i	p	v	L	g	n	t	d	Q	r	s	A	e	K		
																		272P	1	w	c	m	P	d	i	n	g	h	v	q	t	e	F	s	a	l	y	R	k	
y	w	v	t	s	q	p	n	m	l	k	i	h	g	f	e	d	c	a	273R	1	R																			
																		274V	1	w	c	m	p	D	g	n	q	r	l	k	t	h	E	s	V	f	a	l	Y	
				d	h	g	c	n	e	w	s	r	k	p	y	q	t	a	275M	1	f	v	i	M	L															
																		276W	1	c	W	m	p	d	g	n	i	e	q	s	T	v	H	a	f	R	l	k	y	
										c	w	m	f	i	d	v	p	y	277H	1	g	s	l	t	a	n	e	q	H	k	R									
											w	f	y	h	m	c	i	278S	1	l	r	q	p	d	v	n	e	k	g	T	S	A								
																	w	279R	1	c	f	m	y	h	i	p	g	d	l	v	n	q	e	a	s	R	k	T		
						w	h	d	g	n	q	r	e	p	c	y	k	s	280L	1	f	m	a	T	L	l	V													
																	w	281A	1	m	c	h	f	i	y	n	q	d	r	p	v	t	e	k	L	G	s	A		
							w	m	i	f	c	v	l	y	r	h	p	q	282G	1	t	k	a	e	s	n	D	G												
																	w	283R	1	c	f	m	y	h	i	p	V	l	g	n	R	q	D	T	s	a	k	e		
																	w	284P	1	y	c	f	m	h	i	v	l	P	g	n	t	q	d	R	s	A	K	E		
																	w	285E	1	c	m	f	y	h	i	g	n	l	r	q	t	s	P	d	V	k	a	E		
																		286T	1	w	c	d	m	p	g	n	q	r	h	e	k	s	F	y	i	T	l	A	V	
																		287E	0.8	w	c	m	p	d	g	i	n	q	t	h	V	R	s	E	f	k	a	l	Y	
																		288G	0.4	w	c	m	f	i	y	h	p	v	l	t	G	q	d	n	s	e	a	R	k	
y	w	v	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	289A	0.4	A																			
														w	m	h	f	290A	0.4	y	c	i	l	r	q	v	n	d	p	t	k	e	s	G	A					
y	w	v	t	s	r	q	p	n	m	k	i	h	g	f	e	d	c	a	291L	0.2	L																			
y	w	t	s	r	q	p	n	m	l	k	i	h	g	f	e	d	c	a	292V	0.2	V																			