

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
Patent 11,371,055

PATENT OWNER'S RESPONSE

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I. Introduction

The Board’s Institution Decision (Paper 11, “ID”) relied on recent enablement decisions in *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023), and *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362 (Fed. Cir. 2023), and similar written-description decisions such as *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014). ID, 15-16, 40, 52-54; *see also* Pet., 26, 29. These cases stand for the proposition that a claimed genus (usually of antibodies) defined only by function may fail to comply with the written-description or enablement requirements. This PGR, however, involves distinctly different issues.

Unlike in *Amgen*, *Baxalta*, and *AbbVie*, all challenged claims of U.S. Patent No. 11,371,055 (“the ’055 patent”) define sequence-limited *enzymes*, which are significantly different proteins than antibodies. The claims require AAD-12 enzymes having (i) at least 85% sequence identity and (ii) a defined active-site motif. Petitioner failed to prove that either structural feature, let alone both, lacks correlation to the claimed function (dual herbicide-degrading activity). As detailed by Dr. Martin Bollinger, an expert in protein biochemistry and enzymology, several research groups in the early 2000s identified thresholds for predicting enzyme function based on sequence identity. Their results consistently showed that with at least 60% sequence identity, enzymatic function (including substrate specificity)

was conserved with 90% accuracy. With at least 85% sequence identity, as claimed here, the correlation was even stronger:

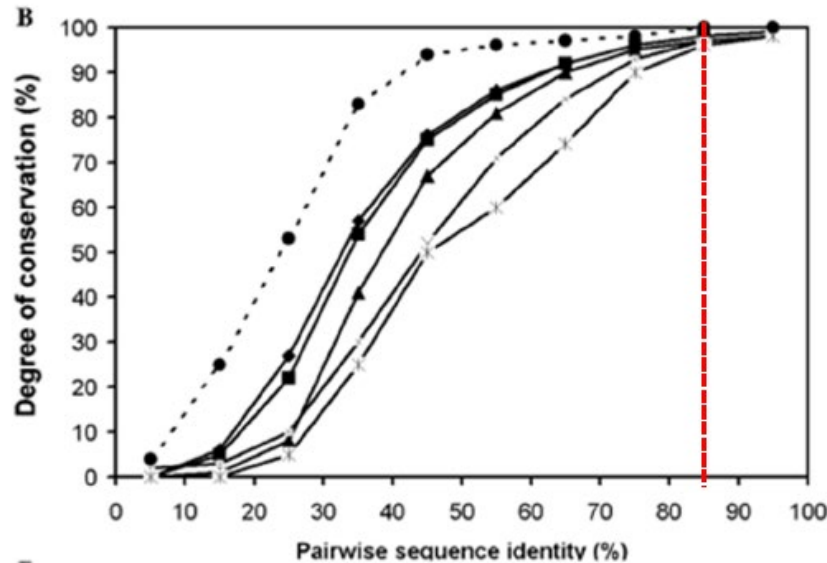


Figure 1, Ex. 2019, 866 (Fig. 1(B)) (graph of enzyme function conservation (y-axis) by percent sequence identity (x-axis); annotation added)

Skilled artisans as of the 2005 and 2006 priority dates thus expected to retain the same or similar function among enzymes having at least 85% sequence identity to SEQ ID NO: 2, *just as the '055 patent discloses*. Ex. 1001, 31:61-32:6 (at 85% sequence identity, enzymes are “highly identical” and “expected to retain similar properties”). Conservation of function was further expected based on the AAD-12 motif, i.e., the catalytic active site defined by specific amino acid residues and their fixed spacing, which is unique to AAD-12 enzymes. The '055 patent therefore cannot be shoehorned into the body of functionally defined genus caselaw (e.g., *Amgen*, *Baxalta*, and *AbbVie*) that involved no function-correlated structure.

The Board should thus reject Petitioner's enablement ground. In *Amgen*, the Supreme Court reaffirmed that enablement may be satisfied by disclosing a “general quality” running throughout a genus that gives it a “fitness” for a claimed function. 598 U.S. at 611. The '055 patent meets that standard, as all AAD-12 enzymes of the challenged claims are *highly identical* in amino acid sequence (i.e., at least 85% identical) and have the *same* active-site motif. A skilled artisan would have understood from the '055 patent that those structural features are correlated to the claimed function, particularly in view of the sequence-function thresholds established in the art before 2005-2006. *See supra* Fig. 1.

Petitioner's *Wands* analysis is also deficient. Dr. Silverstone, who has no enzymology expertise, fails to consider the perspective of skilled artisans who made enzyme variants. He presents only a conclusory, mathematical calculation (10^{106} possible sequences) that falsely assumes an artisan would exercise *no skill* and randomly substitute all 19 alternative amino acids at every possible location. As Dr. Bollinger explains, skilled artisans in 2005-2006 routinely made function-conserved enzyme variants differently. They kept sequence identity high, conserved active site residues, and relied on comparisons to the sequences of related enzymes to identify important conserved residues and residues that could be more freely substituted—i.e., precisely the type of structural guidance that the '055 patent discloses. Regarding the claimed transgenic plants, Dr. Silverstone bases his enablement

positions on his experience with commercial crop development. His positions, however, are directed to unclaimed features and his proposed commercial-development tasks were unnecessary to practice the claimed invention.

The Board should also reject Petitioner's written-description ground. Under *Ariad* and *Ajinomoto*, the common structural features of at least 85% sequence identity and the AAD-12 motif are both amply correlated to the claimed function—together, they compel confirming patentability. Moreover, the genus is comprised of *highly identical* AAD-12 enzymes having an *identical* active-site motif, and thus is essentially the opposite of the functionally and structurally diverse antibody genus considered in *AbbVie*. 759 F.3d at 1301. The disclosed AAD-12 and AAD-12 (v1) enzymes are thus representative members of the non-diverse genus of the claims.

This PGR should also be terminated for lack of jurisdiction because the '055 patent is PGR-ineligible. Dr. Silverstone testified that he *assumed* the '055 patent was entitled only to a 2017 filing date and provided no opinions regarding written description or enablement as of the patent's pre-AIA 2005 and 2006 filing dates. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (en banc) (written description must be analyzed “as of the filing date”). Thus, rather than proving lack of entitlement to priority, Petitioner simply assumed it. The Petition failed to present any legally viable analyses as of the relevant priority dates in 2005-

2006, and neither Petitioner nor the Board can remedy that critical failure now. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016).

Corteva thus respectfully requests that the Board find that Petitioner has not met its burden and either terminate this proceeding or confirm patentability of all challenged claims. *See Gillette Co. v. Sphere USA, LLC*, PGR2022-00030, Paper 31 at 39-40, 54-55 (PTAB Sept. 19, 2023) (terminating for lack of jurisdiction after determining the patent was PGR-ineligible).

II. Scientific Background and State of the Art

A. Enzymes

The following background on enzymes, including SdpA and α KG-dependent dioxygenases, is based on Dr. Bollinger's testimony. Ex. 2011, ¶¶ 1-20. Dr. Bollinger is an expert in protein biochemistry and enzymology, holding the endowed Russell and Mildred Marker professorship in the Department of Biochemistry and Molecular Biology at Penn State University. His research focuses on the structures and mechanisms of enzymes that use transition metals to react with oxygen to transform carbon compounds, which includes 20+ years of experience researching and publishing on α KG-dependent dioxygenases. *Id.*, ¶¶ 10-11. Dr. Bollinger has won many awards for his research, including the American Chemical Society Nobel Laureate Signature Award for Graduate Education in the Chemical Sciences. *Id.*, ¶ 5.

1. Enzyme Classification

Enzymes catalyze biochemical reactions. They bind substrates (compounds required for the reaction) at a location within an interior pocket known as the “active site.” Ex. 2018, 1. To form enzymes, amino-acid building blocks are connected in a linear chain in a specific sequence. An enzyme’s amino acid sequence is called its “primary structure.” *Id.* This linear chain then folds up into a “globular” (meaning more or less spherical) three-dimensional structure in order to function as an enzyme catalyst. Accordingly, an enzyme’s structure and the reaction it catalyzes (its function) are generally dictated by its amino acid sequence. Ex. 2011, ¶¶ 21-22, 24.

Enzymologists classify enzymes using a long-established nomenclature system. An enzyme’s Enzyme Commission or “EC” number refers to its unique four-digit code that categorizes the chemical reaction it catalyzes. *Id.*, ¶ 23; Ex. 2019, 864 (“the Enzyme Commission (EC) is the best developed and most widely used functional classification scheme”). The first three digits of an EC number usually describe the overall type of enzymatic reaction, while the last digit usually represents the substrate specificity of the reaction. Ex. 2020, 36-37.

2. Enzyme Sequence-Function Relationships and Predicting Function Based on Sequence Identity

Skilled artisans have long analyzed the structural and functional similarities between enzymes by comparing their amino acid sequences. By 2005-2006, skilled

artisans had arrived at a general consensus for how to describe the degree of relatedness of enzymes based on their amino acid sequences. Ex. 2011, ¶ 25.

Sequence identities between two or more enzymes may range from less than 10% (few matching residues) to 100% (identical). A sequence identity above 35% or 40% is considered a relatively high level of sequence identity and indicates that two enzymes likely have similar structures and functions. *Id.*, ¶¶ 26-27; Ex. 2021, 85. Often, two enzymes with this level of identity will catalyze the identical reaction or similar reactions. Enzymes having less than 20% sequence identity generally have different structures and functions.

Decades of comparing protein sequences led to the observation of a “twilight zone” for sequence identity. Ex. 2023, 1123. The “twilight zone” represents a range of sequence identity (approximately 20-35%) in which the relatedness of proteins—how similar their structures are, whether they have the same function, and whether they evolved from a common precursor—can be more difficult to judge. *Id.*; Ex. 2021, 85. In other words, relationships between sequence and function are often more unpredictable when sequence identities fall within the twilight zone. Ex. 2011, ¶ 28.

Across the range of possible sequence identities (<10% to 100%), researchers established thresholds for predicting enzyme function in the early 2000s. *Id.*, ¶ 29. These efforts were prompted by genome-sequencing efforts, which were identifying

genes believed to encode enzymes faster than researchers could empirically determine their functions. Skilled artisans therefore conducted studies to determine how reliably one could infer the function of a new sequence by comparing it to the sequence of an enzyme having a known function. *Id.*, ¶¶ 30-34; Ex. 2025, 1.

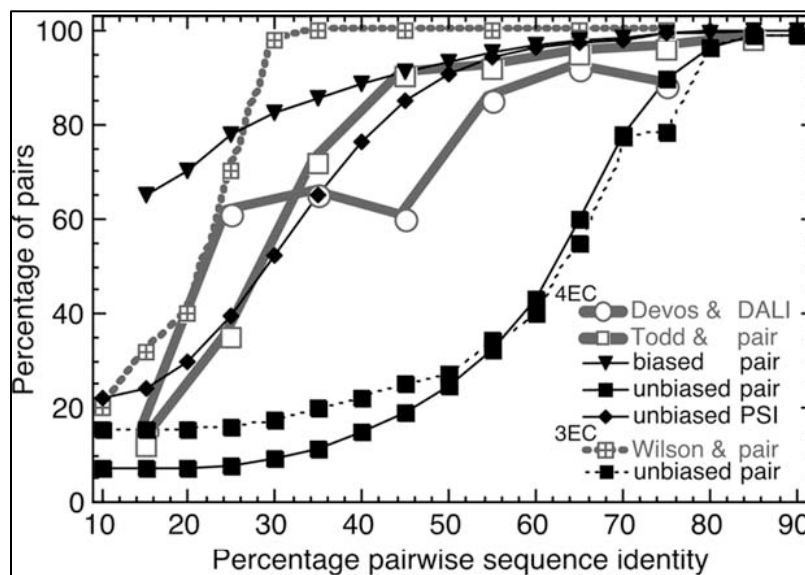
In 2000, Wilson et al. evaluated pairwise sequence, structure, and function comparisons on ~30,000 pairs of protein domains and corresponding EC numbers. Ex. 2024, 233, 242. Wilson found that full conservation of enzyme function can occur between two proteins with as low as ~40% sequence identity. *Id.*, 233. The authors concluded that percent identity is a useful predictor of function for proteins that are close in structure and outside the twilight zone. *Id.*, 245.

A study in 2000 by Devos et al. analyzed a set of over 7,000 protein sequence alignments. Ex. 2026, 99. Devos found that, above a sequence identity threshold of 50-80%, at least the first three digits of an EC number were identical, and above 80% sequence identity, all four digits in the EC codes were “completely identical,” meaning that two enzymes having this level of identity can confidently be assumed to have the same activity. *Id.*, 101-02.

In 2001, a study by Todd et al. assessed the functional variation of 31 diverse structural enzyme superfamilies using the EC classification scheme and found that functional variation is rare when sequence identity is above 40%. Ex. 2027, 1113. Todd et al. reported that “conservation of chemistry does appear to be the dominant

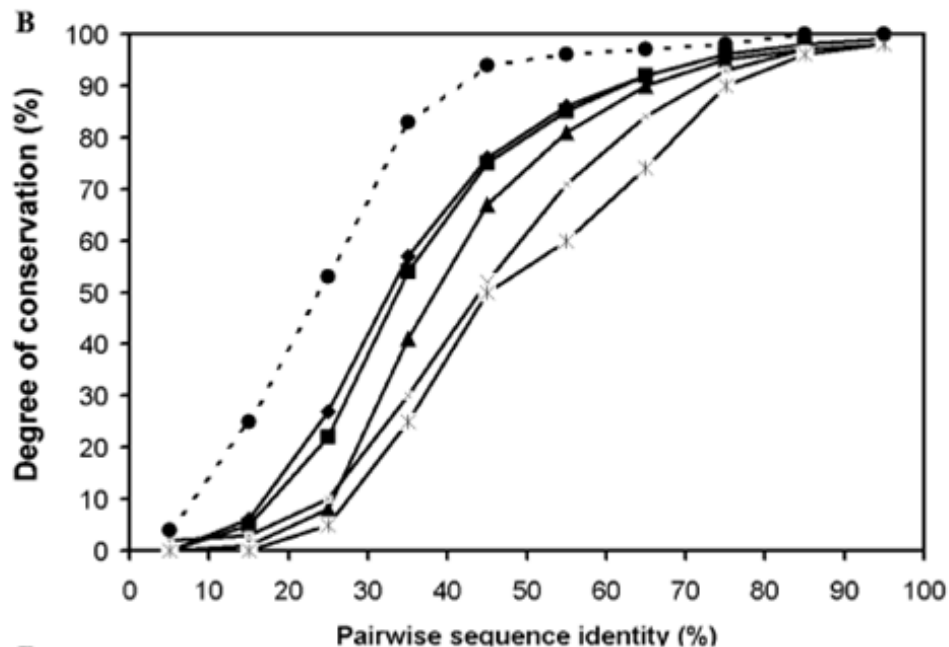
theme,” i.e., high sequence identity between a pair of enzymes implies that they will catalyze the same reaction. *Id.*, 1138.

In 2002, Rost made a more conservative estimate for sequence-based conservation of enzyme function to provide “important benchmarks for everyday sequence analysis,” suggesting that prior analyses were biased or too small. Ex. 2028, 595. Taking a different approach that considered sequence comparisons into the twilight zone, Rost found that, when the sequence identity is below 70%, EC numbers diverge more than others had reported. *Id.*, 603–04; Ex. 2019, 863. Nevertheless, Rost presented a graphical comparison between his results and those of Wilson, Devos, and Todd, confirming strong conservation of function at high levels of sequence identity, including at 85% or greater identity:



Ex. 2028, 604 (Fig. 5) (x-axis: sequence identity; y-axis: conservation of function).

A study by Tian et al. in 2003 consolidated and built on the prior studies by Devos, Wilson, Todd, and Rost, analyzing thousands of protein sequences for the purpose of establishing “the threshold of sequence identity necessary to transfer function from a protein of known function to an unknown protein.” Ex. 2019, 863. Tian found that “above 60% sequence identity,” skilled artisans would have “above 90% accuracy” in predicting function, defined as all four digits of an EC number. *Id.*, 865.



Id., 866 (Fig. 1(B)) (x-axis: sequence identity; y-axis: conservation of function).

Highly identical enzyme sequences were therefore known to correlate well with conservation of structure and function, which enzymologists recognized and referred to as sequence-function relationships. Ex. 2011, ¶ 39. Ex. 2035, 187. These principles were well established and routinely applied in protein engineering to make

enzyme variants with conserved or even improved functional traits. *See infra* Section II.A.3; Ex. 2025, 2-3 (“Using homologous sequences for protein engineering”).

Thus, by 2005-2006, skilled persons routinely predicted enzyme function based on sequence similarity to enzymes whose function had been experimentally determined. Ex. 2011, ¶¶ 35-39; Ex. 2032, 779-80; Ex. 2033, 1712; Ex. 2034, 259. The studies detailed above showed that this was a universal principle applied within the field of enzymology. *See, e.g.*, Ex. 2026, 98; Ex. 2019, 864 (“sequence identity is ... widely used as an indication of functional similarity”). Indeed, amino acid sequence comparisons were accepted as the “gold standard” for predicting protein function. Ex. 2029, 97; Ex. 2024, 233 (“percent identity is more effective at quantifying functional conservation” than other techniques).

3. Enzyme Engineering and Variants

By 2005-2006, skilled artisans commonly developed enzymes with desired functional properties. They generally analyzed an enzyme’s amino acid sequence and compared it to other known, similar sequences. Ex. 2011, ¶¶ 44-50; Ex. 2025, 2-3 (related sequences are “a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function”); Ex. 2040, 3389.

To guide amino acid sequence substitutions, matrices known since the 1970s detailed which amino acid replacements were accepted by the processes of natural

selection. Ex. 2011, ¶ 52; Ex. 2083. One class of matrix, given the acronym PAM (for Point Accepted Mutation), accounts for evolutionary approximations regarding the rates and probabilities of particular amino acid substitutions. Ex. 2041, 761, 763. By 2005-2006, these matrices were automated and computer-implemented (e.g., with the SIFT (Sorting Intolerant From Tolerant) program). Skilled artisans thus had no need to randomly pick from among the 20 naturally occurring amino acids when making enzyme variants.

Skilled artisans also performed sequence alignments with related enzymes to identify highly conserved residues. *See* Ex. 2035, 185 (sequence comparisons “identify residues that can tolerate mutation without radically altering function”). For identifying residues likely important to structure and/or function, comparing related amino acid sequences with lower identity (~30%) was particularly helpful because residues conserved at that lower level were likely important. Ex. 2011, ¶ 53.

As Dr. Bollinger explains, skilled artisans also had established basic principles for making enzyme variants that maintain function. *Id.*, ¶¶ 56-57. In view of the known sequence-function relationships among enzymes, skilled artisans would seek to maintain high sequence identity. *Id.* To maintain function, skilled artisans would also seek to maintain the enzyme’s active-site motif. *Id.* Skilled artisans would also seek to retain (or only conservatively substitute) non-motif residues that are highly conserved across related enzymes, which were presumed to

be functionally and/or structurally important. *Id.* And skilled artisans would avoid making substitutions with oppositely charged amino acids or substitutions with dramatically differently sized amino acids, which could distort the enzyme's overall surface charge or steric bulk. *Id.*

Finally, skilled artisans had programs available to predict and/or confirm the functional activity of engineered variants. Any number of computational tools were suitable and available for protein structure prediction and/or making variants. Ex. 2011, ¶ 54-55 (citing Exs. 2038, 2039, 2044). For example, one available program, SIFT, predicts whether an amino acid substitution affects protein function by considering the position at which the change occurred and the type of amino acid change. Ex. 2044, 3812 (SIFT “relies solely on sequence for prediction, yet performs similarly to tools that use structure”).

4. α Ketoglutarate-Dependent Dioxygenases and SdpA (AAD-12)

Before 2005-2006, researchers identified certain bacteria that could degrade 2,4-D and other phenoxy herbicides. Ex. 2011, ¶¶ 58-61; Ex. 2054, 40; Ex. 1025. To degrade 2,4-D, α KG-dependent dioxygenases require the presence of Fe(II) as the metallocenter, as well as oxygen and α ketoglutarate as co-substrates. Ex. 2001, 24311.

α KG-dependent dioxygenases are generally defined by their consensus motif, which is a simple way to identify their active sites. Ex. 2011, ¶¶ 62, 71. By 2005-2006, skilled artisans recognized that enzymes in the α KG-dependent dioxygenase family varied greatly in the number of amino acids in the spacers separating each pair of consecutive motif residues, reflecting the diversity of reactions catalyzed by these enzymes.

Dr. Silverstone acknowledges that a new protein's structure can be analyzed by comparing "the sequence to a closely related protein of known structure." Ex. 1003, ¶46. That is precisely how the α KG motif and the motifs in TfdA, TauD, SdpA, and related enzymes were identified. Ex. 2011, ¶¶ 63-68; Ex. 2003, 9792-93. In 2002, Elkins et al. reported the crystal structure of TauD and used it to predict the structure of TfdA. Ex. 2022. The authors found that TauD and related α KG-dependent dioxygenases, including TfdA, share the consensus motif HX(D/E)X₂₃₋₂₆(T/S)X₁₁₄₋₁₈₃HX₁₀₋₁₃R. *Id.*, 5185. Comparisons to the TauD crystal structure showed that TfdA and other group II α KG-dependent dioxygenases having ~30% or higher sequence identity share similar structures. *Id.*, 5189, 5188 (Fig. 2).

In addition to TfdA, researchers had discovered other enzymes produced by soil bacteria that degraded phenoxy auxin herbicides. Ex. 2011, ¶ 69. These enzymes included SdpA and RdpA from the bacteria *Delftia acidovorans* MC1, and SdpA and RdpA from *Sphingomonas herbicidovorans* MH. Ex. 1027; Ex. 1023.

By 2006, Müller et al. had reported the motif residues in SdpA and RdpA from *Sphingomonas herbicidovorans*. Ex. 2002. Müller reported that the high degree of active site sequence identity and strong orientation of key side chains by interactions with the Fe^{II} were “supportive of the active site being the most conserved and structurally accurate part of the RdpA and SdpA models.” *Id.*, 1358; Ex. 2011, ¶ 70.

B. Transgenic Plants

The following background on transgenic plants and plant transformation is based on Dr. Paul Christou’s testimony. Ex. 2012, ¶¶ 1-21. Dr. Christou is an expert in plant biotechnology, holding an endowed professorship at the Catalan Institution for Research and Advanced Studies at the University of Lleida, Spain. His research focuses on genetically engineered crops and engineering of novel agronomic traits in plants, including herbicide-tolerance traits. A pioneer in the field, Dr. Christou generated the first biolistics-transformed soybean strain in the world, publishing his research in *Nature Biotechnology* in 1988. In the 1990s, he led the generation of the first commercialized, genetically transformed soybean product, Roundup Ready soybean. *Id.*, ¶ 4. He has published extensively on transgenic plants and holds leadership roles in professional organizations in the field of plant biotechnology, including serving on the International Scientific Advisory Board of The Max Planck Institute. *Id.*, ¶¶ 6-10. He has received grants from the Bill and Melinda Gates

Foundation and was awarded the Narcís Monturioll Medal in 2020 for excellence in scientific research. *Id.*

1. Origins of Plant Transformation

Plants generally fall into two categories: monocots and dicots. *Id.*, ¶ 24. Monocots have a single embryonic leaf (a cotyledon) that emerges from a seed. Dicots typically have two cotyledons. The most common and representative monocot crops in agriculture include corn (i.e., maize) and grass-like crops such as rice and wheat. Dicot crops include tobacco, soybean, and cotton, among others. Long before 2005, there was great interest and substantial effort in the field to genetically modify plants to improve their traits. *Id.*, ¶¶ 24-25.

Plants may be genetically modified by introducing one or more genes foreign to the native plants (i.e., transgenes) into the plant genome to express recombinant proteins. Ex. 2057, 107; Ex. 2061, 570. In the 1980s, transgenic plants were generated to produce insecticidal proteins that protected the plants from insect attack. Ex. 2058, 33. Since the 1980s, researchers have generated transgenic plants with herbicide-tolerance genes that express enzymes conferring tolerance to herbicides, including glyphosate and glufosinate. Ex. 2059, 2513; Ex. 2060, 770. The creation of herbicide-resistant transgenic crops was an important advance in agriculture, allowing selective use of herbicides to minimize the growth of soil-depleting weeds and improving crop yields. Ex. 2012, ¶¶ 22-23.

2. Transgene Preparation and Plant Transformation in 2005-2006

By 2005-2006, plant transformation technology had greatly advanced, as transgene preparation and plant transformation were routinely carried out to generate transgenic plants. *Id.*, ¶¶ 26-57. It was reported in 2004, for example, that plant transformation had “led to an explosion of value-added crops that have the potential to increase food security in developing countries and create pharmaceutical and nutraceutical products for the improvement of human health worldwide.” Ex. 2062, 1. Plant transformation in 2005-2006 involved, at a high level: codon optimization of a transgene (optional), preparing an expression cassette, transforming plant cells, and regenerating transgenic plants. Ex. 2012, ¶ 92.

a. Codon Optimization

Within a transgene, each codon comprises three successive nucleotides that code for an amino acid. Different codons can code for the same amino acid. It was well known before 2005 that plants prefer G and C rich codons compared to bacteria and mammals, referred to as codon bias. *Id.*, ¶¶ 26-27; Ex. 2064, 3325; Ex. 2063. Thus, when needed, the codons in a foreign gene could be modified (without changing the encoded amino acids) to adapt to the codon bias in plant species and optimize expression. Codon optimization was not always necessary, but it was conveniently used and generally led to improved transgene expression and performance. *Id.*, ¶¶ 28-29 (citing Exs. 2065 and 2081).

b. Transgene Expression Cassettes

To deliver a transgene into host plant cells, skilled artisans in 2005-2006 routinely built expression cassettes containing the transgene. *Id.*, ¶¶ 30-45 (citing Exs. 2067, 2069-2072). An expression cassette can be pictured as a sandwich with the transgene sequence located between standard regulatory elements, such as a promoter and a terminator, to facilitate high-expression levels of transgenes in plants. Expression cassette components had been extensively studied since the 1980s and were well understood and readily available to skilled artisans by 2005. *See, e.g.*, Ex. 2057.

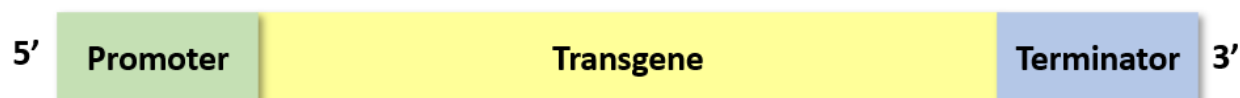


Figure 2

The most common promoters used for robust transgene expression in dicots were derived from plant virus sources, such as the cauliflower mosaic virus promoter (CaMV 35S), which has been widely used in plant transformation since the 1990s. Ex. 2062, 3; Ex. 2066, 1055; Ex. 2012, ¶¶ 32-41. Other established promoters included the cassava vein mosaic virus (CsVMV promoter). In monocots, common promoters included *Act* and *Ubi* promoters. Ex. 2012, ¶¶ 42-45; Ex. 2069, 150; Ex. 2070, 217. A variety of species-specific and broadly applicable promoters that work

across monocot or dicot species were thus available. Ex. 2009, 26:7-27:11, 22:23-23:6.

c. Plant Transformation Techniques

In 2005-2006, two established techniques were used to transform plant cells with a vector containing a transgene of interest. Ex. 2057, 107. One strategy used the soil bacterium *Agrobacterium tumefaciens* to infect a plant cell and transfer a small segment of DNA from a plasmid vector in the bacteria into the host plant cell. *Id.*, 107-08. The other strategy involved directly transferring the foreign DNA into the plant cell by physical force, e.g., using biolistics. *Id.*; Ex. 2012, ¶¶ 46-49 (citing Ex. 2074).

Biolistics involves shooting small DNA-coated metal particles (e.g., gold) into plant tissue with sufficient force to break through the cell wall and membrane and release the foreign DNA. *Id.*, 115. As Dr. Christou reported in 2005, “particle bombardment is a versatile and effective transformation method, not limited by cell type, species or genotype. There are no intrinsic vector requirements so transgenes of any size and arrangement can be introduced, and multiple gene cotransformation is straightforward.” Ex. 2075, 305-06.

d. Plant Regeneration

Following transformation, regenerating the treated plant cells into whole plants for production of seeds and progeny plants was routine by 2005-2006. The

plant regeneration process involved incubating the post-transformation plant cells in known induction media to let them grow into plantlets before planting them and, if desired, growing them to seed to produce progeny. Ex. 2012, ¶¶ 50-51; Ex. 2076, 752.

Skilled artisans generally selected the transformed cells for regeneration by using an herbicide tolerance gene as a selectable marker. Upon incubating the transformed plant cells in an herbicide, transformed cells exhibiting ability to degrade the herbicide would preferentially grow, permitting their selection for regeneration. *Id.*, ¶¶ 52-56 (citing Exs. 2077- 2080); Ex. 2009, 114:11-20. Selectable markers could also be used at later time points to verify herbicide-degrading activity in the regenerated primary transformants (T₀ plants) or in first-generation (T₁) or later progeny through a simple procedure: spraying the herbicide on the plants and selecting those with ability to degrade the herbicide (as reflected in their reduced damage to the herbicide treatment). *Id.*, ¶ 57.

Accordingly, as Dr. Christou explains, once a skilled artisan had transgenes of interest in hand, the process of using them to generate transgenic plants was straightforward and routine in 2005-2006. *Id.*, ¶ 91. Moreover, the time necessary to produce transgenic plants was mainly a function of plant biology (e.g., growing and regenerating plant tissues)—not the efforts of a skilled artisan—as the active steps

required to prepare transgene expression vectors and perform transformation techniques were quick and well established. *Id.*, ¶ 93.

III. The '055 Patent

A. AAD-12 Enzymes

The inventors' creation of transgenic plants expressing the bacterial α KG-dependent dioxygenase enzyme SdpA from *Delftia acidovorans* (i.e., AAD-12) led to a unique discovery—these novel transgenic plants exhibited dual activity against two different classes of herbicides: phenoxy auxins (e.g., 2,4-D) and pyridyloxy auxins (e.g., triclopyr and fluroxypyr). Ex. 1001, 12:23-58. In light of this dual herbicide-tolerance activity, the enzymes and genes of the '055 patent are called “AAD-12” (Aryloxy Alkanoate Dioxygenase) proteins and genes. *Id.*, 4:48-61; Ex. 2011, ¶ 77.

The inventors identified AAD-12 by investigating a broad range of α KG-dependent dioxygenase sequences, ranging from “highly identical (85-98%) to very low identity (23-32%)” to TfdA. *Id.*, 31:55-32:22. Eschewing sequences having more than 50% identity, the inventors searched into the more unpredictable twilight zone of lower identities to TfdA for potentially different enzyme properties and identified SdpA (AAD-12) at 31% identity. *Id.*; Ex. 2011, ¶¶ 78-79. The inventors disclosed *in vitro* and *in planta* characterizations of AAD-12 throughout the

examples, including data confirming dual herbicide-degrading activity, and disclosed the amino acid sequence of AAD-12 as SEQ ID NO: 2. Ex. 1001, 5:48-51.

The '055 patent provides detailed structural guidance regarding variant enzymes “having the same or similar activity” of disclosed enzymes such as AAD-12. *Id.*, 21:41-47; Ex. 2011, ¶¶ 80-90. Consistent with established sequence-identity thresholds for predicting enzyme function, the patent discloses that the sequence identity of such variants “will typically be at least 60%.” *Id.*, 21:49-60; Ex. 2019, 863 (disclosing that “60% sequence identity is needed to have at least 90% accuracy” in predicting function); Ex. 2011, ¶ 96. It also discloses sequence identities of 85% and higher. Ex. 1001, 21:49-60. Indeed, for α KG-dependent dioxygenases, the patent discloses that sequences having 85% to 98% identity are “highly identical” and that such enzymes are “expected to retain similar properties.” *Id.*, 31:61-32:6.

The '055 patent also discloses the location of the known active-site motif in Group II α KG-dependent dioxygenases such as AAD-12, which skilled artisans would seek to conserve. Ex. 2011, ¶ 80. The specification states: “This family of proteins is characterized by three conserved histidine residues in a ‘HX(D/E)X₂₃₋₂₆(T/S)X₁₁₄₋₁₈₃HX₁₀₋₁₃R’ motif which comprises the active site.” Ex. 1001, 10:61-11:14 (citing Hogan, Ex. 1019); *see also id.*, 11:15-34.

Citing Elkins 2002, the '055 patent provides a sequence alignment of five α KG-dependent dioxygenases, including AAD-12 and the 3D-mapped sequence of TauD. *Id.*, 20:23-34, Fig. 2 (citing Ex. 2022). Figure 2 highlights the strictly conserved residues across these enzymes, including active-site motif residues. Ex. 2011, ¶¶ 82-83. It also highlights highly conserved residues known to tolerate changes to similar amino acids. *Id.* In addition to the guidance regarding preferred sequence identities, the AAD-12 active-site motif, and highly conserved non-motif residues, the patent directs skilled artisans to make substitutions that “retain the same or similar ... surface charge distribution” and three-dimensional structure. Ex. 1001, 28:57-60. As Dr. Bollinger explains, skilled artisans in 2005-2006 understood that substituting similarly charged or sized amino acids represented a useful strategy for making variants having the same activity as the original enzyme. Ex. 2011, ¶¶ 56-57.

B. The Specification's Twenty-Four Examples

The '055 patent discloses twenty-four examples providing extensive guidance for making and using AAD-12 genes and transgenic plant cells and plants. *See, e.g.*, Ex. 1001, 13:42-44 (“The transgenic expression of the subject AAD-12 genes is exemplified in, for example, *Arabidopsis*, tobacco, soybean, cotton, rice, corn and canola.”), 31:55-102:49; Ex. 2012, ¶¶ 64-86; Ex. 2011, ¶¶ 84-90.

The '055 patent describes methods of codon-optimization to improve AAD-12 transgene expression in monocots and dicots, including the maize-codon-

optimized AAD-12 (v1) gene used in the transformation examples for monocot and dicot species. Ex. 1001, Example 2, 22:57-23:2. Example 3 discloses a series of AAD-12 expression vectors comprising known promoters, including CsVMV, AtUbi10, ZmUbi1, AtUbi3, and AtAct2. *Id.*, 42:1-36, Table 8. These vectors were used in the transformation examples, with three (pDAB724, pDAB3759, pDAB4101) used across multiple dicot and monocot species. *Id.*

The '055 patent describes known plant transformation methods such as *Agrobacterium*-mediated transformation, biolistics-mediated transformation (microparticle bombardment), and whisker-mediated transformation. *Id.*, 24:25-62 (“A large number of techniques are available for inserting DNA into a plant host cell.”). Examples 7, 8, 10-12, 14, 21, and 22 describe use of the expression cassettes from Table 8 and confirm successful transformation of seven different monocot or dicot plant species (*Arabidopsis*, soybean, cotton, tobacco, canola, rice, and corn) with AAV-12 (v1). Ex. 2012, ¶¶ 67-86.

The specification, for example, describes the successful transformation of *Arabidopsis* with an AAD-12 gene. Ex. 1001, 48:62-56:38. In addition to 2,4-D tolerance, the '055 patent discloses that “AAD-12-transformed plants were . . . clearly protected from the triclopyr and fluroxypyr herbicide injury that was seen in the transformed non-resistant controls” *Id.*, 54:13-16, 54:23-45 (Table 13).

In Example 11, transformed soybean plants were tested for tolerance to the herbicide 2,4-D. The '055 patent discloses that “[a]ll AAD-12 (v1)-containing plants were clearly resistant to the herbicide application,” while “control plants were severely injured” or killed, depending on the 2,4-D application rate. *Id.*, 76:40-50 (“These data are consistent with the fact that AAD-12 (v1) can impart high tolerance (>2x field rates) to a sensitive crop like soybeans.”). The patent also discloses using combinations of 2,4-D, triclopyr, and fluroxypyr with dicot crops such as soybeans. *Id.*, 86:23-87:20 (“One skilled in the art of weed control will now recognize that use of various commercial phenoxy or pyridyloxy auxin herbicides alone or in combination with a herbicide is enabled by AAD-12 (v1) transformation.”). It also describes successful testing of AAD-12-transformed corn, rice, and canola with both classes of herbicides. *Id.*, 64:28-65:53, 94:19-95:15, 98:32-99:20.

The '055 patent established AAD-12 genes as effective selectable markers. Ex. 2012, ¶¶ 72-74, 119. It discloses comparisons of AAD-12 to the known *pat* gene selectable marker for identifying transformed cells immediately after transformation or in regenerated or progeny plants. It reports that AAD-12 genes work effectively to identify transformed plants and plant cells following application of phenoxy or pyridyloxy auxin herbicides. Ex. 1001, Example 24, 53:18-39, 54:11-21.

The '055 patent also discloses stacking AAD-12 genes with other herbicide tolerance traits (e.g., genes providing resistance to glyphosate, glufosinate, and

imidazolinone herbicides) and insect resistance traits to confer multiple tolerance traits in AAD-12-transformed plants. *Id.*, Examples 18-20, 23.

C. The Challenged Claims

The '055 patent claims are directed to novel transgenic plants and plant cells comprising a recombinant polynucleotide encoding a structurally well-defined class of AAD-12 proteins. Ex. 2011, ¶¶ 73-76; Ex. 2012, ¶¶ 60-63. Claim 1, for example, recites:

1. A transgenic plant cell comprising a recombinant polynucleotide that encodes an AAD-12 protein that exhibits aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide, further wherein said AAD-12 protein comprises:

i) *an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2; and*

ii) *an AAD-12 motif having the general formula of:*

$HX_{109}D(X)_{111-134}T(X)_{136-261}H(X)_{263-272}R$, wherein

X_{109} represents a single amino acid at position 109, relative to the sequence of SEQ ID NO: 2;

$(X)_{111-134}$ represents a sequence of 24 amino acids;

$(X)_{136-261}$ represents a sequence of 126 amino acids; and

(X)₂₆₃₋₂₇₂ represents a sequence of 10 amino acids.

The dependent claims recite additional features, including:

- At least 90% sequence identity with SEQ ID NO: 2 (claim 2);
- A dicot plant cell selected from cotton, tobacco, canola, soybean, and *Arabidopsis* cells (claim 3);
- A transgenic plant comprising a plurality of the plant cells of claim 1, wherein expression of the polynucleotide renders the plant tolerant to an aryloxyalkanoate herbicide (claim 4);
- Tolerance to particular herbicides or herbicide classes (claims 5-9);
- A transgenic plant having a second herbicide resistance gene (claims 10 and 11);
- Methods of controlling at least one weed in a field, wherein the field contains at least one plant of claim 4 and the method comprises applying a first herbicide selected from the group of a phenoxy auxin herbicide and a pyridyloxy herbicide, as well as other herbicides and herbicide tolerances (claims 12-27 and 29);
- A seed comprising a plurality of the plant cell of claim 1 (claim 28);
- A plant grown from the seed of claim 28, wherein the plant comprises the polynucleotide (claim 30); and

- A part, progeny, or asexual propagate of the plant of claim 30 comprising the polynucleotide (claim 31).

Independent claim 32 recites similar features as independent claim 1 but requires the AAD-12 motif to have 90% sequence identity with corresponding amino acids of position 108 to 273 of SEQ ID NO: 2. Independent claim 33 recites a method of controlling at least one weed in a field planted with seeds that comprise an AAD-12 recombinant polynucleotide by applying a pyridyloxy auxin herbicide.

IV. Level of Skill in the Art

Regarding aspects of the '055 patent pertaining to plant transformation and crop science, Patent Owner does not dispute Petitioner's high proposed level of skill: "a Ph.D. in biochemistry, cell biology, genetics, or a related field, and 3-5 years of experience in the design or development of transgenic plants including genomics, proteomics, biochemistry, plant transformation and crop science, or the equivalent." Pet., 23. Researchers who designed and made transgenic plants generally had this level of education and experience in 2005-2006. Ex. 2012, ¶ 58.

As Dr. Christou explains, however, some physical tasks involved in making transgenic plants, particularly the preparation of plant tissue samples for transformation, were routinely delegated to lab technicians. *Id.*, ¶ 59. Because protocols for plant transformation were established by 2005-2006, the speed and efficiency of sample preparation depended more on dexterity and skill in working

with small plant tissues (e.g., sometimes no larger than one millimeter) than on scientific education and background. Such technicians often had a bachelor's degree or less. *Id.*

Regarding aspects of the '055 patent pertaining to enzymology, α KG-dependent dioxygenases (e.g., SdpA/AAD-12), and making variants, a skilled artisan would have generally possessed a Ph.D. in molecular biology, biotechnology, or biochemistry, and 3-5 years of experience in the design or development of enzymes and enzyme variants as well as familiarity with α KG-dependent dioxygenases. Ex. 2011, ¶ 72. This proposed level of skill corrects Petitioner's failure to include any background in enzymology, including familiarity with α KG-dependent dioxygenases, which was reflected in the art (e.g., Exs. 1019, 1020, 2019, 2025, 2028). *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *Lifescan Glob. Corp. v. Ikeda Food Rsch., Ltd.*, PGR2019-00032, Paper 11 at 9 (PTAB Aug. 15, 2019) (correcting petitioner's generalized POSA definition to correspond to the "focus of the challenged claims").

V. Issues Raised in the Institution Decision

On the previously limited record before the Board, the Institution Decision found that at least one claim was more likely than not unpatentable based on written description and enablement. ID, 34, 52. The Board identified four main issues for factual development:

1. The Board found it “unclear” how far from 99.3% identity the AAD-12 enzymes can deviate from SEQ ID NO: 2 while still retaining the ability to degrade herbicides. ID, 39, 36.
2. The Board stated it so far had “no evidence” indicating that the location and spacing of the residues in other α KG-dependent dioxygenases differ from the AAD-12 motif. ID, 37.
3. The Board questioned whether a skilled artisan would have been “able to predict” whether an AAD-12 enzyme at lower (e.g., 85%) identity to SEQ ID NO: 2 would retain the function of degrading the recited enzymes. ID, 52, 55.
4. The Board noted Dr. Silverstone’s reliance on a generalized textbook and invited testing the strength of his testimony. ID, 37.

Corteva has now fully addressed these issues, establishing that skilled artisans in 2005-2006 would have expected AAD-12 enzymes of 85% or higher sequence identity to maintain the claimed function as the specification discloses; that the claimed active-site motif is unique to AAD-12 enzymes and their function; and that Dr. Silverstone’s testimony is unsupported, conclusory, and entitled to “little or no weight.” 37 C.F.R. § 42.65(a).

VI. Petitioner's Challenge Is Legally Erroneous

Before delving into the specifics of the Petition's patentability challenges, Corteva respectfully points out that Petitioner invites legal error in multiple ways. First, Petitioner erred by assuming PGR eligibility rather than establishing it. Dr. Silverstone conceded during cross-examination that he never conducted any analysis as of the pre-AIA filing dates that Petitioner needed to address to make the '055 patent PGR-eligible. Ex. 2009, 86:20-88:18 ("A. . . . I used March 24, 2017, as the date for my evaluation. Q. That's what you were instructed to use by counsel, correct? A. That is correct. Counsel advised me to use that date."). The Petition plainly seeks to analyze written description and enablement in view of a later state of the art (e.g., Alpha Fold software), which violates black-letter law. *In re Hogan*, 559 F.2d 595, 606 (CCPA 1977) (criticizing the "erroneous use of a later state of the art in determining enablement"); *Ariad*, 598 F.3d at 1355.

Second, Petitioner errs by presenting no competent expert testimony. The claims recite a genus of AAD-12 enzymes. ID, 39-40, 56-57. Dr. Silverstone, however, has no academic degree or scientific training in enzymology or protein engineering. Ex. 2009, 69:5-12. He has not published or given invited talks in those fields. *Id.*, 68:18-69:4, 67:11-68:12. He could not recall what Enzyme Commission (EC) numbers—the "best developed and most widely used" enzyme classification system—mean. Ex. 2019, 864; Ex. 2009, 107:10-108:17. He confirmed that his CV,

which lacks any mention of expertise in enzyme engineering or enzymology, accurately reflects how he holds himself out to the agricultural industry. Ex. 2009, 65:18-66:13. During cross-examination, Dr. Silverstone sought to supplement his CV to include “experience”—*not expertise*—in enzymology. *Id.*, 31:8-32:15. But he could only identify a single project about 20 years ago involving enzyme variant design—and that was “the last time” he worked on enzyme variants. *Id.*, 67:3-17. Significantly more is required to accord any weight to his testimony. *E.g., Avail Medsys., Inc. v. Teladoc Health, Inc.*, IPR2022-00444, Paper 10 at 24-26 (PTAB July 21, 2022) (rejecting vague reference to past experience as establishing expertise); 37 C.F.R. § 42.65(a).

Even if considered, Dr. Silverstone’s positions are unsupported and legally flawed. Reflecting his lack of enzymology background, Dr. Silverstone relies heavily on a generalized textbook and conclusory calculations (alleging 10^{106} sequences) that assume a skilled artisan would exercise *no skill* by randomly substituting all 19 alternative amino acids at every possible location. Ex. 1003, ¶ 80 n.1; *cf. Baxalta*, 81 F.4th at 1364 (enablement must be assessed from the perspective of a “person skilled in the art” (quoting 35 U.S.C. § 112)). For enablement, he also relies on purported tasks that an artisan would allegedly need to perform in developing *commercially optimized* transgenic crops, including evaluating crop yields, which are not recited in the claims. *E.g.*, Ex. 1003, ¶¶ 92-93; Ex. 2009, 73:8-

74:9, 78:23-79:23, 81:11-82:22; Ex. 2012, ¶¶ 121-128. Section 112 does not require describing or enabling more than what is claimed. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1307 (Fed. Cir. 2010) (a patent need not enable the “most optimized” or “commercial” embodiments).

Accordingly, Petitioner fails to set forth a legally viable Section 112 challenge.

VII. Petitioner Failed to Establish that the Challenged Claims Lack Enablement

To prove lack of enablement, Petitioner must show that a skilled artisan would have been unable to practice the claimed invention without undue experimentation. *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014). Unsubstantiated assertions that experimentation would be “difficult” or “complicated” are insufficient. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013).

In the Institution Decision, the Board relied on the Supreme Court’s *Amgen* decision in assessing enablement of the ’055 patent. ID, 52-54; Paper 9. *Amgen*, however, addressed purely functional claims encompassing *all antibodies of any sequence* that would (1) bind to specific amino acid residues on an antigen and (2) block the antigen from binding to receptors. 598 U.S. at 602. The specification in *Amgen* failed to identify any common quality (e.g., structural feature) running

throughout the claimed antibody genus, as none existed. *Id.* at 613-14. The *Amgen* claims thus sought to “monopolize an entire class of things defined [only] by their function.” *Id.*

The '055 patent's specification and claims are distinctly different. All challenged claims have common structural features, requiring both 85% identity to AAD-12 (SEQ ID NO: 2) and an active-site motif of conserved amino acid residues with fixed spacing between them. These function-correlated structural features provide a “quality common” to AAD-12 enzymes and their dual herbicide-degrading function, satisfying the enablement requirement. *Id.* at 610-11 (“[I]t may suffice to give an example (or a few examples) if the specification also discloses ‘some general quality . . . running through’ the class that gives it ‘a peculiar fitness for the particular purpose.’”).

At institution, the Board acknowledged that the level of skill in the art is high, that the steps required to obtain claimed embodiments were known, and that the specification provides twenty-four examples detailing how to make transgenic plants that produce AAD-12 proteins. *Id.* 56-57, 35-36, 51. Citing Dr. Silverstone's testimony, however, the Board preliminarily found that a “skilled artisan would not have been able to predict whether a modified SEQ ID NO: 2 at the lower (e.g., 85% identity level) would have been able to retain the function of degrading the recited

herbicides.” ID, 52, 55 (similar). That preliminary finding is incorrect, particularly in view of Corteva’s rebuttal evidence.

Petitioner’s *Wands* analysis is fatally flawed. It fails to take into account the disclosures of the ’055 patent and the state of the art, which would have amply guided a skilled artisan to make and use functional AAD-12 enzymes at 85% and greater sequence identity. Dr. Silverstone also bases his conclusory opinions about the amount of experimentation required on tasks that Corteva’s experts, Drs. Bollinger and Christou, explain are unnecessary to make and use the claimed invention.

Accordingly, Petitioner failed to meet its burden of establishing that any challenged claim lacks enablement. Moreover, because the ’055 patent claims were enabled in their priority applications (Exs. 2013-2017), including the pre-AIA 2005 provisional and 2006 nonprovisional applications, the ’055 patent is ineligible for post-grant review and this proceeding should be terminated.

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

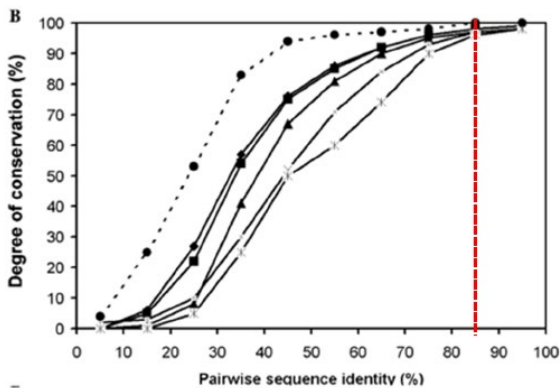
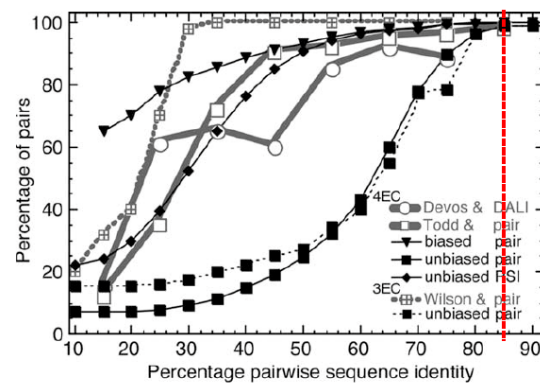
1. The Common Feature of at Least 85% Sequence Identity

The Petition ignored the ’055 patent’s disclosure that among α KG-dependent dioxygenases like AAD-12, enzymes having sequence identities of 85% and higher are “highly identical” and expected to have similar properties (i.e., sequence-

function correlation). Ex. 1001, 31:61-32:6, 21:41-60 (disclosing making enzymes having “the same or similar activity” at identities of 85% and higher); Ex. 2013, ¶¶ [0093], [00123]; Exs. 2014, 2017, ¶¶ [00102], [00150]; Ex. 2015, ¶¶ [00105], [00153]; Ex. 2016, ¶¶ [00108], [00156]. The Board noted these disclosures but discounted them due to the lack of an example at 85% sequence identity to SEQ ID NO: 2, questioning whether a skilled artisan would have been “able to predict” whether an AAD-12 enzyme at lower (e.g., 85%) identity to SEQ ID NO: 2 would retain the function of degrading the recited herbicides. ID, 52, 55.

As Dr. Bollinger explains, a skilled artisan would have expected AAD-12 enzymes to retain the claimed function at 85% and higher sequence identity. Ex. 2011, ¶¶ 91-104. The specification’s description of 85% sequence identity as highly identical and as conferring similar function comports with the contemporaneous understanding of persons skilled in the art. *Id.*, ¶¶ 93-95.

By 2005-2006, several research groups had extensively analyzed enzyme families and published on the strong correlation of high levels of sequence identity to enzymatic function. Ex. 2019, 872; Ex. 2025, 5; Ex. 2011, ¶¶ 96-99. These studies consistently demonstrated that enzyme function and substrate specificity (e.g., all four digits of an EC number) are conserved at sequence identities extending well below the 85% threshold recited in the challenged claims:



Ex. 2019, 866 (annotated Fig. 1(B)). Ex. 2028, 604 (annotated Fig. 5).

For example, as Tian disclosed, only “60% sequence identity is needed to have at least 90% accuracy” in predicting common function and substrate specificity, defined as “all four digits of an EC number.” Ex. 2019, 863.¹ Another study identified a threshold of at least 70% identity—still substantially lower than the 85% minimum of the challenged claims. *Id.* (citing Ex. 2028); Ex. 2011, ¶¶ 98-99. As Dr. Bollinger explains, enzymes having 85% or higher sequence identity were presumed to be essentially the same enzyme having the same function. Ex. 2011, ¶ 118.

Accordingly, a skilled artisan would have considered enzyme variants meeting the ’055 patent’s 85% sequence identity minimum as “highly identical” and as conferring similar properties to a reference sequence (e.g., SEQ ID NO: 2)—*just as the specification discloses*. Ex. 2011, ¶¶ 94-96; Ex. 1001, 21:41-60, 31:61-32:6; Ex. 2013, ¶¶ [0093], [00123]; Exs. 2014, 2017, ¶¶ [00102], [00150]; Ex. 2015,

¹ Emphases added unless otherwise noted.

¶¶ [00105], [00153]; Ex. 2016, ¶¶ [00108], [00156]; Ex. 2009, 106:23-107:9 (Dr. Silverstone’s patent, Ex. 2008, 48:55-66, referring to sequences of 50+% identity as “substantially identical”). Petitioner’s conclusory assertion that sequence-based prediction of enzyme function “was not possible” (Pet., 57) is thus contradicted by the specification and extensive literature from skilled enzymologists before 2005 documenting established sequence-identity thresholds for conserving function:

Petition	Tian 2003
“[I]t would be <i>nearly impossible</i> to reliably predict whether any other sequence within the scope of the claim would work.” Pet., 40.	“Using pairwise sequence comparison, <i>several studies suggested that when the sequence identity is above 40%, enzyme function is well conserved.</i> ” Ex. 2019, 863.
“Due to the <i>highly unpredictable correlation</i> between amino acid sequence and function, combined with the highly unpredictable effects of mutations, . . . all amino acid sequences falling within the scope of the claims would have to be meticulously tested over a period of years” Pet., 49.	“[T]he percentage of sequence identity is <i>simple, quick and widely accepted by the biologist</i> ” for inferring enzymatic function. <i>Id.</i> , 872.

As Dr. Bollinger testifies, this conservation of enzyme function is consistent with the strong conservation of enzyme structure at high levels of sequence identity. Ex. 2011, ¶¶ 100-101. While the Board preliminarily disagreed with Corteva’s argument that tertiary protein structure is more conserved than amino acid sequence (ID, 39), that finding is contrary to the understanding of skilled artisans in the field:

- “When two sequences are very similar[,] we can safely infer that they have similar structures.” Ex. 2028, 604, 596 (“In general, transfer of structure is almost guaranteed to be correct above the twilight zone, e.g., all known pairs of proteins with more than 33 residues in 100 identical have similar structure.”).
- “Sequence alignments unambiguously distinguish between protein pairs of similar and non-similar structure when the pairwise sequence identity is high (> 40% for long alignments).” Ex. 2021, 85.
- “Structural similarity is conserved even at very low levels of sequence similarity.” Ex. 2026, 105, 98 (“The comparison of protein sequences is widely used to infer protein structure and function.”).

Even the generalized textbook Dr. Silverstone relies on acknowledges that “protein tertiary structure is more reliably conserved than primary sequence,” illustrating that tertiary structure is generally forgiving to variations in amino acid sequence. Ex. 1033, 141. Accordingly, a skilled artisan in 2005-2006 would have expected that at 85% identity to SEQ ID NO: 2, the tertiary structure of AAD-12 enzymes *would* remain sufficient to support degradation of the recited herbicides. ID, 39; Ex. 2011, ¶ 101.

Petitioner fails to support its conclusory allegations of unpredictable structure-function correlation. Pet., 49, 57. Dr. Silverstone, for example, speculates that enzymes within 85% sequence identity to SEQ ID NO: 2 might catalyze entirely different reactions or even fall into enzyme families other than α KG-dependent dioxygenases. Ex. 1003, ¶ 48 (referencing hydroxylation, dealkylation, desaturation, epoxidation, and other reactions that can be catalyzed by other α KG-dependent

dioxygenases), ¶ 50 (suggesting that one could not predict that an enzyme within 85% sequence identity “would be an α -ketoglutarate-dependent dioxygenase at all”). During cross-examination, however, he conceded that he had identified no such enzymes. Ex. 2009, 11:5-14:20, 17:5-9.

Dr. Bollinger, in contrast, explains that identifying other types of enzymes within 85% identity to SEQ ID NO: 2 would be highly unusual. Ex. 2011, ¶ 102. The studies detailed above illustrate that for enzymes within 85% sequence identity, skilled artisans recognized that there is 90+% accuracy in predicting similar function. Ex. 2019, 863 (“above 60% sequence identity is needed to have at least 90% accuracy” to predict common function and substrate specificity). Skilled artisans had also used this well-recognized “sequence-activity relationship” of enzymes to develop new protein variants. Ex. 2035, 185 (citing Ex. 2025), 187-88; Ex. 2011, ¶¶ 103-104. Petitioner’s conclusory allegations of structure-function unpredictability are therefore insufficient to establish PGR eligibility or unpatentability. 37 C.F.R. § 42.65(a).

Accordingly, the disclosed and claimed requirement that AAD-12 proteins have at least 85% sequence identity to AAD-12 (SEQ ID NO: 2), which is well above established thresholds for enzyme function conservation, is a common quality running throughout the claimed genus. *See Amgen*, 598 U.S. at 611 (disclosing a “general quality . . . running through” the genus that provides a “fitness for the

particular purpose” reliably enables a skilled artisan to make and use the claimed invention).

2. The Common AAD-12 Active-Site Motif

The '055 patent claims further require maintaining the AAD-12 motif: $\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{T}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$. As Dr. Bollinger explains, this motif requires keeping the active site of dual-activity AAD-12 proteins highly conserved: (1) the position of the motif is anchored to position 109 relative to SEQ ID NO: 2, (2) the distances between the motif residues are fixed (rather than variable), and (3) the key motif amino acids are identified (cannot be substituted). Ex. 2011, ¶¶ 105, 71. Thus, even among “highly identical” variants having at least 85% sequence identity to SEQ ID NO: 2, the claims further restrict the AAD-12 enzymes to those having the same active-site motif as the dual-herbicide degrading enzyme of AAD-12 (SEQ ID NO: 2).

Disregarding the specificity of the claimed AAD-12 motif, Petitioner asserts it is the same as the general motif “attributed to the family” of α KG-dependent dioxygenases. Ex. 1003, ¶ 48; Pet., 47, 28-29. At institution, the Board similarly stated that “no evidence” supported Corteva’s argument that the location and spacing of the AAD-12 motif residues differ from other α KG-dependent dioxygenases. ID, 37. But the location and spacing of the AAD-12 motif residues indeed differ from other α KG-dependent dioxygenases having different substrate specificities, as

a skilled artisan would have readily appreciated from the '055 patent. Ex. 2011, ¶¶ 106-112.

The α KG-dependent dioxygenase family that includes AAD-12 is characterized by a variable motif (referred to as the “ α KG motif”): $\text{HX(D/E)X}_{23-26}\text{(T/S)X}_{114-183}\text{HX}_{10-13}\text{R}$. Ex. 1001, 11:1-6; Ex. 2013, ¶ [0042]; Exs. 2014, 2017, ¶ [0047]; Ex. 2015, ¶ [0050]; Ex. 2016, ¶ [0053]. Depending on the particular enzyme, the location of the required residues in the α KG motif can vary significantly. For instance, one of the spacers of variable amino acids in the general α KG motif can include from 114 to 183 amino acids. Ex. 2011, ¶ 108.

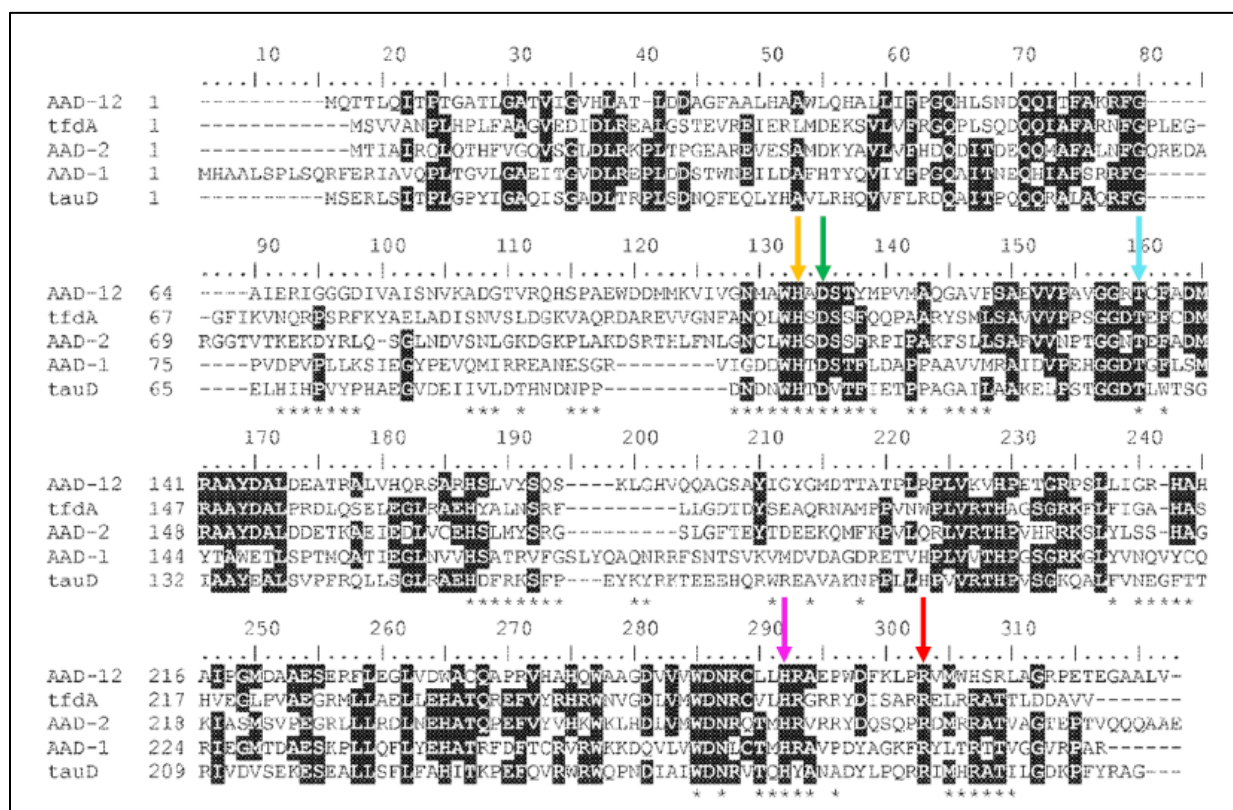
The AAD-12 motif, in contrast, defines fixed distances between the required amino acid residues, with the numbering providing positions for those required residues relative to SEQ ID NO: 2 (i.e., anchored at position 109). Ex. 2011, ¶ 109. Thus, using the positions numbered in SEQ ID NO: 2, the AAD-12 motif is more specific than the general Group II α KG motif, providing detailed guidance regarding the motif residues and their spacing:

Group II αKG Motif Requirements ($\text{HX(D/E)X}_{23-26}\text{(T/S)X}_{114-183}\text{HX}_{10-13}\text{R}$)	AAD-12 Motif Requirements ($\text{HX}_{109}\text{D(X)}_{111-134}\text{T(X)}_{136-261}\text{H(X)}_{263-272}\text{R}$)
Histidine (H)	Histidine (H)
X (anywhere)	X (anchored relative to position 109 in SEQ ID NO: 2)
Aspartic acid (D) or glutamic acid (E)	Aspartic acid (D)
Anywhere from 23 to 26 variable amino acids (X_{23-26})	24 variable amino acids (i.e., from positions 111 to 134)

Threonine (T) or serine (S)	Threonine (T)
Anywhere from 114 to 183 variable amino acids (X ₁₁₄₋₁₈₃)	126 variable amino acids (i.e., from positions 136 to 261)
Histidine (H)	Histidine (H)
Anywhere from 10 to 13 variable amino acids (X ₁₀₋₁₃)	10 variable amino acids (i.e., from positions 263 to 272)
Arginine (R)	Arginine (R)

Accordingly, whether Group II α KG-dependent dioxygenases *as a class* include enzymes that catalyze a variety of reactions as Petitioner contends (Pet., 47; Ex. 1003, ¶ 48) is irrelevant because the sequence and active-site motif of AAD-12 enzymes are far more specific. Ex. 2011, ¶¶ 110-113.

Indeed, even among α KG-dependent dioxygenases having a close relationship to AAD-12, the AAD-12 motif and its correlated dual herbicide-degrading activity remain unique. The '055 patent discloses an alignment of AAD-12 to the 3D-mapped sequence of TauD and other related enzymes, from which their different active-site motifs (including the different residue spacing) were readily apparent to skilled artisans:



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%

Ex. 2011, ¶¶ 111-112; Ex. 1001, Fig. 2 (annotated), 20:23-34 (directing skilled artisans to Fig. 2 regarding active site residues); Exs. 2014-2017, Fig. 2.

As Dr. Bollinger testifies, and Dr. Silverstone does not dispute, the substrate specificities of tfdA (phenoxy auxins), AAD-2 (phenoxy auxins), AAD-1 (phenoxy auxins and (R)-aryloxyphenoxypropionate herbicides), and TauD (taurine) do not include pyridyloxy auxin herbicides. Ex. 2011, ¶ 112; Ex. 1019, 12400; Ex. 1001,

71:61-72:24. 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. Ex. 2011, ¶ 113.

3. The Disclosed AAD-12 Structural Features Distinguish *Amgen* and *Baxalta*

The AAD-12 enzymes recited in the challenged claims are distinctly different than the antibodies of the *Amgen* and *Baxalta* cases. Petitioner and the Board focus on. As Dr. Bollinger explains, enzymes are unique among proteins because they evolved into distinct, closely related structures and functions over long periods of time. Ex. 2011, ¶¶ 40-43; Ex. 2037. Antibodies, in contrast, exhibit far more diversity within close ranges of sequence identity. By evolutionary design, antibodies rapidly evolve in great numbers to respond to immunological threats within weeks of encountering a new antigen, and thus even minute changes in amino acid sequence were known to significantly change functionality, as *Amgen* recognized. Ex. 2011, ¶¶ 41-42; Ex. 2018; *Amgen*, 598 U.S. at 600 (“Despite recent advances, aspects of antibody science remain unpredictable. For example, scientists understand that changing even one amino acid in the sequence can alter an antibody’s structure and function.”).

Accordingly, *Amgen* and *Baxalta* were predicated on significantly different types of proteins (antibodies) than AAD-12 enzymes. Indeed, skilled artisans

recognized strong correlations between sequence identity and enzyme function, as disclosed in the '055 patent and its priority applications. *See supra* Sections III.A, II.A.2. And that strong correlation was established as of 2005-2006 and continued through the 2017 filing date that Petitioner relies upon. Ex. 2011, ¶ 29; Ex. 1001, 32:1-6; Ex. 2013, ¶ [00123]; Exs. 2014, 2017, ¶ [00150]; Ex. 2015, ¶ [00153]; Ex. 2016, ¶ [00156]; Ex. 2030, 1 (reporting in 2017 that enzymes with “over 30% similarity are likely to have similar functions, but to be 90% confident of the substrate of an enzyme, over 60% similarity may be required” (citing Ex. 2019)); *Lifescan*, PGR2019-00032, Paper 11 at 26, 30 (crediting expert testimony that skilled artisans could identify enzymes within a claim by making a “fair guess” based on sequence).

Accordingly, the structural requirements of the '055 patent claims and their AAD-12 enzymes are distinguishable from *Amgen* and *Baxalta*.

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

The Board preliminarily stated at institution that the specification illustrates that a skilled artisan would need to perform the same iterative process described in the '055 patent's examples. ID, 55-56. To the contrary, as Drs. Bollinger and Christou testify, the specification provides skilled artisans with detailed guidance in making and using the claimed transgenic plants and plant cells by describing

expression cassettes, transformation techniques, and structural characteristics of AAD-12 enzymes that skilled artisans in 2005-2006 would have been able to use in making embodiments of the claimed invention without undue experimentation.

1. Level of Skill in the Art (Factor 6)

Petitioner and the Board have acknowledged the level of skill was high, which weighs in favor of enablement. Pet., 55; ID, 56; Ex. 2012, ¶¶ 87-88; Ex. 2011, ¶¶ 114-116, 120. But Petitioner erred by limiting its analysis to the perspective of one skilled in the “genetic modification of plants,” ignoring the skilled artisan’s knowledge of enzymology and ability to make enzyme variants with retained activity. Ex. 1003, ¶ 62. Regarding AAD-12 variants, Dr. Silverstone presents a simplistic mathematical calculation (10^{106}) that assumes a *skilled* artisan would use *no skill* in making AAD-12 variants and randomly substitute all 19 alternative amino acids at each permitted location. *Id.*, ¶ 80 n.1. Such conclusory, unsupported assertions, citing only a generalized textbook, are legally deficient for this reason alone. 37 C.F.R. § 42.65(a); *Baxalta*, 81 F.4th at 1364 (enablement is assessed from the perspective of a “person skilled in the art” (quoting 35 U.S.C. § 112)).

2. Nature of the Invention and Scope of the Claims (Factors 4 and 8)

The challenged claims are generally directed to (i) transgenic plants and plant cells that produce AAD-12 proteins that degrade two classes of herbicides, phenoxy and pyridyloxy auxins; and (ii) methods of controlling weeds in a field including

such transgenic plants. The claims require the AAD-12 proteins to have two structural features that a skilled artisan would have recognized are correlated to function—the AAD-12 motif and at least 85% identity to SdpA (SEQ ID NO: 2). As detailed in the '055 patent's examples, AAD-12 was confirmed to exhibit the dual herbicide-degrading activity in plants. *See supra* Section III.B.

To an artisan skilled in enzymology, the scope of the recited AAD-12 enzymes is narrow. *Amgen*, 598 U.S. at 612 (what is “reasonable” for enablement must account for the “nature of the invention and the underlying art”). As Dr. Bollinger explains, enzymes having 85% or higher sequence identity are presumed to be essentially the same enzyme with the same function. Ex. 2011, ¶¶ 117-118. Consistent with the recognized conservation of enzyme function at high levels of sequence identity, the specification discloses that enzymes having 85% or higher sequence identity are “highly identical” and should have the same or similar function. Ex. 1001, 32:1-6, 21:41-60; Ex. 2013, ¶¶ [0093], [00123]; Exs. 2014, 2017, ¶¶ [00102], [00150]; Ex. 2015, ¶¶ [00105], [00153]; Ex. 2016, ¶¶ [00108], [00156]. As Dr. Bollinger points out, the AAD-12 motif requirement further narrows the scope of the claims by requiring a fixed active site, rather than permitting modifications to the required residues or their spacing. Ex. 2011, ¶ 119. The claims and disclosures of the '055 patent thus direct skilled artisans to a narrow, well-defined class of highly identical sequences correlated to the claimed activity with

the conserved AAD-12 active-site motif. Ex. 2011, ¶¶ 120-121; Ex. 2025, 6 (“[C]hanges at key active site residues . . . are generally deleterious.”).

To one skilled in plant transformation, the scope of the claimed transgenic plants is also reasonable. *Amgen*, 598 U.S. at 612. Petitioner contends that efficacy of an enzyme “in one plant species is not predictive of its efficacy in all plant species.” Pet., 59-60. But this argument misses the point. It was well known in 2005-2006 how to transform both monocot and dicot plants. Ex. 2012, ¶¶ 89-90. Protocols for plant transformation were established. *Id.* For AAD-12, the ’055 patent discloses working examples in multiple monocot crops (corn and rice) and dicot crops (tobacco, soybean, canola, cotton, and *Arabidopsis*). As Dr. Christou explains, because successful transformation and expression had been confirmed across multiple transformed monocots, a skilled artisan would have expected similar performance generally across monocots. *Id.*; Ex. 2075, 305-06 (describing “versatile and effective transformation . . . , not limited by cell type, species or genotype”). The same holds true for dicots. Ex. 2012, ¶ 90. Nothing in the ’055 patent’s detailed disclosure requires extrapolating from just one transformed plant species.

3. The Specification's Direction, Guidance, and Working Examples in View of the State of the Art (Factors 2, 3, and 5)

a. Making AAD-12 Enzymes and Recombinant Genes

The '055 patent provides extensive structural guidance to skilled artisans in making AAD-12 enzymes to maintain the claimed dual herbicide-degrading function. Ex. 2011, ¶¶ 122-131; Ex. 1001, 11:35-38, 12:37-39; Ex. 2013, ¶¶ [0044], [0051]; Exs. 2014, 2017, ¶¶ [0049], [0056]; Ex. 2015, ¶¶ [0052], [0059]; Ex. 2016, ¶¶ [0055], [0062]. This guidance includes directing skilled artisans with respect to overall sequence identity, conserving the active site, identifying and maintaining highly conserved residues, and maintaining charge and steric bulk distribution within the sequence so that the overall three-dimensional shape of the enzyme's active site and enzymatic function are maintained.

The '055 patent discloses making variants of the disclosed sequences (e.g., SEQ ID NO: 2) "having the same or similar activity of the exemplified proteins." Ex. 1001, 21:42-52; Ex. 2013, ¶ [0093]; Exs. 2014, 2017, ¶ [00102]; Ex. 2015, ¶ [00105]; Ex. 2016, ¶ [00108]. For such variants, the specification states that the "amino acid identity will typically be at least 60%" Ex. 1001, 21:42-52. These disclosures support and confirm a skilled artisan's understanding that high sequence identity is predictive of enzymatic function, including among α -KG dioxygenases. Ex. 2011, ¶ 123; *see* Ex. 2019, 863 ("60% sequence identity is needed to have at

least 90% accuracy” in predicting common function and substrate specificity). In particular, the '055 patent calls out 85% as a threshold among α KG-dependent dioxygenases at which a skilled artisan would “expect[] to retain similar properties.” Ex. 1001, 31:61-32:6; Ex. 2013, ¶ [00123]; Exs. 2014, 2017, ¶ [00150]; Ex. 2015, ¶ [00153]; Ex. 2016, ¶ [00156]. Thus, the specification instructs skilled artisans to maintain high (i.e., at least 85%) sequence identity to SEQ ID NO: 2 when making AAD-12 variants, just as the challenged claims require.

The '055 patent also discloses where to locate the active-site motif in AAD-12, which a skilled artisan would seek to maintain (as required by all claims) to avoid losing enzymatic activity. Ex. 1001, 11:1-6, 20:23-34, Fig. 2; Ex. 2011, ¶ 124; Ex. 2013, ¶ [0042]; Exs. 2014, 2017, ¶ [0047], Fig. 2; Ex. 2015, ¶ [0050], Fig. 2; Ex. 2016, ¶ [0053], Fig. 2. Figure 2 also discloses sequence alignments of SEQ ID NO: 2 to other related α KG-dependent dioxygenases having lower sequence identities, using shading to highlight the highly conserved residues across these enzymes. Ex. 1001, Fig. 2; Ex. 2025, 2-3 (sequences of related proteins are “a potentially rich source of information regarding sequences changes that are acceptable without drastically disrupting protein function”). As Dr. Bollinger testifies, skilled artisans understood that highly conserved residues among related proteins having lower sequence identity are presumptively structurally and functionally important. Ex. 2011, ¶ 125. Figure 2 thus provides significant guidance

to avoid making changes (or at least use conservative substitutions) at those positions when seeking to maintain AAD-12's enzymatic function. *Id.* Other unshaded residues, in contrast, may be more freely mutated. *Id.*, ¶ 126.

The '055 patent also reinforces that skilled artisans should use known protein engineering principles for making function-conserved enzyme variants. *See supra* Sections III.A, II.A. It discloses, for example, maintaining the surface charge distribution and same or similar overall essential three-dimensional structure, consistent with a skilled artisan's understanding that oppositely charged amino acids should not be exchanged and that steric bulk should be maintained. Ex. 1001, 28:57-60; Ex. 2011, ¶¶ 128-130. The specification also discloses known conservative mutations that skilled artisans understood would generally not have a deleterious effect on enzymatic activity. Ex. 1001, 22:13-37; Ex. 2013, ¶¶ [0095]-[0096]; Exs. 2014, 2017, ¶¶ [00104]-[00105]; Ex. 2015, ¶¶ [00107]-[00108]; Ex. 2016, ¶¶ [00110]-[00111].

The '055 patent thus amply discloses the types of amino acid substitutions that should or should not be made and provides significant guidance on where such mutations (or avoidance of mutations) should occur within SEQ ID NO: 2. Ex. 2011, ¶¶ 123-128; Ex. 2055, Table 1.

b. Making AAD-12-Transformed Plants and Plant Cells

The '055 patent also provides extensive guidance on making transgenic AAD-12 plants. Ex. 2012, ¶¶ 92-93. This includes twenty-four examples related to the invention, including successful *in vivo* AAD-12 transformations in multiple dicot and monocot plant species. As Dr. Christou summarizes, the steps needed to make transgenic plants across the scope of the challenged claims were well established by 2005-2006 and would not have required undue experimentation to carry out. *Id.*, ¶¶ 91-128; Ex. 2009, 99:21-100:19 (Dr. Silverstone acknowledging three basic steps for plant transformation).

Codon optimization (optional): While not required, the '055 patent discloses that AAD-12 genes may be optimized for expression in plants through an established technique known as codon optimization. Ex. 1001, 13:6-14, 22:57-23:2, 32:24-41:2 (Example 2); Exs. 2013-2017, Example 2. The specification discloses preferred codons, preferred codon frequencies, and a maize-optimized nucleotide sequence for AAD-12, designated AAD-12 (v1). Ex. 1001, 32:62-36:6 (Tables 3-5); Ex. 2013, ¶¶ [00128]-[00135]; Exs. 2014, 2017, ¶¶ [00155]-[00162]; Ex. 2015, ¶¶ [00158]-[00165]; Ex. 2016, ¶¶ [00161]-[00168]. By 2005-2006, codon optimization was computer-implemented, requiring little input from a skilled artisan. Ex. 1001,

39:26-29 (describing the OptGene™ program); Ex. 2013, ¶ [00141]; Exs. 2014, 2017, ¶ [00168]; Ex. 2015, ¶ [00171]; Ex. 2016, ¶ [00174]; Ex. 2012, ¶¶ 94-96.

Transformation vectors: The '055 patent discloses a variety of exemplary transformation vectors and cassette components for transforming plants. Ex. 2012, ¶¶ 97-105. It discloses using strong promoters to “super-charge” expression, including the cauliflower mosaic virus 35S and 35T promoters, maize ubiquitin, *Arabidopsis* ubiquitin, and others. Ex. 1001, 28:45-53, 27:35-28:3; Ex. 2013, ¶ [00117]; Exs. 2014, 2017, ¶¶ [00127], [00132]; Ex. 2015, ¶¶ [00130], [00135]; Ex. 2016, ¶¶ [00133], [00138]. For dicot transformations in the examples, the cassettes contained the *Arabidopsis* ubiquitin 10 promoter (AtUbi10) or the cassava vein mosaic virus promoter (CsVMV). Ex. 1001, 42:1-28 (Table 8). For monocot transformations, the cassettes contained the maize ubiquitin 1 promoter (ZmUbi1). *Id.*

The examples confirm that the same transformation vectors and cassettes containing dicot promoters will generally work across dicot species. Ex. 2012, ¶ 123. For example, vectors pDAB724 and pDAB3759 were each used to transform multiple dicot species. Ex. 1001, Table 8. Vector pDAB4101 was used to transform monocots, corn, and rice. The specification also illustrates that expression cassettes may be reused with different genes, as AAD-2 (v1) and AAD-12 (v1) genes were cloned into the same cassettes to produce transformation vectors. *Id.*, 42:14-21,

84:35-42; Ex. 2013, ¶¶ [00150], [00292]; Exs. 2014, 2017, ¶¶ [00177], [00365]; Ex. 2015, ¶¶ [00180], [00368]; Ex. 2016, ¶¶ [00183], [00370]; Ex. 2012, ¶ 123. Such disclosures are consistent with Dr. Silverstone's own published work, where the same expression vectors were reused with different genes for crop transformation. Ex. 2009, 101:9-102:6, 109:24-111:25; Ex. 2010, 482-83.

Transformation techniques: The '055 patent discloses well-established transformation techniques that had previously been applied to a variety of monocot and dicot plants. Ex. 1001, 24:25-31 ("A large number of techniques are available for inserting DNA into a plant host cell."), 1:23-27 (disclosing previous development of glyphosate-resistant corn, soybeans, canola, cotton, sugar beets, wheat, turf, and rice); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987) (the specification need disclose only one method for making the claimed invention).

The disclosed transformation techniques include particle bombardment (biolistics), *Agrobacterium*-mediated transformation, and WHISKERS-mediated transformation, which were used according to established protocols in the '055 patent's examples. Using these techniques, plants were successfully transformed to express the AAD-12 (v1) gene, either alone or stacked with other genes (e.g., AAD-1 or *pat*). Ex. 2012, ¶¶ 106-109; Ex. 1001, Examples 7, 10-12, 22 (*Agrobacterium*-mediated transformation of *Arabidopsis*, tobacco, soybean, cotton, and canola),

Example 8 (WHISKERS-mediated transformation of corn), Example 21 (biolistics-mediated transformation of rice).

Regeneration of AAD-12 transformants: The '055 patent discloses that successfully transformed plant cells may be regenerated into plants using techniques and standard media known in 2005-2006. Ex. 1001, 24:54-25:2, 26:38-57, Examples 7, 8, 10-12, 21, 22; Ex. 2012, ¶ 110. In parallel, the transformed plant cells or plants may be detected using a selectable marker, i.e., an herbicide-resistance gene, at essentially any desired time. Ex. 2012, ¶¶ 111-112; Ex. 2009, 114:11-20.

The '055 patent established that AAD-12 genes function well as selectable markers. Ex. 2012, ¶ 119; Ex. 1001, 53:18-39, 42:1-28, Table 8, Example 24; Ex. 2013, ¶¶ [00192]-[00193], Table 7; Exs. 2014, 2017, ¶¶ [00223]-[00224], Table 8, Example 24; Ex. 2015, ¶¶ [00226]-[00227], Table 8, Example 24; Ex. 2016, ¶¶ [00229]-[00230], Table 8, Example 24. The '055 patent thus discloses a significant shortcut for skilled artisans practicing the claimed invention because the act of identifying successful transformants using an AAD-12 gene and a matching herbicide application (e.g., a phenoxy auxin and a pyridyloxy auxin) would also confirm that the transformed plants exhibit the claimed dual enzyme-degrading activity. *E.g.*, Ex. 1001, 68:8-69:12 (confirming dual activity in T₀ tobacco), 75:34-77:30 (T₀ soybean), 97:12-39 (T₀ canola), 52:12-54:45 (T₁ and T₂ *Arabidopsis*),

64:28-65:53 (describing “high level tolerance in corn to 2,4-D, triclopyr, and fluroxypyr” in field testing), 93:9-95:15 (T₁ rice), 97:46-99:20 (T₁ canola).

As Dr. Christou explains, nothing is needed beyond what the '055 patent discloses to successfully produce AAD-12-transformed plant cells and plants across the full scope of the claims. Ex. 2012, ¶ 113.

4. The Amount of Experimentation Is Not Undue or Unpredictable (Factors 1 and 7)

The amount of experimentation required to practice the full scope of the claimed invention would have been reasonable, particularly in view of the nature of the invention and the underlying art in the fields of enzymology and plant transformation. *Amgen*, 598 U.S. at 612 (“[A] specification may call for a reasonable amount of experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art.”); *Minerals Separation v. Hyde*, 242 U.S. 261, 270 (1916) (“the certainty which the law requires in patents is not greater than is reasonable”).

a. It Would Have Required Only Routine Experimentation to Make AAD-12 Enzymes and Recombinant Genes

Legally erring by ignoring the perspective and background knowledge of a skilled artisan (*see supra* Section VII.B.1), Petitioner contends that the challenged claims allow for 10¹⁰⁶ unique sequences. Pet., 39-40. Petitioner then errs again by asserting that enabling “the full scope of the claims of the '055 patent *would require*

the testing of all proteins” within 85% sequence identity to SEQ ID NO: 2 and having the AAD-12 motif. *Id.* But *Amgen* held the opposite: “enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim.” 598 U.S. at 615. The Board has similarly rejected arguments that a skilled artisan “could not feasibly test every possible sequence” where the petitioner, as here, failed to account for how the “knowledge in the art . . . would have informed and narrowed the degree of experimentation necessary.” *Lifescan*, PGR2019-00032, Paper 11 at 23-24.

The ’055 patent’s extensive guidance, sequence-limited claims, and the knowledge in the art significantly narrow the amount of required experimentation, differentiating this case from *Amgen* and *Baxalta*. *See* ID, 52-54. In those cases, it was undisputed that the specification disclosed no structural features that would guide skilled artisans towards additional antibodies having the claimed functions. *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021), *aff’d*, 598 U.S. 594 (2023); *Baxalta*, 81 F.4th at 1366 (“The patent does not disclose any common structural (or other) feature delineating which antibodies will bind to Factor IX/IXa and increase procoagulant activity from those that will not.”). Instead, as the Institution Decision noted, skilled artisans in those cases would have had to start from scratch to make additional claimed antibodies, e.g., by immunizing mice with

an antigen to induce an immunological response producing a range of antibodies, forming hybridomas, and screening the antibodies recovered for activity. ID, 54.

Unlike in *Amgen* and *Baxalta*, the '055 patent discloses that the inventors already investigated α KG-dependent dioxygenase sequences ranging from “highly identical (85-98%) to very low identity (23-32%)” to TfdA, identified AAD-12 at a relatively low (i.e., 31%) sequence identity to TfdA, and disclosed AAD-12’s amino acid sequence and dual herbicide-degrading activity *in vitro* and *in planta*. Ex. 1001, 31:55-32:22; Ex. 2013, ¶¶ [00123]-[00124]; Exs. 2014, 2017, ¶¶ [00150]-[00151]; Ex. 2015, ¶¶ [00153]-[00154]; Ex. 2016, ¶¶ [00156]-[00157]. There was thus no need for skilled artisans to investigate unpredictable ranges of sequence identity. Ex. 2011, ¶¶ 132-134. Instead, the specification discloses that skilled artisans making function-conserved variants of the disclosed sequences (e.g., SEQ ID NO: 2) should typically stay within “at least 60%” identity, including at least 85% identity, as claimed, consistent with a skilled artisan’s background understanding of sequence-function conservation among enzymes. Ex. 1001, 21:41-60, 32:1-6 (85% or higher sequence identity is “highly identical” and “[t]raditionally ... sequences with high homology would be expected to retain similar properties”); Ex. 2019, 863 (only “60% sequence identity is needed to have at least 90% accuracy” in predicting common function and substrate specificity).

Accordingly, the '055 patent provides significant guidance to skilled artisans by directing them to a well-defined and function-correlated sequence space for making other AAD-12 enzymes, while requiring conserving the same active site as in SEQ ID NO: 2 and providing a sequence alignment in Figure 2 identifying other highly conserved (and thus presumptively important) residues. Ex. 2011, ¶¶ 123-128. The specification's structural guidance makes this case distinctly different than *Amgen* and *Baxalta*, which involved a stark "lack of structural guidance." *Amgen*, 987 F.3d at 1086; *Baxalta*, 81 F.4th at 1366.

As Dr. Bollinger notes, skilled enzymologists often seek to make variants with targeted improvements (e.g., higher catalytic rate or increased thermostability), focusing attention on top-performing variants. Ex. 2011, ¶ 135. Here, in contrast, 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—one would just need to not entirely destroy the enzymatic function of SEQ ID NO: 2. *Id.* In other words, even mediocre or relatively poor-performing AAD-12 variants compared to SEQ ID NO: 2 are successes in this context. *Id.*; Ex. 1003, ¶ 82 (Petitioner stating that AAD-12 variants will include "worse," "equivalent," and "better" enzymes, but failing to acknowledge that all three categories of AAD-12 variants would be within the claim scope).

In making enzyme variants that retain function, skilled artisans in 2005-2006 would have followed established protein engineering principles, which Petitioner fails to address. *See supra* Section II.A.2-3; *see* Ex. 2025, 5-6. These included:

- 1) Maintaining high sequence identity;
- 2) Maintaining active-site motif residues;
- 3) Retaining or conservatively substituting non-motif residues that are highly conserved across related enzymes; and
- 4) Retaining overall surface charge distribution and steric bulk.

Ex. 2011, ¶¶ 136-140.

Notwithstanding *Amgen*'s admonition that enablement is not weighed against the time and effort required to make "every embodiment within a claim," 598 U.S. at 615, skilled artisans in 2005-2006 nonetheless would have been routinely able to make AAD-12 variants. Ex. 2011, ¶¶ 55 (citing Exs. 2038, 2039), 129-130. For example, directed evolution techniques mimicked natural protein evolution in a high-throughput manner. *Id.* Known computational techniques in 2005-2006 were even more powerful. Ex. 2038, 382 ("Computational screening can screen libraries of 10^{80} variants...."). Dr. Silverstone's patents also reflect further development of high-throughput techniques (e.g., synthetic ligation assembly) before 2017, allowing researchers to generate over 10^{100} to 10^{1000} different progeny genes encoding proteins. Ex. 2008, 71:18-72:36. Thus, Petitioner's enablement arguments based on

a flawed numerosity theory fail. *Alcon*, 745 F.3d at 1188-89 (conclusory arguments about the alleged “breadth of the claims” and generalized “variables” are insufficient).

Moreover, while skilled artisans *could* rely on a three-dimensional enzyme crystal structure when making variants (Ex. 1003, ¶¶ 45-46), they were not so limited. Ex. 2011, ¶¶ 141-142. Skilled artisans recognized that a “wide variety” of approaches could be used, including “sequence alignments.” Ex. 2035, 180; Ex. 2035, 180. Dr. Silverstone thus applies too high a standard in demanding three-dimensional structural information. Ex. 1003, ¶ 47; Ex. 2009, 116:18-119:17; Ex. 2010, 484 (Dr. Silverstone and co-authors reporting that similar function for enzymes having 89% sequence identity was “not surprising[]”). The information presented in the ’055 patent and known in the art provided ample guidance for making functional AAD-12 variants, particularly in view of the narrow sequence space (85% or higher identity to SEQ ID NO: 2) in which skilled artisans would expect to readily make claimed enzymes. *See supra* Section VII.B.3.

The ’055 patent also provides significant guidance on *in vitro* assays for confirming degradation activity against phenoxy and pyridyloxy auxin herbicides. Examples 5 and 6 disclose colorimetric assay techniques, which had been available since 1993 and were increasingly implemented in high-throughput well plate formats. Ex. 1001, 45:50-48:60 (describing rapid testing of AAD-12 activity,

requiring only 5- to 10-minute incubation times), 46:23-45 (10-minute spectrophotometric assays); Exs. 2013-2017, Examples 5, 6. As Dr. Bollinger summarizes, these types of assays were automated and could be run with little hands-on intervention. Ex. 2011, ¶¶ 143-144. Petitioner’s argument that *in vitro* data “does not *guarantee* performance in planta” is legally deficient. Ex. 1003, ¶ 91; Pet., 41-42.² No such guarantee is required. *Lifescan*, PGR2019-00032, Paper 11 at 23 (“Nor does the law require that the POSA be able to predict each species encompassed within a claim that would have the required characteristics.” (citing *In re Angstadt*, 537 F.2d 498, 503 (CCPA 1976))).

Thus, as of 2005-2006, it would have required only reasonable experimentation using routine techniques to make and use AAD-12 enzymes and genes across the full scope of the claims for transformation into plants. Ex. 2011, ¶ 145.

² Petitioner’s argument about “surprising[]” *in vitro* versus *in vivo* activity disregards the specification’s disclosure that what was surprising was the comparative *magnitude* of activity, with AAD-2 having some (but low) activity against 2,4-D compared to AAD-12. Pet. 42 n.10; Ex. 1001, 84:60-85:23. Here, the claims do not require any minimum level of dual herbicide-degrading activity.

b. It Would Have Required Only Routine Experimentation to Make AAD-12-Transformed Plants and Plant Cells

Making the claimed transgenic plants would have involved, after any optional codon optimization, inserting the AAD-12 gene into one of the '055 patent's exemplary transformation vectors, carrying out a known transformation technique (e.g., *Agrobacterium*-mediated transformation or biolistics), and regenerating the transformed plant cells into plants. *See supra* Sections III.B, II.B. Petitioner does not dispute that plant transformation techniques were routine by 2005. Ex. 2009, 104:13-105:11 (Dr. Silverstone acknowledging that “[t]ransformation techniques for dicotyledons are *well known in the art*” and “[t]ransformation of most monocotyledon species has now also become *routine*”); ID, 56 (“The parties do not appear to dispute that the skill level is high or that the steps required to obtain embodiments of the claims are known”).

As Dr. Christou testifies, once a skilled artisan had an AAD-12 gene in hand, the time required to produce a transformed AAD-12 plant expressing that variant would mainly be a function of plant biology. Ex. 2012, ¶ 113. To produce genetically transformed plants, skilled artisans used samples of immature embryogenic plant tissue because older tissues are less susceptible (or not susceptible) to transformation. *Id.*, ¶ 114; Ex. 2082. The time required to obtain suitable plant tissue for transformation varies by species but was quite short in 2005-2006. *See, e.g.,*

Ex. 1001, 80:7-9 (cotyledon segments prepared from 7- to 10-day-old cotton seedlings), 56:61-57:38 (maize embryos extracted 9-10 days post-pollination used to form callus tissue for transformation over 2-3 months); Ex. 2013, ¶¶ [00275], [00210]-[00213]; Exs. 2014, 2017, ¶¶ [00347], [00244]-[00247]; Ex. 2015, ¶¶ [00350], [00247]-[00250]; Ex. 2016, ¶¶ [00353], [00250]-[00253].

Immature plant tissues for genetic transformation were routinely prepared on a rapid basis. For example, a technician (*see supra* Section IV) was able to trim small cotton seedlings with a scalpel into transformation-ready cotyledon segments within a matter of seconds (i.e., a few hundred per hour). Ex. 2012, ¶ 115. A technician was also able to extract hundreds of maize embryos from kernels on a cob per hour. *Id.* Those immature tissues could then be used immediately for transformation via, e.g., particle bombardment. *Id.*

In parallel, skilled artisans would have been able to rapidly codon-optimize and insert recombinant AAD-12 genes into expression vectors. *Id.*, ¶ 116. The '055 patent discloses several exemplary expression vectors that a skilled artisan would have been able to reuse to transform monocot and/or dicot crops through the disclosed techniques (e.g., particle bombardment or *Agrobacterium*-mediated transformation). *See supra* Section III.B; Ex. 1001, 42:1-36, Table 8; Ex. 2013, ¶¶ [00151]-[00152], Table 7; Exs. 2014, 2017, ¶¶ [00178]-[00179], Table 8; Ex. 2015, ¶¶ [00181]-[00182], Table 8; Ex. 2016, ¶¶ [00184]-[00185], Table 8. As

the '055 patent discloses, small gold particles can be coated with plasmid DNA having an expression vector in minutes. Ex. 1001, 92:44-59. Alternatively, expression vectors may be incorporated into *Agrobacterium*, and culturing a suitable population of such *Agrobacterium* for plant transformation purposes requires only about 2-4 days. Ex. 2012, ¶ 116; Ex. 1001, 49:18-50:7; Ex. 2013, ¶¶ [00176]-[00180]; Exs. 2014, 2017, ¶¶ [00206]-[00210]; Ex. 2015, ¶¶ [00209]-[00213]; Ex. 2016, ¶¶ [00212]-[00216].

Skilled artisans were then readily capable of performing the disclosed transformation techniques on plant tissues, regenerating the transformed tissues into plants, and identifying AAD-12 transformants using a selectable marker. Ex. 2012, ¶¶ 117-120. Indeed, the '055 patent provided a significant shortcut to skilled artisans by establishing the AAD-12 gene as a selectable marker, enabling transformed plants showing improved herbicide-degradation activity to be identified by simply applying (e.g., spraying) a phenoxy and/or pyridyloxy auxin herbicide. Ex. 1001, 53:18-54:45.

c. Dr. Silverstone Relies on Unnecessary Tasks to Form His Opinions Regarding the Amount of Experimentation

Failing to acknowledge the straightforward, established steps for making genetically transformed plants in 2005-2006, Dr. Silverstone overcomplicates the

process. Ex. 2012, ¶¶ 121-128. His positions should be rejected as factually incorrect and as directed to unclaimed features.

First, Dr. Silverstone asserts that AAD-12 genes would need codon optimization for each plant species. Ex. 1003, ¶ 72. To the contrary, as Dr. Christou testifies, codon optimization is optional and a single optimization, if needed, generally suffices. Ex. 2012, ¶¶ 117-120. Indeed, all plant transformations in the '055 patent's examples—in monocots and dicots—were successfully carried out using a maize codon-optimized AAD-12 (v1) gene. Ex. 1001, Example 2; *id.*, 42:1-28; Ex. 2013, ¶¶ [00149]-[00150]; Exs. 2014, 2017, ¶¶ [00176]-[00177]; Ex. 2015, ¶¶ [00179]-[00180]; Ex. 2016, ¶¶ [00182]-[00183]. Further, the claims do not require codon optimization and, thus, Petitioner's argument is directed to an unclaimed feature.

Second, Dr. Silverstone incorrectly states that expression cassettes will also “likely require[] modification for each plant species.” Ex. 1003, ¶ 72. As Dr. Christou explains, this is incorrect. Ex. 2012, ¶ 123. The '055 patent discloses that the same expression vectors may generally be used across monocot and dicot plant species, respectively. Ex. 1001, 42:1-28, Table 8; Ex. 2009, 27:15-30:21 (Dr. Silverstone acknowledging that that vectors pDAB724, pDAB3759, and pDAB4101 in Table 8 were each used to transform multiple dicot or monocot species). Likewise, the same expression cassettes can generally be reused with each

gene. Ex. 2012, ¶ 44; Ex. 2009, 101:9-102:6, 109:24-111:25 (Dr. Silverstone reusing the same cassettes with different genes); Ex. 2010, 482-83. To the extent that a skilled artisan would want to change expression vectors for some reason, the '055 patent discloses plenty of alternatives, and Dr. Silverstone has acknowledged that it was a “routine” matter to select appropriate promoters and other expression cassette components. Ex. 2009, 104:13-105:11; Ex. 2007, 19:29-30, 18:35-40; Ex. 1001, 28:45-53, 27:35-28:3, Table 8; Ex. 2013, ¶ [00117]; Exs. 2014, 2017, ¶ [00127]; Ex. 2015, ¶ [00130]; Ex. 2016, ¶ [00133].

Third, Dr. Silverstone states that “meticulous experimentation” (Ex. 1003, ¶ 74) would be required to confirm proper expression of a protein in a transgenic plant, including the use of “protein and nucleic acid analytic techniques to confirm the presence of the transgene, number of copies, intactness of the inserted DNA, its location in the genome, and the expression of the protein” (*id.*, ¶ 75). But none of these proposed tasks are necessary, as Dr. Christou explains, because proper expression can be confirmed by a much simpler technique—using a selectable marker (i.e., applying the relevant herbicides). Ex. 2012, ¶ 124; Ex. 1001, 53:18-54:45 (disclosing the AAD-12 gene as an effective selectable marker). Moreover, the claims do not require any particular level of expression. Ex. 2009, 80:24-81:5. Detailed DNA analysis may only be required by regulatory authorities when a final, optimized commercial transgenic event is submitted for regulatory approval.

Ex. 2012, ¶ 124; *Transocean*, 617 F.3d at 1307 (reversing because there is no requirement to enable “the most efficient commercial embodiment, rather than the claims”).

Fourth, Dr. Silverstone incorrectly relies on another unclaimed feature, i.e., that the plants allegedly “need to be propagated for *several generations*” for testing of herbicide tolerance. Ex. 1003, ¶ 75; Ex. 2009, 73:18-74:9, 77:12-20. The ’055 patent contains numerous examples of using the AAD-12 gene as a selectable marker to evaluate tolerance much earlier—i.e., in transformed cells or in the initially transformed plant generation by incubating or spraying with phenoxy and/or pyridyloxy auxin herbicides. *See supra* Sections III.B, VII.B.3. Moreover, skilled artisans generally would have expected to maintain AAD-12 genetic transformations into subsequent plant generations. Ex. 2012, ¶ 125; *see also* Ex. 1001, 25:10-12 (“Once the inserted DNA has been integrated in the genome, it is relatively stable there (and does not come out again).”), 53:55-57; Ex. 2013, ¶¶ [00109], [00196]; Exs. 2014, 2017, ¶¶ [00119], [00228]; Ex. 2015, ¶¶ [00122], [00231]; Ex. 2016, ¶¶ [00125], [00234].

Fifth, Dr. Silverstone incorrectly maintains that a “large number” of transgenic plants would need to be generated for each AAD-12 variant. Ex. 1003, ¶¶ 73, 76. To the contrary, because the transformation techniques randomly insert the genes into the plant genomes, skilled artisans already had a routine practice of

transforming a modest number of plants. Ex. 2012, ¶ 127. For instance, 20 to 30 immature plant embryos (each on the order of millimeters in size) typically fit on a single particle bombardment plate, and thus can be bombarded simultaneously with a single “shot” and then regenerated into plants. *Id.* Such numbers, regardless of the transformation technique used, would be more than sufficient to identify successful transformants expressing AAD-12 genes. *Id.*; Ex. 1001, 68:20-22 (“*Every event tested* was more tolerant to 2,4-D than the untransformed control line KY160.” (emphasis added)), 97:12-45 (verifying AAD-12 transformation in 24 of 45 T₀ canola plants). While Dr. Silverstone points out variability in expression levels in the examples, the claims do not require any particular expression level, and Dr. Christou explains that such variation is entirely within normal ranges for skilled artisans. Ex. 1003, ¶¶ 76-77; Ex. 2012, ¶¶ 102-105.

Accordingly, the '055 patent provides extensive disclosure and guidance to skilled artisans to make and use AAD-12 transformed plants and plant cells across the full scope of the claims. Petitioner’s enablement challenge should be rejected.

VIII. Petitioner Failed to Establish that the Challenged Claims Lack Written-Description Support

Petitioner failed to establish lack of written description, particularly in view of Corteva’s rebuttal evidence presented above regarding enablement, which applies

equally to written description and includes established sequence-identity thresholds for expecting conserved enzyme function.

Written description requires that the specification “reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter.” *Ariad*, 598 F.3d at 1351. The *Ariad* standard for genus claims requires describing *either* a reasonable number of species or common, function-correlated structure so that a skilled artisan can “recognize” the members of the genus. *Id.* at 1350.

The '055 patent discloses function-correlated structures common to the genus of AAD-12 enzymes, requiring 85% sequence identity to SEQ ID NO: 2 and the AAD-12 motif. The claimed genus of AAD-12 enzymes is also essentially the opposite of the structurally and functionally diverse genus in *AbbVie*, and thus the disclosed AAD-12 and AAD-12 (v1) enzymes are also sufficient representative species. Moreover, because the '055 patent claims have written-description support in the pre-AIA priority applications, including the 2005 provisional and 2006 nonprovisional applications, the '055 patent is ineligible for post-grant review and this proceeding should be terminated.

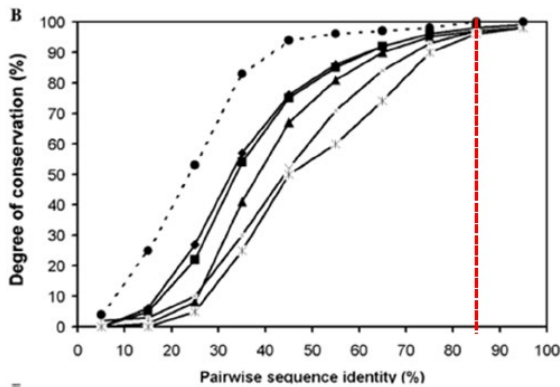
A. The '055 Patent Describes the AAD-12 Proteins of the Challenged Claims

1. Petitioner Fails to Establish that the '055 Patent Lacks Disclosure of Common, Function-Correlated Structure

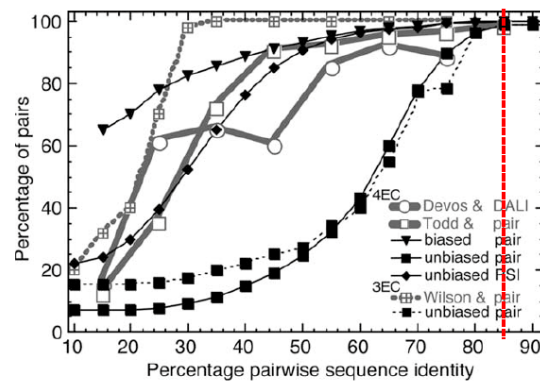
Petitioner's written-description challenge should be rejected because the challenged claims are amply supported. *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1360-61 (Fed. Cir. 2019); Ex. 2011, ¶¶ 146-170; Ex. 2012, ¶¶ 129-147.

The specification discloses that enzymes having the "same or similar activity of the exemplified proteins" (e.g., AAD-12) typically have at least 60% sequence identity, including 85% or higher sequence identity. Ex. 1001, 21:41-60, 32:1-6; Ex. 2013, ¶¶ [0093], [00123]; Exs. 2014, 2017, ¶¶ [00102], [00150]; Ex. 2015, ¶¶ [00105], [00153]; Ex. 2016, ¶¶ [00108], [00156]. The '055 patent further describes 85% sequence identity as "highly identical" among α KG-dependent dioxygenases like AAD-12 and as carrying an expectation of "similar properties." Ex. 1001, 32:1-6. These disclosures that 85% and higher sequence identity are correlated to conservation of function comport with the background knowledge of skilled artisans, who knew that sequence identity thresholds for predicting enzyme function had been established in the early 2000s. Ex. 2011, ¶¶ 148-150; *Ariad*, 598 F.3d at 1351 (a written-description analysis must account for (1) existing knowledge in the particular field, (2) extent and content of the prior art, (3) maturity of the science, and (4) predictability of the technology at issue).

Indeed, by 2005-2006, skilled artisans recognized that high sequence identity is strongly correlated to enzyme function, with several research groups reporting studies showing that sequence identities above 40-60% provide 90% accuracy in predicting the same enzymatic function. Ex. 2011, ¶ 151.



Ex. 2019, 866 (annotated Fig. 1(B)).



Ex. 2028, 604 (annotated Fig. 5).

For example, as Tian 2003 disclosed, only “60% sequence identity is needed to have at least 90% accuracy” in predicting common function and substrate specificity, defined as “all four digits of an EC number.” Ex. 2019, 863. Accordingly, in view of the ’055 patent’s disclosures—which must be read from a skilled artisan’s perspective—it would *not* have been “unclear to the skilled artisan how far from 99.3% identity the [AAD-12] polypeptide can deviate while still retaining the ability to degrade herbicides,” as the Board stated. ID, 39. Instead, 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. Ex. 2011, ¶¶ 152-153.

The specification also describes the AAD-12 active-site motif. *See supra* Section III.A. As Dr. Bollinger explains, an enzyme’s active-site motif was understood to be correlated to its function. Ex. 2011, ¶¶ 154-156. For example, skilled artisans in 2005 recognized that “changes at key active site residues . . . are generally deleterious,” confirming the intuitive correlation between an enzyme’s active site and the enzyme’s function. Ex. 2025, 6; Ex. 2011, ¶ 156. Indeed, Petitioner acknowledges that the AAD-12 motif is not just correlated to the claimed function—it is “necessary.” Pet., 33; *Ajinomoto*, 932 F.3d at 1360.

The Board has previously rejected the same types of arguments that Petitioner raises here. In *Lifescan*, the Board considered claims reciting an enzyme having 90% sequence identity to a sequence having 593 amino acids, which permitted up to 59 mutations. PGR2019-00032, Paper 11 at 18-19. The Board found the petitioner’s written-description challenge unpersuasive based on evidence that a six amino-acid sequence, “or some close variation thereof, is *necessary*” for its activity. *Id.* at 29. Here, by comparison, Petitioner’s case is far more deficient: (i) SEQ ID NO: 2 is shorter (292 amino acids); (ii) the number of possible mutations is lower (Pet. 39, asserting a maximum of 43 mutations); (iii) the five amino acid AAD-12 motif has fixed residues and spacing; and (iv) Petitioner concedes that the AAD-12 motif is “necessary” for the claimed function, exceeding the legal standard for function-correlated structure. Pet., 33; *Ajinomoto*, 932 F.3d at 1360.

Petitioner's demand for additional disclosure of three-dimensional features fails. Pet., 33. First, the law does not require such disclosures, and Petitioner cites no authority supporting its position. *See Ajinomoto*, 932 F.3d at 1360. Second, Petitioner ignores the skilled artisan's understanding in 2005-2006 that three-dimensional structure would be highly conserved at the claimed levels of sequence identity. Ex. 2028, 604 ("When two sequences are very similar[,] we can *safely infer* that they have similar structures."); *id.*, 596 ("In general, transfer of structure is *almost guaranteed* to be correct above the twilight zone"); Ex. 2026, 98 ("The comparison of protein sequences is widely used to infer protein structure and function."). Ex. 2011, ¶ 157.

Third, Petitioner fails to account for the specification's disclosures and the state of the art in 2005-2006. Petitioner acknowledges that there were alternatives to using crystal structures for modeling an enzyme, including comparisons to the sequence of a closely related protein of known structure—i.e., precisely what Figure 2 of the '055 patent discloses. Ex. 2011, ¶ 158 (citing Ex. 2035); Ex. 1003, ¶¶ 45-46. Elkins 2002 previously reported the crystal structure of the related α KG-dependent dioxygenase TauD and showed which residues corresponded to three-dimensional structural features such as α -helices and β -strands. Ex. 2022, 5190. Citing Elkins 2002, the '055 patent discloses a sequence comparison between the three-dimensionally mapped TauD and AAD-12 enzymes, showing their conserved

residues (including their active sites), identifying structurally and functionally important amino acid residues. Ex. 1001, Fig. 2, 20:23-34; Ex. 2011, ¶ 159. Accordingly, the disclosures Dr. Silverstone demands *are* provided in the '055 patent.

Here, the structural AAD-12 motif and 85% sequence identity features of the claims are each common structures correlated to the claimed function and they each independently provide adequate written-description support. Together, they compel confirming patentability. *See Ajinomoto*, 932 F.3d at 1360-61.

2. Petitioner Fails to Apply a Correct Legal Standard for Function-Correlated Structure

Petitioner incorrectly seeks to raise the legal standard for written description by asserting that a common structural feature must be more than correlated to function—it must also be “necessary” and “sufficient.” Pet., 33. Petitioner, however, cites no legal authority for its position, which effectively rewrites *Ariad*’s correlation standard. *Id.*; *Ariad*, 598 F.3d at 1350.

The challenged claims should be upheld “if a reasonable structure-function correlation is established, whether by the inventor as described in the specification or known in the art at the time of the filing date.” *AbbVie*, 759 F.3d at 1301; *Ariad*, 598 F.3d at 1350. Under this reasonableness standard, a common structural feature need not be “necessary,” much less “sufficient,” for the claimed function, as

correlation does not require *causation* of the claimed function. *Cf.* Pet., 33; *see Datamaxx Applied Techs., Inc. v. Brown & Brown, Inc.*, No. 21-13451, 2022 WL 3597311, at *4 (11th Cir. Aug. 23, 2022) (“correlation does not imply causation” (citing *Merriam-Webster Dictionary* and *Brown v. Ent. Merchs. Ass’n*, 564 U.S. 786, 800 (2011))). Rather, as *Ajinomoto* illustrates, the law requires only a relationship—i.e., a correlation—between structure and function, which the “at least 85% sequence identity” and AAD-12 motif features satisfy here. *See supra* Section VIII.A.1.

In *Ajinomoto*, the ITC accepted that a “consensus sequence” did not necessarily provide the most potent promoter within the scope of the claims. *Certain L-Tryptophan, L-Tryptophan Products, and Their Methods of Production*, Inv. No. 337-TA-1005, 2018 WL 8648370, at *25 (USITC Jan. 11, 2018). In other words, the consensus sequence was *not* necessary—let alone sufficient—to produce more potent promoters. *See id.* The ITC nonetheless reversed the ALJ’s finding of inadequate written description, concluding that the challenger failed to establish that the consensus sequence was “*unrelated* to promoter strength” or failed to yield a more potent promoter, as claimed. *Id.*

The Federal Circuit affirmed. *Ajinomoto*, 932 F.3d at 1360-61. The challenger argued that similarity to a consensus sequence “is still not enough to predict the site and strength of a promoter from a given sequence,” and that “a promoter closer to the consensus sequence will not always be stronger than one farther from that

sequence.” *Id.*; see Pet., 31 (Petitioner similarly arguing that structure and function “cannot be accurately predicted solely from the primary amino acid sequence”). The Federal Circuit rejected those arguments as assuming “too strict a legal standard.” *Ajinomoto*, 932 F.3d at 1360. Here, Petitioner’s asserted requirement that a disclosed structural feature must be “necessary” and “sufficient” to achieve the claimed function demands the same level of “perfect correspondence” that *Ajinomoto* rejected. *Id.*; Pet., 33.

Indeed, in *PureCircle*, the court recently reiterated that “*Ajinomoto* stands for the idea that where there are structural features common to a genus,” as here, “the structure-function correlation does not need to be perfect and some testing—appropriate to the knowledge of a POSA—is allowed.” *PureCircle USA Inc. v. SweeGen, Inc.*, No. 2022-1946, slip op. at 12 n.10 (Fed. Cir. Jan. 2, 2024). There, the Federal Circuit found that claims reciting a *purely functionally defined genus* of enzymes lacked written description where they contained no sequence limitations and a skilled artisan would need to empirically determine the active site’s location. *Id.* at 5-6. Here, in contrast, the ’055 patent discloses the AAD-12 active-site motif and restricts the AAD-12 enzymes to those having highly identical (at least 85%) sequences.

In the Institution Decision, the Board stated that the “two examples” of AAD-12 proteins within 99.3% identity to SEQ ID NO: 2 were not sufficient

description and for “this reason” rejected Corteva’s reliance on *Ajinomoto*. ID, 39; *but see Lifescan*, PGR2019-00032, Paper 11 at 28-30 (finding three examples and disclosure of a consensus sequence sufficient description). Corteva respectfully submits that the Board’s reasoning is incorrect.

As *Ariad* explains, the law only requires disclosure of *either* representative examples (e.g., species) or common structure—not both. 598 F.3d at 1350; *Ajinomoto*, 932 F.3d at 1359-60. The Board cited the disclosure of “four examples of potent promoters” in *Ajinomoto* as a distinguishing feature because they provided guidance on methods for evaluating promoter strength and relative data. ID, 39-40. But the Board fails to distinguish those methods and guidance from the twenty-four examples of the ’055 patent, which likewise provide data and methods for evaluating AAD-12 performance on herbicide degradation and tolerance. *See supra* Sections III.B, VII.B.3; Ex. 1001, Examples 5-8, 10-12, 21, 22, 24. The Board’s only criticism of the ’055 patent’s examples was to again point out that they used the two AAD-12 enzymes within 99% sequence identity, again demanding representative species rather than common structure correlated to the claimed function. ID, 35.

The Board and Petitioner also collectively rely on the nonanalogous decisions in *AbbVie* and *Regents*. ID, 40 (citing *AbbVie*, 759 F.3d at 1300); Pet., 26, 28-29, 31-32. The Federal Circuit has already held that those cases are “inapposite” in the common-structure context. *Ajinomoto*, 932 F.3d at 1360-61. Indeed, in *Regents*,

there was no disclosure of “relevant structural or physical characteristics,” including “[n]o sequence information” for the claimed human cDNA. *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567-68 (Fed. Cir. 1997). *AbbVie* involved a similar lack of structural disclosures. 759 F.3d at 1299-301. Petitioner and the Institution Decision thus relied on inapposite case law, have not distinguished *Ajinomoto*, and have not established that either high sequence identity to SEQ ID NO: 2 or the AAD-12 motif are uncorrelated to the claimed function. *Magnum Oil*, 829 F.3d at 1375 (the burden of proving unpatentability rests with the petitioner and “that burden never shifts to the patentee”).

3. Petitioner’s Protein-Folding Argument Is Also Misplaced and Fails to Account for the State of the Art

Relying on a generalized textbook, Dr. Silverstone asserts that proteins are known to fold into three-dimensional structures and that a skilled artisan would need to be able to predict and rule out many sequences that could misfold. Ex. 1003, ¶ 47; Pet., 33. Petitioner’s protein-folding argument fails for at least two reasons.

First, the law does not require predicting the relative performance of particular embodiments within the scope of the claims. *Lifescan*, PGR2019-00032, Paper 11 at 23-24. The Federal Circuit in *Ajinomoto* rejected arguments that similarity to a consensus sequence is “not enough to predict the site and strength of [a] promoter from a given sequence” and found adequate written description. 932 F.3d at 1360

(explaining that the challenger’s prediction-based argument assumed “too strict a legal standard”); *Lifescan*, PGR2019-00032, Paper 11 at 30 (rejecting argument that it would be impossible to “predict the behavior” of 5×10^{76} protein sequences covered by the claims because such arguments derived solely from the size of the genus rather than the factors informing a written-description analysis, including the state of the art). As the Supreme Court has explained, the “certainty which the law requires in patents is not greater than is reasonable.” *Amgen*, 598 U.S. at 611.

Second, Petitioner’s hypothetical folding concerns are inconsistent with the state of the art in 2005-2006. Skilled artisans at that time recognized that structure was generally forgiving to changes in amino acid sequence, as enzyme structure and function were conserved at 85% and higher sequence identities. *See supra* Section II.A.2; Ex. 2028, 604 (“When two sequences are very similar[,] we can safely infer that they have similar structures.”); Ex. 2026, 98 (“The comparison of protein sequences is widely used to infer protein structure and function.”).³ As detailed above, and as Dr. Bollinger testifies, skilled artisans were well equipped to avoid total function loss when making enzyme variants. *See supra* Sections II.A.3, VII.B.4.a; Ex. 2011, ¶¶ 160-161.

³ Protein sequences and analyses have also been submitted as Exs. 2084-2095.

B. Petitioner Fails to Establish that the Disclosed AAD-12 Enzymes Are Not Representative of the Genus

Petitioner’s written-description challenge also fails for an independent reason: Petitioner has not met its burden of establishing that the ’055 patent’s disclosed AAD-12 enzymes are nonrepresentative of the genus claimed. *Ajinomoto*, 932 F.3d at 1358-59.

Disclosed species are representative when they reflect the diversity of a claimed genus. *AbbVie*, 759 F.3d at 1301. Here, the analysis is simpler than in most cases because the claimed genus of AAD-12 enzymes is essentially the opposite of a structurally or functionally diverse genus—it is a group of *highly identical* enzymes with a conserved active-site motif. Ex. 1001, 32:3-6 (85% and higher identity is “highly identical”), 21:41-60; Ex. 2011, ¶¶ 163-166; Ex. 2019, 863 (“[S]everal studies suggested that when the sequence identity is above 40%, enzyme function is well conserved.”); Ex. 2028, 604 (“When two sequences are very similar[,] we can safely infer that they have similar structures.”); Ex. 2021, 85; *Ajinomoto*, 932 F.3d at 1359 (finding disclosure of four exemplary promoters and “background knowledge in the art” sufficiently representative to support claims with no promoter sequence limitations).

Petitioner’s argument that the claimed genus “embraces widely variant species” is incorrect. Pet., 28; Ex. 2011, ¶ 167. Dr. Silverstone speculates that

enzymes within 85% sequence identity to SEQ ID NO: 2 might catalyze entirely different reactions or fall into enzyme families other than α KG-dependent dioxygenases. Ex. 1003, ¶¶ 48, 50. But he cites no such evidence and conceded at his deposition that he had none, and thus his unsupported testimony “is entitled to little or no weight.” 37 C.F.R. § 42.65(a); Ex. 2009, 11:5-14:20, 17:5-9.

The Board’s and Petitioner’s reliance on *AbbVie* is misplaced. Pet., 29; ID, 40. There, the claims encompassed all antibodies *regardless of amino acid sequence* that exhibited the claimed activity. *AbbVie*, 759 F.3d at 1292. The Federal Circuit noted that the patents did “not describe any common structural features of the claimed antibodies.” *Id.* at 1301. Indeed, as Dr. Bollinger points out, antibodies generally do not exhibit the sequence-function correlation that is typical for enzymes. Ex. 2011, ¶¶ 40-43. The diversity of the genus of antibodies in *AbbVie* thus bears no resemblance to this case, as skilled artisans expected enzymes having at least 85% sequence identity to be “highly identical” and have the same or similar activity as the specification discloses. Ex. 1001, 32:3-6, 21:41-60; *see also Ex parte Campbell*, No. 2021-000865, Decision on Appeal at 15 (PTAB July 20, 2021) (upholding antibody claims requiring at least 90% sequence identity based on disclosure of two antibody sequences, where sequence comparisons provided guidance on where amino acid substitutions could be made).

C. The '055 Patent Describes the Claimed Transgenic Plants

The '055 patent discloses extensive examples of transgenic plants and plant cells comprising a recombinant polynucleotide encoding an AAD-12 enzyme. Working examples are provided in a variety of monocots and dicots, including *Arabidopsis* (Example 7), corn (Example 8), tobacco (Example 10), soybeans (Example 11), cotton (Example 12), rice (Example 21), and canola (Example 22), as well as exemplary disclosures directed to other crops (Examples 13, 16, and 17). *See supra* Sections III.B, VII.B.3. These disclosures illustrate preparation of the claimed transgenic plants, describing codon-optimization (if desired), expression vectors, transformation techniques, and confirmation that AAD-12-transformed plants and plant cells exhibit the claimed dual herbicide-degrading activity when the relevant herbicides are applied (e.g., sprayed). Ex. 2012, ¶¶ 129-147.

These disclosures of AAD-12-transformed monocot and dicot crops more than sufficiently demonstrate possession of the transgenic plants of the challenged claims. *Id.*, ¶¶ 131-139. Indeed, the only alleged deficiency the Board identified in the examples was directed to the scope of AAD-12 enzymes used. ID, 35. But as detailed above, the genus of highly identical AAD-12 enzymes within the scope of the claims is adequately described. *See supra* Sections VIII.A-B.

At institution, the Board noted but did not credit Petitioner's argument based on Corteva's Technology Use Agreement ("TUA") and other commercial product

materials that AAD-12 does not have activity against pyridyloxy auxin herbicides in soybeans. ID, 26. Petitioner's argument is indeed unsupported and based on an incorrect interpretation of these materials.

Herbicides and their uses are comprehensively regulated by the EPA in the U.S. Under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and the EPA's implementing regulations, it is unlawful to "place or sponsor advertisements which recommend or suggest the purchase or use of: . . . [a] pesticide product for an unregistered use" 40 C.F.R. § 168.22(b)(5).⁴ Thus, until the EPA registers triclopyr, fluroxypyr, or other pyridyloxy auxin herbicides for post-burndown use with Enlist E3[®] soybeans, Corteva *cannot*, under FIFRA, suggest or advertise pyridyloxy auxin herbicides for use with Enlist E3[®] soybeans. Corteva's TUA appropriately warns farmers against running afoul of EPA regulations by using those herbicides off-label for unregistered uses. During cross-examination, Dr. Silverstone conceded that regulatory approval would be required to market an herbicide for such a new use. Ex. 2009, 36:17-20 ("Q. So to register an herbicide for

⁴ For clarity, herbicides, which "kill weeds and other plants that grow where they are not wanted" (i.e., weedy plants are considered pests), are covered by the EPA's regulation of pesticides under FIFRA. *See* Ex. 2005, 1 ("Well known pesticides (terms defined below) include: . . . herbicides").

a new use, you may have to go through the USDA, the EPA and also some state governmental authorities? A. Yes.”), 35:24-36:5, 48:25-49:3, 50:21-51:3 (“The marketing has to ... reflect where your approvals are”). Accordingly, Corteva’s commercial product and stewardship materials simply are not pertinent to Petitioner’s written-description ground.

Petitioner asserts that *test data* against both pyridyloxy auxin and phenoxy auxin herbicides were not reported for two transgenic plants: soybeans and cotton. Pet., 34-35; Ex. 1003, ¶ 53 (Dr. Silverstone asserting that Patent Owner failed to “perform *all experiments* with *each species* of transgenic plant”). No such data, however, are required to satisfy the written-description requirement. *Ariad*, 598 F.3d at 1352 (“[T]he written description requirement does not demand either examples or an actual reduction to practice”); *Sandoz Inc. v. Boehringer Ingelheim Int’l GmbH*, PGR2022-00037, Paper 11 at 17-18, 23-24, 29 (PTAB Nov. 7, 2022) (“[T]here is no legal requirement that a patent specification must include test results or working examples”).

Moreover, further contradicting Petitioner’s position, the specification repeatedly reports test data showing tolerance to pyridyloxy auxin herbicides and phenoxy auxin herbicides. *See supra* Sections III.A-B. As Dr. Christou testifies, because AAD-12 was shown to exhibit activity in multiple dicot crops, a skilled artisan would expect similar activity across dicots. Ex. 2012, ¶ 142. The specification

further discloses data confirming the claimed dual activity in *Arabidopsis* (Example 7) and tobacco (Example 10), which were established model crops. *Id.*, ¶ 131; Ex. 2009, 40:6-18 (Dr. Silverstone testifying that *Arabidopsis* is a model crop for extrapolating results to “other plants”). It thus would not have mattered to a skilled artisan that a pyridyloxy auxin was not tested on soybeans, for example, particularly in view of the specification’s disclosures that “AAD-12 *is able* to degrade the pyridyloxyacetates auxins (e.g., triclopyr, fluroxypyr) in addition to ... 2,4-D.” Ex. 1001, 6:41-46; Ex. 2013, ¶ [0034]; Exs. 2014, 2017, ¶ [0038]; Ex. 2015, ¶ [0041]; Ex. 2016, ¶ [0044]; Ex. 1003, ¶ 70 (Dr. Silverstone acknowledging that AAD-12 was “found to have significant activity on the pyridyloxy auxin herbicides”). Indeed, the ’055 patent discloses that “[s]oybeans are a preferred crop for transformation according to the subject invention,” discloses AAD-12-transformed soybeans in Example 11, and discloses combinations of triclopyr and fluroxypyr for use with dicots such as soybeans in Example 16. Ex. 1001, 13:42-45, 72:48-79:61, 86:23-87:20; Ex. 2013, ¶¶ [0058], [00256]-[00272], [00299]-[00302]; Exs. 2014, 2017, ¶¶ [0063], [00311]-[00344], [00372]-[00376]; Ex. 2015, ¶¶ [0066], [00314]-[00347], [00375]-[00379]; Ex. 2016, ¶¶ [0069], [00317]-[00350], [00377]-[00381].

Accordingly, Petitioner has failed to meet its burden of establishing that any challenged claim lacks written-description support.

IX. Conclusion

Petitioner failed to establish PGR eligibility, lack of enablement, or lack of written description. Corteva thus respectfully requests that the Board terminate this proceeding for lack of jurisdiction or confirm the patentability all challenged claims of the '055 patent.

Respectfully submitted,

Dated: January 22, 2024

/Pier D. DeRoo/

Pier D. DeRoo

Reg. No. 69,340

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Pier D. DeRoo, certify that **Patent Owner's Response** contains 18,452 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: January 22, 2024

/Pier D. DeRoo/
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on January 22, 2024, in its entirety on the following:

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