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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Merck Sharp & Dohme LLC,
Petitioner,

v.

Halozyme Inc.,
Patent Owner.

Case No. PGR2025-00030
U.S. Patent No. 12,054,758

REPLY TO PATENT OWNER'S DISCRETIONARY DENIAL BRIEF

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I. Introduction

The vast majority of Halozyme’s “discretionary denial” brief is nothing of the sort—it is focused almost exclusively on the merits of the Petition. DD Br., 1-7, 10-13. There is a reason for that. Neither of the recognized criteria for discretionary denial that Halozyme does address is an appropriate basis for the Board to deny institution. DD Br., 1, 5.

First, discretionary denial is not warranted under 35 U.S.C. § 325(d). Halozyme identifies no arguments raised during examination that are “substantially the same” as those in the grounds. DD Br., 52-61. And Chao (EX1006) is not cumulative to Stern (EX1008) or two other references as Halozyme asserts—Chao actually *corrects errors* in the passages in Stern (EX1008) over which Halozyme contends Chao is cumulative.

Second, the lawsuit Halozyme commenced *over a month after* Merck filed this Petition does not warrant discretionary denial—every *Fintiv* factor instead supports institution. The target of that lawsuit also is an unapproved biological product presently undergoing FDA review that is shielded by 35 U.S.C. § 271(e)(1)—it is doubtful that litigation can even proceed. In any event, given the Board’s four institution decisions to date, pending institutions decisions for all PGR-eligible patents asserted in the district court proceedings, and the highly

similar § 112 deficiencies that plague all patents asserted in the district court, a stay of that litigation is likely.

Halozyme’s “strength of the grounds” assertions also have no merit. That much can be readily appreciated by looking at Halozyme’s *conduct* in response to Merck’s § 112(a) grounds—it *disclaimed* rather than defended many of the ’758 Patent claims Merck challenged. EX2003, 3. In fact, Halozyme has cancelled 66 such claims across 9 patents in response to Merck identifying the same types of written description and enablement problems it identified for the ’758 Patent claims. If Halozyme actually believed the merits of Merck’s § 112(a) challenges were weak, it would not have disclaimed all these claims.

Halozyme’s narrative before the Board also stands in stark contrast to its narrative in the district court. Here, Halozyme downplays the importance of the claimed modified PH20 polypeptides retaining enzymatic activity. Its complaint tells a different story—there, Halozyme touts its ’758 Patent as reflecting its “success” in making *enzymatically active mutants*.¹ But *every* mutant Halozyme made and described in its ’758 Patent has *only one change* relative to its nearly 20+ year old Hylenex® product. And the only way Halozyme could try to capture the novel and improved PH20 enzyme in Merck’s unapproved subcutaneous

¹ EX2058, ¶¶ 43-45, 51, 55.

pembrolizumab product—a PH20 with ***more than 30 changes*** from Hylenex®—was with claims that violate long-established law governing written description and enablement.

Third, Halozyme advances a false narrative of the relative equities of the parties. DD Br., § VI. Halozyme earns more than a billion dollars every year from its “ENHANZE®” business (*i.e.*, selling its Hylenex® product and licensing its patents on that ***unmodified*** PH20 enzyme). And Halozyme has told investors (but not the Board) that the outcome of these PGRs would have “***no impact*** on [its] ENHANZE business.”² Halozyme’s “ENHANZE” patents on unmodified PH20 are not infringed by the novel multiply-modified PH20 enzyme (“ALT-B4”) in Merck’s unapproved subcutaneous pembrolizumab product. And there is no evidence Halozyme is developing ***any*** new multiply-modified PH20 polypeptide

² DD Br., 64-65; EX2052; EX1086 (Halozyme Therapeutics, Inc. Q1 2025 Earnings Call Transcript (May 6, 2025)), 13-14 (“So that's it bottom line with regard to what would happen, so specifically with the outcome of the PGRs, yes, absolutely no impact on our ENHANZE business.”); 13 (“And to be very clear, what is going on in the MDASE, which is a separate and distinct set of patents from ENHANZE, will have absolutely no impact whatsoever on our ENHANZE business,...”).

covered by the challenged patents. Instead, it strains those patents past their breaking point in an attempt to capture the materially different ALT-B4 enzyme. This is not a case about Halozyme’s alleged “innovation,” but of its overreach in trying to reap what it has not sown. Merck is entitled to defend itself from Halozyme’s unwarranted aggression via post-grant review.

Finally, a PTAB panel and the Acting Director have recently and repeatedly considered Halozyme’s arguments presented again nearly identically here, and have consistently rejected them. The Board instituted post-grant review on four related U.S. patents—11,952,600, 12,018,298, 12,152,262, and 12,123,035—which include similar claims to modified PH20 polypeptides as those of this patent. *See Merck Sharp & Dohme LLC v. Halozyme, Inc.*, PGR2025-00003, Paper 25 (P.T.A.B. June 2, 2025); PGR2025-00004, Paper 26 (P.T.A.B. June 11, 2025); PGR2025-00006, Paper 30 (P.T.A.B. June 16, 2025); PGR2025-00009, Paper 29 (P.T.A.B. July 11, 2025). In each of the four post-grant review proceedings for which the Board has already instituted trial, the Board found that Merck had established that it will more likely than not prevail in showing that at least one of the challenged claims is unpatentable for lack of written description and enablement.³ And, in instituting trial, the Board rejected Halozyme’s arguments

³ *See Merck Sharp & Dohme LLC v. Halozyme, Inc.*, PGR2025-00003, Paper

that the '600, '298, '262, and '035 Patents were not PGR eligible, its assertions regarding claim construction, and (in the case of the '600 and '298 Patents) that discretionary denial was warranted under §325(d). For the '262 Patent and related US Patent Nos. 12,123,035 and 12,110,520, the Acting Director has also repeatedly considered the same arguments presented here, and based on review of “the parties’ arguments and the record, and in view of all relevant considerations” *denied* Halozyme’s requests for discretionary denial. *See* PGR2025-00006, Paper 29; PGR2025-00009, Paper 25; PGR2025-00017, Paper 25. Halozyme presents no reason for the Acting Director to reach a different conclusion here. The Acting Director should refer this Petition to the Board for a decision on the merits.

II. Halozyme’s Challenge to PGR Eligibility Rests on a Mischaracterization of the Petition and the Evidence

Halozyme contends that Merck has not established that the '758 Patent is eligible for post-grant review. Their arguments rest on a mischaracterization of the Petition and the evidence.

Merck established that the '758 Patent is PGR eligible by showing that its claims are not supported as required by 35 U.S.C. § 112(a) by the disclosure of U.S. Patent Application No. 13/694,731 (the '731 Application), the only

25 at 60; PGR2025-00004, Paper 26 at 61; PGR2025-00006, Paper 30 at 55; PGR2025-00009, Paper 29 at 57.

application filed before 2013 to which the '758 Patent claims § 120 benefit. The Petition also explained that the disclosure in the '731 Application is essentially identical to the disclosure in the '758 Patent (referring to both as “the common disclosure”) (Pet., 5-6), and that for the same reasons, the contested claims are unpatentable (*id.*).

The Petition first explained that the '731 Application was filed on December 28, 2012, and claims priority to two provisional applications. Pet., 4-6, 15. It also specifically identified the content added in the '731 Application that is not in the disclosures in the two provisional applications. Pet., 4-6, n.5. Because the '731 Application does not support the claims as § 112(a) requires, the two provisionals (which each contain *less* information) cannot either.

Turning to the claims, the Petition explained that the claim parameters capture more than 10^{59} + distinct PH20 polypeptides, all of which contain at least one substitution at position 317. Pet., § IV.D.1. Halozyme does not dispute this. The Petition then identified numerous distinct types of PH20 polypeptides that are claimed by the '758 Patent but are not described in the common disclosure. Pet., § V.A. Those include innumerable *multiply*-modified PH20 polypeptides with: (i) a position 317 substitution plus (ii) myriad combinations of 2, 5, 10, 15, or more substitutions to any other amino acid at any positions within 37 different PH20 sequences of varying length (between 430 and 474 residues). Pet., 31-32. These

claimed “multiply-modified” PH20 mutants also included those with significant C-terminal truncations that render native PH20 inactive (Pet., 31-32) as well as those with a C-terminal sequence extending past position 456 that renders native PH20 insoluble. (Pet., V.A.2.b). And the Petition explained that within these vast genera of PH20 polypeptides of bewildering structural variation being claimed are an unidentified and unknowable number of enzymatically active modified PH20 polypeptides—the only type of PH20 polypeptide with a credible utility. Pet., § V.A, 23-25, 79-83.

The Petition then exhaustively explained why the common disclosure (*i.e.*, ***the disclosure in the ’731 Application filed on December 28, 2012***) did not describe any of these distinct types of modified PH20 polypeptides being claimed nor did it enable them. Pet., § V.A (written description), § V.B (enablement).

Grossly mischaracterizing the Petition, Halozyme contends that Merck “never assessed the ’731 Application as of its December 2012 filing date and provided their opinions using the wrong date (***and only the wrong date***)...” DD Br., 2 (emphasis added). This red herring of an argument rests on Halozyme’s mischaracterization of the Petition and its record, and ignores the substance of what the Petition and the expert testimony established.

First, the Petition did not limit its analysis of the disclosure of the ’731 Application to a “2011 date.” Instead, as the Petition states:

While the '758 Patent claims priority to provisional applications dating to December 30, 2011 and benefit to the '731 Application (filed December 28, 2012), *they are not supported as § 112(a) requires by those earlier-filed applications*. See §§ II.A, V.A, V.B. Regardless, *the prior art of the grounds was published before December 2011*, and the obviousness grounds use that date to assess the knowledge and perspectives of the skilled artisan.⁴

The Petition thus expressly limited the *obviousness* grounds to the pre-December 2011 date, but not the § 112(a) grounds.

Second, even Halozyme recognizes that its proposed reading of the Petition's analysis of the disclosure of the '731 Application is "illogical."⁵ What

⁴ Pet., 15 (emphases added). Halozyme contends Merck changed its position in subsequent petitions (PGR2025-00042, PGR2025-00046, PGR2025-00050). DD Br., 12. That is incorrect—like this Petition, Merck stated there that the claims of the contested patent are not entitled to the filing dates of either the 2011 provisional applications or the 2012 non-provisional '731 Application. PGR2025-00042, Pet., Paper 10 at 5-6, 15-16; PGR2025-00046, Pet., Paper 1 at 5-6, 15-16; PGR2025-00050, Pet., Paper 1 at 4-6, 19.

⁵ DD Br., 11-12 ("Merck's attempt to mix-and-match applications and dates—assessing the '731 Application in view of the state of the art at the time of a

the Petition clearly explained was that **none** of the pre-2013 applications provided the § 112(a) support required for the '758 Patent claims. Pet., 5-6. The Petition also provided an extensive and detailed analysis of **what is** and **what is not** described in the disclosure **of the '731 Application**, and demonstrated how, in particular, **the absence** of necessary information and guidance demonstrates that the '731 Application does not provide a sufficient written description of and does not enable the full scope of multiply-modified PH20 polypeptides being claimed.⁶ Pet., § V. Halozyme's arguments target its **inaccurate abstraction** of the Petition's

different application—... **is illogical to boot.**").

⁶ Halozyme quotes statements by Merck's experts who explained they used a 2011-timeframe to assess issues including obviousness. For example, Dr. Park provided opinions on what a skilled artisan would have done to carry out the guidance in Halozyme's prior art '429 Patent (EX1005). Dr. Hecht also addressed obviousness as well as the contents of the '731 Application filed in 2012. His latter analysis identified what is not described in or taught by the disclosure of the '731 Application. Consideration of the state of the art just prior to the earliest priority date claimed also was appropriate. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (“written description analysis occurs ‘as of the filing date sought’”).

arguments and the experts' testimony because it has no answer to the numerous shortcomings of the disclosure of the '731 Application that were identified with particularity in the Petition and by the experts—shortcomings that render the claims unpatentable under § 112(a). At bottom, Halozyme's assertions about the Petition *are simply false*.

Halozyme mischaracterizes the legal authority it cites, or relies on inapposite cases. For example, Halozyme places great emphasis on *Reiffin* but ignores that the error critical to that decision was that the patent challenger did not address the disclosure of an intervening application.⁷ Here, the analysis correctly addressed the intervening application (the '731 Application), which includes and supplements the disclosures of the two earlier provisional applications. Pet., 4-6, n.5.

Halozyme also cites Board decisions denying institution due to the failure of a petitioner to address whether various earlier-filed applications provided § 112(a) support for the claims. DD Br., 12-13. The Petition, however, addressed all three pre-2013 applications. Pet., 5, 15. First, it explained that the contents of the two provisional applications filed in 2011 were incorporated into and supplemented by additional information in the '731 Application (and the Petition identified what was added). Pet., 5-6, n.4. Then the Petition explained why the claims of the '758

⁷ *Reiffin v. Microsoft*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000).

Patent were not entitled *to those dates* (i.e., the 2011 dates of the two provisionals) *or the filing date of the '731 Application (December 28, 2012)* (Pet., 15).

Halozyme's semantic gymnastics do not alter what Petition established—that *omissions* in the common disclosure of the '731 Application and the '758 Patent demonstrate that the claims lack adequate written description and are not enabled, which renders the '758 Patent PGR eligible. Pet., § V. Discretionary denial based on Halozyme's incorrect portrayal of the Petition would be improper.

III. Halozyme Identifies No Credible Basis for Denying Institution Under Established Criteria Governing Discretionary Denial

The Board has provided extensive guidance setting forth a framework with defined factors for determining whether to exercise discretion in denying institution. Halozyme dedicates only three pages to advancing a series of conclusory arguments that denial of institution is warranted under the *Fintiv* framework, leaning heavily on incorrect assertions about the strength of Merck's grounds. Halozyme does not engage these established discretionary factors again until page 52 of its brief. There, it argues (incorrectly) that Merck is advancing the same or substantially the same art and/or arguments considered during examination. DD Br., 52. Under the multi-factor discretionary denial tests, there is no basis for the Board to decline to institute trial in this proceeding.

A. The Arguments and Art Used in the Grounds Are Not Substantially the Same as Any Considered During Examination

The Board’s framework for evaluating discretionary denial under 35 U.S.C.

§ 325(d) based on the examination record focuses on two inquiries:

- (1) First, were the same or substantially the same art or arguments presented to the Office?
- (2) If so, did the petitioner demonstrate that the Office erred in a manner material to the patentability of challenged claims?⁸

See Advanced Bionics v. MED-EL Elektromedizinische Geräte, IPR2019-01469, Paper 6 at 7–11 (P.T.A.B. Feb. 13, 2020); *Beckton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017). In answering these questions, the Board considers six factors summarized in *Becton*.⁹ Under this framework, the Board should not exercise § 325(d) discretion.

1. Advanced Bionics Inquiry 1—The Grounds Advance No Arguments Related to Any Raised During Examination, and Rest on Prior Art That is Not the Same or Substantially the Same as That Considered During Examination

Halozyme does not identify any argument advanced in the grounds that is “the same or substantially the same” as one addressed during examination. DD

⁸ *Advanced Bionics*, IPR2019-01469, Paper 6 at 8.

⁹ *Becton*, IPR2017-01586, Paper 8 at 17-18.

Br., 52-53. None are—the Examiner’s rejections were cursory and are unrelated to the written description, enablement, and obviousness grounds.¹⁰ The arguments advanced in Merck’s grounds thus are not the same or substantially the same as any arguments or issues addressed during examination.

The prior art supporting the grounds was also not the same or substantially the same as that considered during examination. Most notably, Chao (EX1006) was not considered during examination, and is used to support both the obviousness and § 112(a) grounds in the Petition. Pet., 35-39, § VI.

Halozyme contends that Chao (EX1006) is cumulative to certain prior art of record during examination, particularly Stern (EX1008), Arming (EX1011), and Zhang (EX1010), asserting:

Chao *adds nothing materially new* to what the Examiner considered, because these references *include the same teachings regarding PH20’s structure* that are relevant to Merck’s obviousness challenge.

DD Br., 54-61 (emphases added). This assertion is demonstrably incorrect.

¹⁰ See Pet., 16. EX1002, 477-78, 549-51 (indefiniteness rejection due to unclear references to “modifications” and “Fc” domain and failure to define “c-terminally truncated” resolved by claim amendment).

(a) *Chao Identifies a Material Error in the “Ab Initio” Hyaluronidase Models Used by Stern*

Chao is the first publication that reported an *experimentally determined* structure of a *human* hyaluronidase enzyme (*i.e.*, the HYAL1 enzyme).¹¹ The only such structure prior to Chao was that of a bee venom hyaluronidase,¹² but, as Stern’s sequence alignment shows, it lacks the entirety of the C-terminal region found in all human hyaluronidases (including PH20) (below, highlighting added).¹³

¹¹ EX1006 (Chao), 6912; EX1003 (Hecht), § II.E.2.

¹² EX1008 (Stern), 824 (“There is only one 3D structure of a vertebrate-like Hyal enzyme available, which is ironically the bee venom enzyme.”); 828 (“the 3D structure of the BVHyal enzyme is the best and is the only structural template available for modeling these proteins.”).

¹³ EX1008 (Stern), 826, Figure 3 (annotated). Also *id.* at 829 (“For all human Hyals at their C-termini, the catalytic domain is followed by the second domain, which is not present in the BVHyal homologue structure.”).

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Hyal-1      QAIKEYMDTTLGPFILNVTSGALLCSQALCSGHGRCVRRTS-HPKALLLNPAFSIQLT 392
Hyal-2      QYLKDYLTRLLVPYVVNVSWATQYCSRAQCHGHG-CVPGNP-SASTFLHLSTNSFRLVPG 397
Hyal-3      WHLHDYLVDTLGPYVINVTRAAMACSHQRCHGHGRCARRDPGQMEAFHLWPDGSLGDWK 391
Hyal-4      TKVKQFVSSDLGSYIANVTRAAEVCSLHLCRNNGRCIRKMW-NAPSYLHLNPASYHIEAS 410
PH-20/SPAM1 LLLDNYMETILNPYIINVTLAAKMCQVLCQEQGVCIRKNW-NSSDYLHLNPDNFAIQLE 410
BVHyal      LQFREYLNNELGPAVKRIALNNNANDRLTVDVSVDOV----- 382
           . : : : * . : : : .

Hyal-1      PGGG--PLSLRGALSLEDQAQMAVEFKCRCYPGW----QAPWCERKSMW----- 435
Hyal-2      HAPGEPQLRPVGELESWADIDHLQTHFRQCQYLGW-SGEQCQWDRQAAG----- 445
Hyal-3      SFSCHCYWGWGPTCQEPSLGLKKQYKARAPA---TASSFPCCHFSSPG----- 437
Hyal-4      EDG---EFTVKGKASDSDLAVMADTFSCHCYQGY---EGADCREIKTADGCSG----- 457
PH-20/SPAM1 KGG---KFTVRGKPTLEDLEOFSEKFCYSCYSTLSCKEKADVKTDAVDVCIADGVCIDA 467
BVHyal      -----

Hyal-1      -----
Hyal-2      -----GANAWAGSHLTSLLALALAFWTL- 471
Hyal-3      -----TTLSHSCSIQFTVNPCKHTPRFPWNP- 463
Hyal-4      -----VSPSPGSLMTLCLLLASYRSIQL--- 481
PH-20/SPAM1 FLKPPMETEEPQIFYNASPSTLSATMFIWRLEVWDQGISRIGF 510
BVHyal      -----
    
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Omitted C-terminal residues in bee venom hyal shown in **yellow highlighting**

Stern used the bee venom hyaluronidase structure to create “ab initio” models of the human hyaluronidases (including PH20), and stated those models “represent *reliable* structural models for all five human Hyal enzymes.”¹⁴ Stern’s structure and mechanistic observations about human hyaluronidases are also based

¹⁴ EX1008 (Stern), 828 (emphasis added). The Stern authors were Robert Stern and Mark J. Jedrzejewski.

on these “ab initio” models.¹⁵ Stern also cautioned against relying on its observations about the C-terminal region in human hyaluronidases.¹⁶

In its brief, Halozyme ignores Stern’s warnings about the limitations of its findings and cites these “ab initio” structures as proof that Chao’s teachings are cumulative to Stern’s. DD Br., 58-59. But Chao reported that Stern’s “ab initio” models of human hyaluronidases *were wrong*:

The HyalEGF-like fold *does not resemble the Hyal-1 C-terminal domain fold predicted by ab initio approaches* (33). The close interaction between the two domains is *also very different from the earlier prediction* that proposed a flexible linker and lack of interactions between the two domains. Moreover, the *modeling* of the five human

¹⁵ EX1008 (Stern), 828 (“Obtaining such models facilitated exploration of the mechanisms by which the vertebrate-like Hyals degrade HA and by which differences between the Hyals occur...”); 828-829 (hyaluronidases have a “major, catalytic domain” and “a significantly smaller C-terminal domain of unknown function”); 829-833.

¹⁶ EX1008 (Stern), 829 (structural models of C-terminal domain “need to be looked upon with caution”); 833 (“The lack of experimental data and of sequence/structural homologue(s) for the C-terminus makes functional studies of this human Hyal domain purely speculative.”).

hyaluronidases C-terminal domains *yielded a different fold in each case*, whereas we expect that these domains adopt the HyalEGF-like fold because the amino acid sequences contain the characteristic disulfide bond pattern.¹⁷

Other insights that Chao reports but are not found in Stern, Arming (EX1011), or Zhang (EX1010), include that all five human hyaluronidases share a characteristic pattern of residues that yields an “EGF-like” domain called the “HyalEGF” and details about that characteristic HyalEGF pattern.¹⁸ For example, Chao reports this “HyalEGF” structure is likely involved in protein-protein interactions, again correcting Stern’s suggestion that the “...different structures of this domain for each of the five human Hyals imply a different function for each Hyal.”¹⁹

¹⁷ EX1006 (Chao), 6913 (emphases added); *also* 6916 (suggesting HyalEGF mediate protein-protein interactions). Footnote 33 cites to EX1009 (Jedrzejewski), which is the same paper cited as footnote 12 in EX1008 (Stern). Both papers describe the same “ab initio” models addressed in Stern.

¹⁸ EX1006 (Chao), 6912 (reporting “cysteine-rich pattern” that is identified in “databases as an epidermal growth factor (EGF)-like motif”).

¹⁹ EX1006 (Chao), 6916-17; EX1008 (Stern), 833.

A skilled artisan would not have dismissed these additional findings and observations in Chao (DD Br., 60-61), as they are relevant to both Merck's § 112(a) and obviousness grounds. For example, the additional knowledge provided by Chao about the characteristic pattern of residues that creates the HyalEGF domain would have influenced expectations about the potential impact of amino acid substitutions in that region, which is relevant to both grounds.²⁰

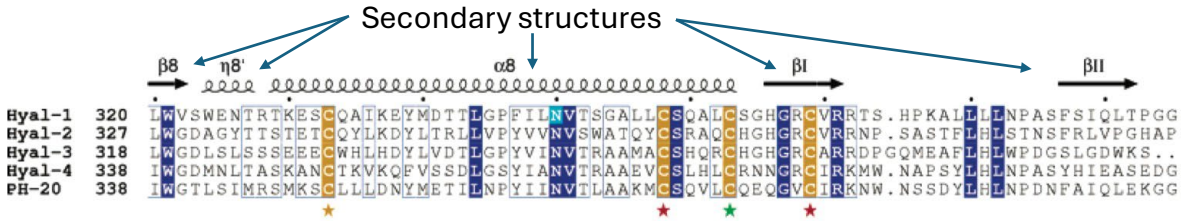
(b) Chao Provides Information About Secondary Structures Relevant to Making Amino Acid Substitutions That Was Not Provided by Stern, Arming, or Zhang

Chao provides detailed information on the secondary structures present in human hyaluronidases and which amino acid sequences are responsible for each structure (below).²¹ As Dr. Hecht explained, secondary structures derive from characteristic patterns of amino acids, and amino acid substitutions incompatible with those patterns can disrupt those structures, with concomitant adverse effects on the protein's ability to fold and maintain its overall structure.²²

²⁰ EX1003 (Hecht), ¶¶ 84-88, 92, 95.

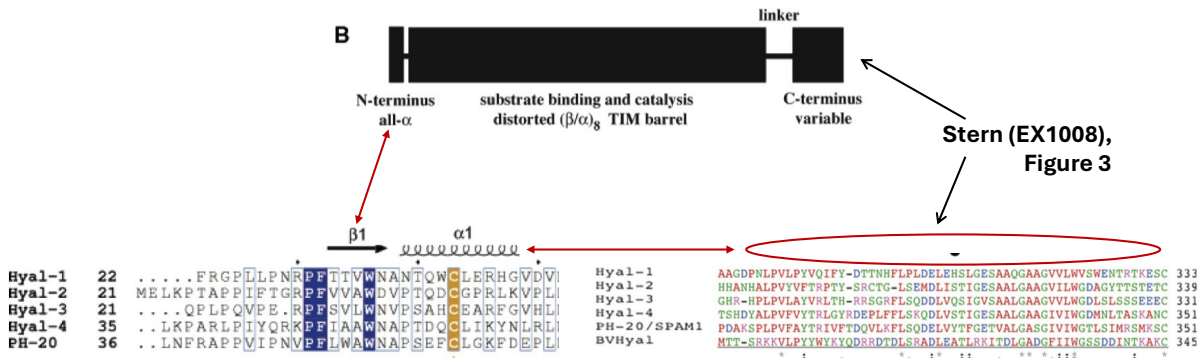
²¹ EX1006 (Chao), 6916 (Fig. 3).

²² EX1003 (Hecht), ¶¶ 40-42.



None of this information in Chao is provided in Stern, Arming, or Zhang.

Halozyme misleadingly suggests that Stern’s Figure 3 provides the same information about secondary structures as Chao. DD Br., 57. But Stern’s Figure 3B is a block image that does not identify any (much less all) secondary structures in the five proteins or the amino acid sequences that produce those secondary structures. Chao also *corrects* Stern’s statement that the secondary structures in the N-terminus are α -helical; it shows the first secondary structure in that region is an entirely different type of structure, a β -sheet (“ $\beta 1$ ”) (Fig. 3 below, annotated).



Chao (EX1006), Figure 3

This information in Chao is relevant to the obviousness and \S 112(a) grounds of the Petition (Pet., 35-39, \S VI), and is not cumulative to Stern, Arming, and Zhang.

(c) *Chao Identifies Additional Essential Residues Not Identified in Arming, Stern, or Zhang*

Halozyme contends that Chao provides only cumulative information about which residues in PH20 are essential relative to what is taught in Arming, Stern, and Zhang. DD Br., 55-56. This too is demonstrably incorrect.

The four publications identify different sets of essential residues either experimentally or via sequence alignments that show conserved residues (*i.e.*, positions where the same amino acid is found in the compared proteins).²³ These conserved, invariant residues are what a skilled artisan would consider to be “essential residues.”²⁴

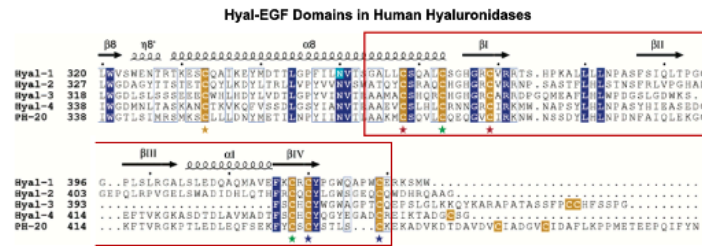
Simply inspecting the four publications shows that Chao identifies more and different essential residues in PH20 than each of Arming, Stern, and Zhang. Most notably, Chao’s alignment of the five human hyaluronidases (Figure 3) differs from Stern’s alignment in the C-terminal region, reflecting Chao’s discovery of the characteristic pattern of the HyalEGF domain, and identifies essential residues in

²³ Arming and Zhang reported effects of mutations at specific positions. *See* EX1010 (Zhang), 9437-9438, Fig. 2, Table 1; EX1011 (Arming), 812-813.

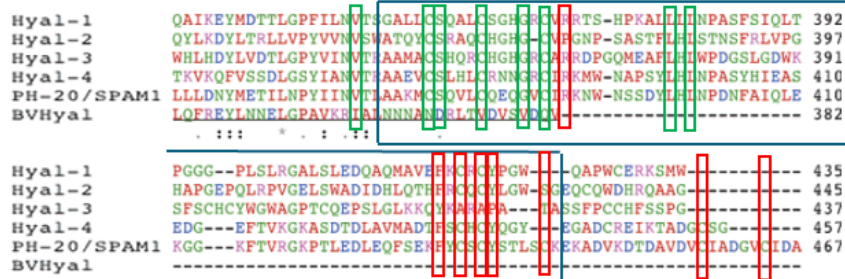
²⁴ EX1003 (Hecht), ¶ 212; EX1004 (Park), ¶ 25.

that domain (*i.e.*, R354, F398, C400, C402, Y403, C408, C423, and C429) that were not identified by Stern’s incorrect structure and alignment.²⁵

EX1006 (Chao), Figure 3, PH20 HYAL-EGF (boxed)



EX1008 (Stern), Figure 3, PH20 HYAL-EGF (boxed)
(red = different than Chao)



Chao’s identification of *different* essential residues not identified by Stern, Arming, or Zhang is relevant to both grounds. Regarding obviousness, it would lead a skilled artisan to consider different “non-essential regions” of PH20 for single amino acid substitutions pursuant to the rationale of Halozyyme’s ’429 Patent. Pet., 88-94. Regarding § 112(a), Chao’s identification of additional essential residues in the HyalEGF domain alters expectations about the effects of

²⁵ EX1004 (Park), ¶ 98 (HyalEGF in PH20 is at positions 337 to 409 (372 to 444 w/leader)); EX1006 (Chao), Fig. 3, EX1008, Fig. 3.

modifications to those residues that could unexpectedly disrupt PH20 structures relative to expectations set by Stern, Arming, and Zhang.²⁶

Halozyme argues that Stern identified two of the essential residues that Chao identified, which are addressed in the § 103 grounds (*i.e.*, C316 and L327). DD Br., 56-57. This is a misdirection. The relevant questions are (i) does Chao provide *more and different* information than Stern (it does), and (ii) is that additional information relevant to the grounds (it is).

2. *Advanced Bionics Inquiry 2—While Unnecessary to Show, the Examiner Erred by Not Finding the Claims Unpatentable*

Under the Board's precedent, if the grounds present arguments and prior art that are *not* the same or substantially the same as those considered during examination, there is no need to proceed to the second inquiry (*i.e.*, whether the Office erred in a manner material to the patentability of challenged claims). As explained in the previous section, that is the case here. Regardless, the Petition establishes that the Examiner erred in at least three ways material to patentability.

First, the Examiner failed to appreciate that Halozyme was claiming a massive genus of chemical compounds—modified PH20 polypeptides—that included many distinct types of multiply-modified PH20 polypeptides that are not

²⁶ EX1003 (Hecht), ¶¶ 54, 92, 95.

described anywhere in the common disclosure. *See* Pet., § V.A. Such claims should have been rejected for lack of written description.

Second, the Examiner failed to appreciate that the only description in the disclosure of a process for making enzymatically active, modified PH20 polypeptides with multiple substitutions is a prophetic roadmap that requires producing and testing each mutant in the genus—which is literally impossible given the size of the claimed genera ($>10^{59}$ + species). Pet., 70-76. Pursuant to *Amgen*, that “make and test” methodology cannot enable the subgenus of active mutant modified PH20 polypeptides the ’758 Patent continues to claim.²⁷ The Examiner erred by not rejecting the claims as not being enabled for their *full scope* by the common disclosure as *Amgen* requires.²⁸

Finally, the Examiner failed to appreciate that Patentee’s own ’429 Patent taught making single substitutions in non-essential regions of the PH20₁₋₄₄₇ enzyme, that skilled artisans would expect such substitutions to not affect PH20’s activity, and that one such substitution (L317Q) yield a “modified PH20 polypeptide” satisfying every claim. Pet., § VI; EX1005 (’429 Patent), 16:14-22.

²⁷ *Amgen Inc. v. Sanofi*, 143 S.Ct. 1243, 1250, 1257-58 (2023).

²⁸ *Id.*

The failure of the Examiner to reject the claims due to these patentability deficiencies was clear error. Pursuant to the framework set forth in the Board’s precedential decisions, there is no basis to deny institution under § 325(d).

B. The *Fintiv* Factors Weigh Strongly in Favor of Institution

Under § 324(a) and *Fintiv*, if a challenged patent is involved in parallel district court litigation, the Board may discretionarily deny institution if the district court will likely hold a trial before the Board’s final written decision.²⁹ Although Halozyme raises *Fintiv* in its brief, it does not apply here.

This PGR is significantly ahead of the action in the District of New Jersey (“DNJ”). Halozyme filed suit on April 24, 2025, more than a month after Merck filed this Petition. The Board’s institution decision is due by October 17, 2025—at which point little is likely to have happened in the district court.³⁰ There is no trial date, and in DNJ, the median time to trial is 60 months (5 years), which would be

²⁹ See *Apple Inc. v. Fintiv Inc.*, IPR2020-00019, Paper 11 at 2 (P.T.A.B. Mar. 20, 2020); *Catalyst Orthoscience Inc. v. Shoulder Innovations, Inc.*, PGR2025-00001, Paper 8 at 10-11 (P.T.A.B. Apr. 24, 2025).

³⁰ *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), Dkt. No. 8.

in May 2030.³¹ A final written decision in this PGR would be due years before then (*i.e.*, October 17, 2026). Merck also sought post-grant review early in the life of the '758 Patent, thus encouraging a prompt and robust determination of the Halozyme's patent rights.

Although *Fintiv* should not apply here, even if it did, the six *Fintiv* factors weigh strongly in favor of instituting this PGR.

1. Factors 1 and 2: No Trial Date Has Been Set and the Court Will Likely Grant a Stay

Because it was only recently filed and Merck has only just filed its response to the complaint on July 14, 2025, it is too soon for Merck to move to stay the case. Halozyme invites the Board to speculate whether the District Court would grant a stay, but offers no “specific evidence” to support its suggestion that a stay would likely be denied. DD Br. 8; *see Sand Revolution II, LLC v. Cont'l Intermodal Grp. – Trucking LLC*, IPR2019-01393, Paper 24 at 7 (P.T.A.B. June 16, 2020) (informative) (“In the absence of specific evidence, we will not attempt to predict how the district court in the related district court litigation will proceed[.]”).

³¹ EX1082 (United States District Court – National Judicial Caseload Profile, navigable from: <https://www.uscourts.gov/data-news/reports/statistical-reports/federal-court-management-statistics/federal-court-management-statistics-december-2024>).

Contrary to Halozyme’s suggestion, courts in DNJ are likely to grant a stay if (as is now the case here) the PTAB has instituted an IPR or PGR on several of the asserted patents: since 2013, DNJ has granted 17 of 25 motions to stay pending IPRs.³² Courts in DNJ also have stayed cases where IPRs/PGRs are instituted on some but not all of the asserted patents. *See SPG Dry Cooling USA, LLC v. Evapco Dry Cooling, Inc.*, Case No. 20-20131 (FLW) (LHG) (D.N.J.), Dkt. No. 48. As discussed above, in the earlier-filed proceedings that have reached their institution date, the Board has already instituted post-grant review on four related U.S. patents—11,952,600, 12,018,298, 12,152,262, and 12,123,035—which each include similar claims to modified PH20 polypeptides as those of the ’758 Patent, and, notably, suffer from the same written description and enablement deficiencies as have been explained here.³³ Further, the Director declined exercise of discretionary denial in PGR2025-00006 because “it is likely that a final written

³² EX1083 (Table Showing Outcomes of Disputed Motions to Stay Pending IPRs in DNJ).

³³ *See Merck Sharp & Dohme LLC v. Halozyme, Inc.*, PGR2025-00003, Paper 25 (P.T.A.B. June 2, 2025); PGR2025-00004, Paper 26 (P.T.A.B. June 11, 2025); PGR2025-00006, Paper 30 (P.T.A.B. June 16, 2025); PGR2025-00009, Paper 29 (P.T.A.B. July 11, 2025).

decision in [those] proceeding[s] will issue nearly four years before the district court trial occurs.” See *Merck Sharp & Dohme LLC v. Halozyme, Inc.*, PGR2025-00006, Paper 29 at 2 (P.T.A.B. June 12, 2025). The Director reached the same conclusions in PGR2025-00009 (Paper 25) and PGR2025-00017 (Paper 25), as well. That conclusion applies equally here. The Board would render its decision in this case over three-and-a-half years before time-to-trial statistics suggest the district court trial would begin (*i.e.*, May 2030).³⁴ The likelihood that the DNJ court would stay the litigation improves if the Board continues to institute at least some of Merck’s pending PGRs. Notably, all patents in the district court litigation (including those which are not PGR-eligible) contain the same § 112 flaws as in the PGRs that have been instituted to date and in the petitions still awaiting institution decisions (including this proceeding). Thus, the Board’s decisions in these proceedings will significantly simplify and streamline the district court proceedings.

³⁴ EX1082 (United States District Court – National Judicial Caseload Profile, navigable from: <https://www.uscourts.gov/data-news/reports/statistical-reports/federal-court-management-statistics/federal-court-management-statistics-december-2024>).

2. Factor 3: The Parties Have Made Substantial Investments in the PGRs, and Almost None in the District Court Case

No significant investment has been made in the district court action.

Halozyme's complaint and Merck's recently-filed answer are the only substantive filings, and the court has not issued any substantive orders, other than granting the parties' stipulation substituting the correct Merck entity as the defendant, affecting service, and setting the deadline for Merck's response to the complaint as July 14, 2025.³⁵ By contrast, both parties have made significant investments into this PGR and the related PGRs through briefing and preparing expert declarations.

3. Factors 4 and 5: Overlap in Issues Raised in the Petition and Litigation and Whether They Involve the Same Parties

Presently, there is no overlap in the issues raised in this PGR and the litigation. Although the litigation involves the same parties, Merck has just filed its response to the complaint.³⁶ The Board's final written decision—due years before the typical DNJ trial date—will either significantly streamline the district

³⁵ *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), Dkt. No. 8. The court has also granted one motion for leave to appear *pro hac vice*. *Id.*, Dkt. No. 13.

³⁶ *Halozyme, Inc. v. Merck Sharp & Dohme Corp.*, Case No. 2-25-cv-03179 (D.N.J.), Dkt. No. 18.

court litigation or completely resolve it. Halozyme criticizes the lack of a *Sotera* stipulation, but the purpose of such stipulations is to “mitigate[] any concerns of duplicative efforts between the district court and the Board, as well as concerns of potentially conflicting decisions.” *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 at 19 (Dec. 1, 2020). Here, given the relative timing of the district court case, there is no risk of duplication of effort or conflicting decisions with respect to the ’758 patent.

4. Factor 6: The Merits Weigh in Favor of Institution

The sixth *Fintiv* factor, the merits of the challenge, only matters where other factors weigh in favor of discretionary denial; under the Board’s precedent, it is not a standalone basis for discretionary denial. *Fintiv*, IPR2020-00019, Paper 11 at 15. A strong challenge on the merits, however, can justify institution, even if other factors weigh against it. *Id.*; *Souls Adv. Materials Co. Ltd. v. SK Nexilis Co., Ltd.*, IPR2024-01463, Paper 14 at 12 (P.T.A.B. Apr. 25, 2025).

Despite the limited role of the “strength of the challenge” factor under *Fintiv*, Halozyme devoted most of its brief to it, choosing to repeat and supplement its challenges to the merits. As explained in Section IV, below, Halozyme’s criticisms of the merits are wrong, which is demonstrated by *their actions* in disclaiming (rather than defending) many of the claims Merck has challenged. The sixth factor weighs in favor of institution.

The *Fintiv* factors, evaluated with a holistic view of the efficiency and integrity of the patent system, weigh in favor of institution. *Catalyst*, PGR2025-00001, Paper 8 at 11.

IV. Halozyme’s Grab Bag of “Strength of the Grounds” Arguments Mischaracterize the Record and the Law, and Are Not a Basis to Deny Institution

The bulk of Halozyme’s “discretionary denial” brief is devoted to its challenges to the merits of the grounds. But “strength of the challenge” is not a free-standing discretionary denial factor, and where it is relevant, it is typically used to support a decision to institute. *See* § III.B.4. Regardless, as the examples discussed below illustrate, Halozyme’s “strength of the grounds” assertions are riddled with mischaracterizations of the Petition, governing law and evidence. They lack any merit and cannot support a decision to not institute based on discretionary factors. DD Br., 3-4.

A. Halozyme Mischaracterizes Merck’s Position on Claim Construction

Halozyme argues that (1) Merck did no claim construction analysis at all, but also that, paradoxically, (2) Merck’s claim construction was “flawed” because it “imports a functional requirement.” DD Br., 18-30. Both points are wrong. And, regardless, Merck explained why the claims were unpatentable even if the claims are not limited to only “active mutants.” Pet., § V.C.

Halozyme starts by asserting that Merck did not “undertake[] *any* claim construction analysis.” DD Br., 19 (emphasis added). That is false. Merck’s Petition *expressly stated* that no special constructions of specific claim terms were necessary because those terms were either expressly defined in the disclosure or were being used with their common and ordinary meaning. Pet., 16-17. The Petition then *literally quoted* the patent’s definition of “modified PH20 polypeptides” (Pet., 17, 25). It also *used* the terms’ defined meanings to explain what the claims defined, including “modification” (Pet., 19; EX1001, 47:43-47), “sequence identity” (Pet., 18; EX1001, 60:16-18), and “X% ... identical” (Pet., 18; EX1001, 60:49-60). There thus was no need for Merck to propose different or special meanings for claim terms that the common disclosure had defined. That is a basic tenet of claim construction and the opposite of “no actual claim construction.” *Contra* DD Br., 4. Every aspect of Merck’s explanation of what the claims defined was proper.

Then, after accusing Merck of failing to engage in claim construction, Halozyme spends nine pages criticizing what Halozyme calls “Merck’s flawed interpretation of the claims.” DD Br., 22-30. Halozyme again mischaracterizes the Petition, which explained why the claims (including those disclaimed after it was filed) were directed to one type of what the common disclosure portrays as alternative embodiments of “modified PH20 polypeptides” (*i.e.*, “active mutants”

that exhibit >40% of the hyaluronidase activity of an unmodified PH20). Pet., 21-22. That analysis was based on Federal Circuit precedent holding that “[w]hen a specification discloses alternative embodiments, the language used in the claims may cause them to be limited to only one.” *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1375 (Fed. Cir. 2008).

Halozyme then argues that Merck’s analysis of the claims was flawed because the term “modified PH20 polypeptide” is explicitly defined in a single sentence in the ’758 Patent, and the sentences that follow this definition are allegedly exemplary and do not limit the claims to active molecules. DD Br., 22-25. Halozyme is incorrect based on its own cited case law. According to Halozyme’s cited case, *Alnylam v. Moderna*³⁷, the Petition addresses the language used to define “modified PH20 polypeptide.” Pet., 17, 25. This includes assessing the entire passage (1) appears under the title “Definitions,” (2) includes the term “modified PH20 polypeptide” set off in quotation marks, and (3) includes the term “refer to.”³⁸ That passage explains that a “modified PH20 polypeptide” “can have up to 150 amino acid replacements, *so long as the resulting modified PH20 polypeptide exhibits hyaluronidase activity.*” EX1001, 48:38-46. Merck fully

³⁷ *Alnylam v. Moderna*, Case No. 23-2357 (Fed. Cir. June 4, 2025).

³⁸ EX1001, 48:38-53.

explained why this and other passages of the specification, and the claim language itself, indicates that the claims are directed to active mutants. Pet., § IV.D.3.

Halozyme cannot use *Alnylam* to pick only the single sentence that supports its construction of “modified PH20 polypeptide,” and exclude all other definitional language from that same definition. To the extent there are disputes about how to apply the disclosure’s definitional language, those are best addressed at trial on a full record.

After explaining why the claims were unpatentable for lack of written description and non-enablement under the correct reading of the claims (as articulated in the Petition), Merck *also* explained in § V.C of the Petition why the claims were unpatentable even when read more broadly, as Halozyme now contends. *See* Pet., 79-83 (§ V.C). In that section, Merck explained that even if the claims were read more broadly as claiming not only all “active mutants” but also all “inactive mutants” (which do not have a credible utility), they remain unpatentable as lacking sufficient written description and not being enabled at least because the common disclosure does not identify or enable the unknown numbers of “active mutants” as well as the unknown numbers of “inactive mutants” with implausible contraceptive utility (if any) within the claimed genera of 10^{59+} distinct PH20 polypeptides. *Id.*

B. Halozyme's Portrayal of Merck's Grounds as "Weak" Rests on its Flawed Understanding of the Law Governing Written Description and Enablement

Merck's Petition established that the parameters in claim 1 cause them to claim more than 10^{12} distinct modified PH20 polypeptides having innumerable distinct structures. Pet., 16-20. Now-disclaimed claims 3-5 and 31-40 depended from claim 1 and required the modified PH20 polypeptides of claim 1 to exhibit "increased resistance to or stability" (claim 3), exhibit "increased hyaluronidase activity" (claim 4), be "soluble" (claims 5 and 35), be administered in methods of treating hyaluronan-associated diseases (claims 30-33), be conjugated to certain moieties (claims 34-35), or be administered in methods of increasing delivery of therapeutic agents (claims 36-40). When the '758 Patent issued (before Halozyme's statutory disclaimer), the enzymatically active modified PH20 polypeptides claimed by claims 3-5 and 31-40 were within the genus defined by claim 1, and they remain within claim 1's genus after Halozyme's disclaimer. Pet., § V.A.2 (all disclaimed claims), § V.B.2 (all disclaimed claims). Halozyme cannot dispute this.³⁹

³⁹ DD Br., 25-26, 32-33.

Citing a 2025 decision (*In re Entresto*),⁴⁰ Halozyme argues that, because its remaining claims no longer “require” the modified PH20 polypeptides to have hyaluronidase activity, those claims do not require a written description demonstrating “that the applicant has invented species sufficient to support a claim to a genus”⁴¹ or enabling “the full scope of the invention as defined by its claims.”⁴² Halozyme is incorrect on both points.

Entresto addressed a claim to a pharmaceutical composition of *two* defined molecules, each with established utility—valsartan and sacubitril.⁴³ There were no “unknown compounds” in this composition. After the patent was filed, the inventors discovered the two molecules form a complex, which was not disclosed in the patent.⁴⁴ The district court found that the claims only required a pharmaceutical composition comprising the two molecules, thereby rejecting the

⁴⁰ *In re Entresto*, 125 F.4th 1090 (Fed. Cir. 2025).

⁴¹ *Ariad*, 598 F.3d at 1349.

⁴² *Amgen*, 143 S.Ct. at 1254.

⁴³ *Entresto*, 125 F.4th at 1097 (“The issue on appeal is whether the ’659 patent describes what is claimed, viz., a pharmaceutical composition comprising valsartan and sacubitril administered ‘in combination.’”)

⁴⁴ *Id.* at 1098.

defendant's effort to avoid infringement by reading the claims as requiring the two molecules "to be separate (and not complexed)."⁴⁵ It then found the claim enabled but not supported by an adequate written description.

Entresto is factually and legally irrelevant to this case. Here, the vast majority of the 10⁵⁹⁺ different modified PH20 polypeptides being claimed are uncharacterized and not identified in the common disclosure. Pet., § V.A. And the 91% sequence identity language used in claim 1 causes the vast majority of those uncharacterized and unidentified modified PH20 polypeptides to be multiply-modified PH20 polypeptides (*i.e.*, mutants with between 2 and 42 total substitutions).⁴⁶

Regarding enablement, the Federal Circuit affirmed the district court's conclusion that the *Entresto* claims were enabled because the complex in question—a single embodiment of the claimed combination—was a "later arising" technology and need not be enabled.⁴⁷ No analogous issue exists in this proceeding. Instead, as the Petition demonstrated, the common disclosure plainly contemplated "active mutants" and the '758 Patent claimed (and still claims) all

⁴⁵ *Id.*

⁴⁶ DD Br., 3-4, 35-36; Pet., 17, 57-58.

⁴⁷ *Entresto*, 125 F.4th at 1099-1100.

modified PH20 polypeptides meeting the claims' parameters (including all of those that are "active mutants"). Pet., 21-25. However, the only procedure the common disclosure describes for producing the innumerable number of multiply modified PH20 polypeptides being claimed (and particularly the ones that are "active mutants") is a "make and test" methodology that requires producing and testing $10^{59}+$ distinct polypeptides—something requiring not just undue experimentation, but which is impossible. See Pet., 70-76. Because the common disclosure does not enable the subgenus of "active mutant" multiply-modified PH20 polypeptides within the claims' scope (or, for that matter, the subgenus of "inactive mutants" also within the claims' scope), it cannot enable the *full scope* of the claims pursuant to *Amgen*.⁴⁸ Pet., § V.B.

Regarding written description, the *Entresto* panel reversed the district court's finding that the lack of description of the later-discovered complex was fatal to the claims. Instead, it found, unsurprisingly, that the pharmaceutical composition that was claimed—one comprising two known active ingredients (*i.e.*, each with established utility)—met the written description requirement because

⁴⁸ *Amgen*, 143 S.Ct. at 1254.

both the compounds and the pharmaceutical composition containing them was described in the disclosure.⁴⁹

Entresto certainly did not alter decades of Federal Circuit precedent holding that generic claims defining “the boundaries of a vast genus of chemical compounds” (as here) must be supported by a disclosure that “demonstrates that the [inventor] has invented species sufficient to support a claim to [the] genus.”⁵⁰ Nor did it alter precedent governing the nature of descriptions required for chemical compounds (*e.g.*, modified PH20 polypeptides), which “requires a precise definition, such as by structure, formula, chemical name, or physical properties,’ not a mere wish or plan for obtaining the claimed invention,”⁵¹ rather

⁴⁹ *Entresto*, 125 F.4th at 1098.

⁵⁰ *Ariad*, 598 F.3d at 1349.

⁵¹ *Regents of Univ. Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-1567 (Fed. Cir. 1997). *See also Ariad*, 598 F.3d at 1350; *Fiers v. Revel*, 984 F.2d 1164, 1168-1169 (Fed. Cir. 1993).

than descriptions that simply define the boundaries of the genus,⁵² provide laundry lists of possible substitutions,⁵³ or list desired attributes of an enzyme.⁵⁴

Entresto, thus, does not help Halozyme on written description. Halozyme repeatedly references the 91% sequence identity limitation of the claims when arguing that the modified PH20 polypeptides are defined only by their structure. *See* DD Br., 3, 22-23, 36. But, the claim does exactly what *Ariad* says is insufficient: “merely drawing a fence around the outer limits of the purported genus [without] describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.”⁵⁵ The common disclosure fails to describe the myriad multiply-modified PH20 polypeptide structures being claimed—instead, it merely contains general disclosures and laundry lists of substitutions contemplating the *possibility* of such mutants.⁵⁶ Such disclosures are insufficient descriptions of different species of modified PH20

⁵² *Ariad*, 598 F.3d at 1349, 1350.

⁵³ *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570-71 (Fed. Cir. 1996).

⁵⁴ *Novozymes et al., v. DuPont Nutrition Biosciences et al.*, 723 F.3d 1336, 1349 (Fed. Cir. 2013).

⁵⁵ *Ariad*, 598 F.3d at 1350.

⁵⁶ *See, e.g.*, EX1001, 14:25-17:64.

polypeptides with varying characteristics (*e.g.*, individual modified PH20 polypeptides with specific combinations of 2, 5, 10, or more substitutions) under Federal Circuit precedent.⁵⁷ And the only examples of modified PH20 polypeptides that are described in the disclosure have ***only one*** amino acid substitution in ***one*** PH20₁₋₄₄₇ sequence. Thus, Halozyme’s lack of disclosure regarding multiply modified polypeptides confirms lack of possession of what makes up the bulk of the claimed genera—***multiply***-modified PH20 polypeptides generally—and particularly the unknown numbers of the multiply-modified PH20 polypeptides being claimed that are “active mutants” (the primary focus of the disclosure, and the only type of modified PH20 with practical utility).⁵⁸

Pursuant to established precedent, the Petition demonstrated that the written description identifies no “common structure” shared by the modified PH20 polypeptides being claimed (there is none), nor does it provide descriptions of

⁵⁷ *Fujikawa*, 93 F.3d at 1570-71.

⁵⁸ Unlike the complex that formed between valsartan and sacubitril at issue in *Entresto*, the possibility that multiple mutations in a single PH20 could yield a modified PH20 polypeptide that retains or loses enzymatic activity was identified in the common disclosure, and is not a later-discovered characteristic of modified PH20 polypeptides.

different modified PH20 polypeptides that are “representative” of the myriad structures within those genera. Pet., § V.A. It also explained this was true for the unidentified numbers of *multiply*-modified PH20 polypeptides within these massive, claimed genera. Pet., 26-65, 79-83. As such, the Petition established that the written description of the common disclosure did not describe sufficient species of multiply-modified PH20 polypeptides to demonstrate the inventors had possession of the claimed genera of modified PH20 polypeptides. Pet., 31, § V.A.

At bottom, Halozyme’s arguments rest on a preposterous theory—that it can sidestep the written description and enablement deficiencies of its claims to “active mutant” multiply-modified PH20 polypeptides by cancelling some and relying on broader ones that claim *even more* PH20 polypeptides not described and not enabled by their common disclosure. That only bolsters Merck’s § 112(a) arguments, as the Petition fully explained. Pet., § V.C.

C. Halozyme’s Criticisms of the Obviousness Grounds Rest on Foundational Misrepresentations

1. Halozyme Misrepresents the Testimony of Dr. Park and Dr. Hecht in Advancing its Hindsight Criticisms

Halozyme contends that Merck’s obviousness grounds “...utilizes hindsight and relies almost exclusively on the counsel-directed testimony of both Hecht and Park instead of the asserted prior art.” DD Br., 46. That is false—Dr. Park’s testimony, especially that which Halozyme does not discuss, expressly refutes

Halozyme's assertion that the witnesses were only asked to evaluate substitutions at position 317. Instead, Dr. Park testified:

- he “was asked if a person of ordinary skill in the art in 2011 would have been able to identify the single amino acid substitutions within non-essential regions of PH20₁₋₄₄₇ that would be tolerated by the protein...” (EX1004 (Park), ¶ 15),
- he assessed *all* non-essential residues of PH20₁₋₄₄₇ to “develop [his] unbiased scoring system” (*id.*, ¶ 102),
- he “conducted [his] analysis in a manner that *did not focus on any particular position*” (*id.*, ¶ 103 (emphasis added)), and
- only after forming his opinions about each of the non-essential residues in PH20 that his own analysis had identified, Dr. Park was asked to report opinions he had formed about position 317 (*id.*, ¶¶ 103-104).⁵⁹

As for Dr. Hecht, the Petition makes clear based on his assessment, that “the L317Q substitution would be expected to be a neutral change with the potential to have a slightly favorable impact to the protein structure ... [and] a skilled artisan

⁵⁹ Dr. Park did not review the common disclosure of the '731 Application and the '758 Patent—his opinions rest exclusively on prior art knowledge.

would have expected the L317Q substitution in PH20₁₋₄₄₇ to be tolerated.” Pet., 106; EX1003 (Hecht), ¶ 230.

Halozyme’s “hindsight” criticisms of the obviousness grounds thus rest on a falsehood that the experts were directed to position 317 by counsel.

2. Halozyme’s Assertion That the Petition’s Reasonable Expectation of Success Arguments Rest Solely on Expert Testimony is False

Halozyme asserts that the Petition relied “exclusively on declarant testimony” to support its arguments about “reasonable expectation of success.” That too is false. In § VI.B.5(a), the Petition relied on a statement in Halozyme’s ’429 Patent (which is *evidence*) that Halozyme’s inventors swore was accurate:

Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity.⁶⁰

This is not some abstract statement in an irrelevant paper—it is a statement in *a Halozyme-owned patent directed to the PH20 enzyme*. It also directly addresses the reasonable expectations of the skilled artisan, stating *such persons* would believe the statement to be true. And Halozyme relied on this and similar statements in its ’429 Patent to secure patent claims to PH20₁₋₄₄₇ proteins having

⁶⁰ EX1005 (’429 Patent), 16:17-20.

one or more amino acid substitutions. This *admission* by Halozyme should be credited as true.

Halozyme's criticisms of the Petition's use of expert testimony to address the reasonable expectations of a skilled artisan also are baseless. Such testimony is directly probative to that question—indeed, if there were published experimental evidence showing that a PH20₁₋₄₄₇ protein with a single L317Q substitution did retain its hyaluronidase activity, that would *anticipate* Halozyme's claims. And under Halozyme's interpretation of the claims (for § 112), there is no requirement that the modified PH20 polypeptides even have hyaluronidase activity, which means the '429 Patent's suggestion to make single-substitution mutants at non-essential positions (such as position 317) would lead a skilled artisan directly to a member of the claimed genus, regardless of the effect that mutation would ultimately have on the enzyme's activity. Halozyme's unfounded criticisms of sworn expert testimony are irrelevant.

D. Protein Structure Knowledge is the Most Relevant Expertise of a Skilled Artisan for This Patent

Halozyme contends the Board should decline to institute because Drs. Park and Hecht do not have “requisite” experience with hyaluronidase enzymes. DD Br., 14-17. This contention strains credulity.

Drs. Park and Hecht are eminently qualified to address the effects of modifying proteins like PH20—the central inquiry for each ground in the Petition.

Pet., 2-4. Doing that involves consideration of general principles governing all proteins—there is no “special science” reserved for hyaluronidase enzymes. And while Halozyme attacks the “hyaluronidase” credentials of Merck’s experts, it simultaneously downplays any significance of the claimed polypeptides retaining the structure or enzymatic activity of hyaluronidases. DD Br., 32-33. These are baseless assertions and cannot warrant discretionary denial.

V. Merck Is Entitled to Use Post-Grant Review to Defend its Interests From the Aggression of Halozyme

The Director should ignore Halozyme’s false rhetoric about being a “small compan[y]” with “two FDA-approved products” that is “fighting” to survive. DD Br., 5-7, 64-66. Halozyme is an established company that earns more than a billion dollars each year selling its Hylenex® product and licensing patents on that *unmodified* PH20 product.⁶¹ The patents being challenged by Merck do not claim the Hylenex® product, and Halozyme’s licensing concerns are irrelevant. Halozyme is not the small and vulnerable company that its brief claims it to be.

⁶¹ See EX1084 (News Release: “Halozyme Raises 2025 Financial Guidance Ranges and Reports Strong First Quarter 2025 Results,” navigable from: <https://www.prnewswire.com/news-releases/halozyme-raises-2025-financial-guidance-ranges-and-reports-strong-first-quarter-2025-results-302447541.html>).

The Director should also ignore Halozyme’s accusation of a “harassment campaign” because Merck filed these PGRs. DD Br., 66. This is backwards—Halozyme is the opportunistic aggressor here, seeking to force Merck to take a license for a product that Halozyme did not invent or develop. Merck is using an innovative new PH20 enzyme (“ALT-B4”) developed by its partner Alteogen that is unlike any of the 6,000+ single substitution PH20 mutants in Halozyme’s ’758 Patent. Merck also has invested tremendous time and resources in developing its subcutaneous pembrolizumab product that includes ALT-B4. And, of course, Merck is an innovation-driven U.S. company that invests heavily in its US-based manufacturing and R&D infrastructure, including more than \$12 billion since 2017.⁶² Merck’s new product will improve cancer patients’ access to lifesaving treatment (Keytruda®), and Merck has brought this PGR early in the life of the patent to resolve disputes involving Merck’s effort to bring to market this new version of this important drug.

⁶² See EX1085 (News Release: “Merck Breaks Ground on New \$1 Billion Biologics Center of Excellence in Wilmington, Delaware,” navigable from: <https://www.merck.com/news/merck-breaks-ground-on-new-1-billion-biologics-center-of-excellence-in-wilmington-delaware/>).

Merck is entitled to use the PGR system for the reason it was created—to prove Halozyme’s patents are invalid and to defend itself from Halozyme’s opportunistic aggression. Granting the PGR, not denying it, would best protect American innovation and benefit patients.

VI. Conclusion

Halozyme has identified no legitimate basis for the Board to deny institution based on any discretionary factors. The Board should institute trial.

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EXHIBIT LIST

No.	Exhibit Description
1001	U.S. Patent No. 12,054,758
1002	File History of U.S. Patent No. 12,054,758
1003	Declaration of Dr. Michael Hecht
1004	Declaration of Dr. Sheldon Park
1005	U.S. Patent No. 7,767,429
1006	Chao et al., "Structure of Human Hyaluronidase-1, a Hyaluronan Hydrolyzing Enzyme Involved in Tumor Growth and Angiogenesis," <i>Biochemistry</i> , 46:6911-6920 (2007)
1007	WO 2010/077297, published 8 July 2010
1008	Stern et al., "The Hyaluronidases: Their Genomics, Structures, and Mechanisms of Action," <i>Chem. Rev.</i> 106:818-839 (2006)
1009	Jedrzejewski et al., "Structures of Vertebrate Hyaluronidases and Their Unique Enzymatic Mechanism of Hydrolysis," <i>Proteins: Structure, Function and Bioinformatics</i> , 61:227-238 (2005)
1010	Zhang et al., "Hyaluronidase Activity of Human Hyal1 Requires Active Site Acidic and Tyrosine Residues," <i>J. Biol. Chem.</i> , 284(14):9433-9442 (2009)
1011	Arming et al., "In vitro mutagenesis of PH-20 hyaluronidase from human sperm," <i>Eur. J. Biochem.</i> , 247:810-814 (1997)
1012	Bordoli et al., "Protein structure homology modeling using SWISS-MODEL workspace," <i>Nature Protocols</i> , 4(1):1-13 (2008)
1013	Frost, "Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration," <i>Expert Opinion on Drug Delivery</i> , 4(4):427-440 (2007)
1014	Brandon & Tooze, "Introduction to Protein Structure," Second Ed., Chapters 1-6, 11-12, 17-18 (1999)
1015	Table Associating Citations from the '758 Patent (EX1001) to Corresponding Citations in the '731 Application (EX1026)

No.	Exhibit Description
1016	Steipe, “Consensus-Based Engineering of Protein Stability: From Intrabodies to Thermostable Enzymes,” <i>Methods in Enzymology</i> , 388:176-186 (2004)
1017	Green, “Computer Graphics, Homology Modeling, and Bioinformatics,” <i>Protein Eng’g & Design</i> , Ch. 10, 223-237 (2010)
1018	Chica et al., “Semi-rational approaches to engineering enzyme activity: combining the benefits of directed evolution and rational design,” <i>Curr. Opin. Biotechnol.</i> , (4):378-384 (2005)
1019	Hardy et al., “Assessment of contraceptive vaccines based on recombinant mouse sperm protein PH20,” <i>Reprod.</i> , 127:325-334 (2004)
1020	Pomering et al., “Restricted Entry of IgG into Male and Female Rabbit Reproductive Ducts Following Immunization with Recombinant Rabbit PH-20,” <i>Am. J. Reprod. Immunol.</i> , (3):174-82 (2002)
1021	Baba et al., “Mouse Sperm Lacking Cell Surface Hyaluronidase PH-20 Can Pass through the Layer of Cumulus Cells and Fertilize the Egg,” <i>J. Biol. Chem.</i> , 277(33):30310-4 (2002)
1022	Primakoff et al., “Reversible Contraceptive Effect of PH-20 Immunization in Male Guinea Pigs,” <i>Biol Reprod.</i> , 56(5):1142-6 (1997)
1023	Tung et al., “Mechanism of Infertility in Male Guinea Pigs Immunized with Sperm PH-20,” <i>Biol. Reprod.</i> , 56(5):1133-41 (1997)
1024	Rosengren et al., “Recombinant Human PH20: Baseline Analysis of the Reactive Antibody Prevalence in the General Population Using Healthy Subjects,” <i>BioDrugs</i> , 32(1):83-89 (2018)
1025	U.S. Patent No. 9,447,401
1026	U.S. Patent Application No. 13/694,731
1027	[Reserved]
1028	[Reserved]
1029	Gmachl et al., “The human sperm protein PH-20 has hyaluronidase activity,” <i>FEBS Letters</i> , 3:545-548 (1993)

No.	Exhibit Description
1030	Sills, "Retraction," <i>Science</i> , 319:569 (2008)
1031	Yue et al., "Loss of Protein Structure Stability as a Major Causative Factor in Monogenic Disease," <i>J. Mol. Biol.</i> , 353:459-473 (2005)
1032	Wang & Moulton, "SNPs, Protein Structure, and Disease," <i>Hum. Mutation</i> , 17:263-270 (2001)
1033	Marković-Housley et al., "Crystal Structure of Hyaluronidase, a Major Allergen of Bee Venom," <i>Structure</i> , 8:1025-1035 (2000)
1034	"Negative Results," <i>Nature: Editorials</i> , 453:258 (2008)
1035	Lins et al., "Analysis of Accessible Surface of Residues in Proteins," <i>Protein Sci.</i> , 12:1406-1417 (2003)
1036	Hayden, "Chemistry: Designer Debacle," <i>Nature</i> , 453:275-278 (2008)
1037	Benkert et al., "Toward the Estimation of the Absolute Quality of Individual Protein Structure Models," <i>Bioinformatics</i> , 27:343-350 (2010)
1038	Schwede et al., "SWISS-MODEL: An Automated Protein Homology-Modeling Server," <i>Nucleic Acids Res.</i> , 31:3381-3385 (2003)
1039	Alberts, "Molecular Biology of the Cell," Fifth Edition, Chapter 3 (2007).
1040	He et al., "NMR Structures of Two Designed Proteins with High Sequence Identity but Different Fold and Function," <i>PNAS</i> , 105:14412-14417 (2008)
1041	Alexander et al., "A Minimal Sequence Code for Switching Protein Structure and Function," <i>PNAS</i> , 106:21149-21154 (2009)
1042	Ruan et al., "Design and Characterization of a Protein Fold Switching Network," <i>Nature Comm.</i> , 14 (2023)
1043	Sievers et al., "Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega," <i>Molecular Sys. Biology</i> , 7.1 (2011)
1044	Mihel, "PSAIA – Protein Structure and Interaction Analyzer," <i>BMC Structural Biology</i> , 8:21 (2008)

No.	Exhibit Description
1045	Redline Comparison of the '731 and '758 Specifications
1046	Beasley & Hecht, "Protein Design: The Choice of <i>de Novo</i> Sequences," J. Biological Chemistry, 272:2031-2034 (1997)
1047	Xiong et al., "Periodicity of Polar and Nonpolar Amino Acids is the Major Determinant of Secondary Structure in Self-Assembling Oligomeric Peptides," PNAS, 92: 6349-6353 (1995)
1048	Hayden, "Key Protein-Design Papers Challenged," Nature, 461:859 (2009)
1049	KEGG, DRUG: Hyaluronidase (human recombinant), available at: https://www.genome.jp/entry/D06604
1050	Pace & Scholtz, "A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins," Biophysical J. 75:422-427 (1998)
1051	U.S. Patent Application No. 61/631,313
1052	U.S. Patent Application No. 61/796,208
1053	Hom_pre2011
1054	Hom_pre2011_header
1055	Hom_pre2011_header_clean
1056	Hom_pre2011.fasta
1057	Ph20_pre2011.aln-clustal_num
1058	Ph20_pre2011 Alignment html
1059	Leisola & Turunen, "Protein Engineering: Opportunities and Challenges," Appl. Microbiol. Biotechnol. 75:1225-1232 (2007)
1060	Hecht et al., "De Novo Proteins from Designed Combinatorial Libraries," Protein Sci., 13:1711-1723 (2004)
1061	Rosengren et al., "Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration," AAPS J., 17:1144-1156 (2015)
1062	[Reserved]
1063	[Reserved]

No.	Exhibit Description
1064	Collection of BLAST Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1065	Collection of Clustal Omega Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20111022151531/http://www.clustal.org/omega/
1066	Collection of SWISS-MODEL Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110519141121/http://swissmodel.expasy.org/?pid=smh01&uid=&token=
1067	Collection of PyMol Webpages from the Internet Archive, navigable from: https://web.archive.org/web/20110701072314/http://pymol.org/
1068	Declaration of Jeffrey P. Kushan
1069	Swiss Model Printout of PH20 Model
1070	Swiss Model Printout of PH20 Model with L317Q Mutation
1071	Swiss Model Printout of PH20 Model with L317R Mutation
1072	Swiss Model Printout of PH20 Model with L317M Mutation
1073	[Reserved]
1074	Swiss Model Printout of PH20 Model with L317I Mutation
1075	[Reserved]
1076	[Reserved]
1077	[Reserved]
1078	[Reserved]
1079	[Reserved]
1080	[Reserved]
1081	[Reserved]

No.	Exhibit Description
1082 [NEW]	United States District Court – National Judicial Caseload Profile, navigable from: https://www.uscourts.gov/data-news/reports/statistical-reports/federal-court-management-statistics/federal-court-management-statistics-december-2024
1083 [NEW]	Table Showing Outcomes of Disputed Motions to Stay Pending IPRs in DNJ
1084 [NEW]	News Release: “Halozyme Raises 2025 Financial Guidance Ranges and Reports Strong First Quarter 2025 Results,” navigable from: https://www.prnewswire.com/news-releases/halozyme-raises-2025-financial-guidance-ranges-and-reports-strong-first-quarter-2025-results-302447541.html
1085 [NEW]	News Release: “Merck Breaks Ground on New \$1 Billion Biologics Center of Excellence in Wilmington, Delaware,” navigable from: https://www.merck.com/news/merck-breaks-ground-on-new-1-billion-biologics-center-of-excellence-in-wilmington-delaware/
1086 [NEW]	Halozyme Therapeutics, Inc. Q1 2025 Earnings Call Transcript (May 6, 2025)

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 9,024 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 17th day of July, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by e-mail on the following counsel:

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