

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. PGR2025-00017
U.S. Patent No. 12,110,520

REPLY IN SUPPORT OF PETITION FOR POST GRANT REVIEW

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I. The Statutory Disclaimer Does Not Salvage the Remaining Claims

After Merck filed its Petition, Halozyme disclaimed (rather than defended) dependent claims 3-5, 16, and 31-35 (POPR, 1-6, 9), which claimed modified PH20s with “increased hyaluronidase activity” (4), “increased resistance or stability” (3), that are “soluble” (5, 16)), and treatment methods (31-33)). Halozyme contends this cured the § 112(a) deficiencies of its remaining claims, even though they *still claim* every modified PH20 polypeptide with those traits within the 10⁵⁹⁺ captured by claims’ parameters, and Halozyme still accuses Merck of infringement based on use of an enzymatically active PH20). POPR, 5, 29, 44-45; EX2058, ¶¶55-56, 66, 231 (alleging ’520 Patent claims “cover[]” active mutants). Grossly mischaracterizing precedent, Halozyme contends § 112 only requires a disclosure that repeats those claim parameters. POPR, 36-45, 48-54, 60-61. Halozyme is incorrect.

“The specification must enable the full scope of the invention as defined by its claims” and “[t]he more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 609-11 (2023). Functionally distinct “subset[s]” within a genus, whether described in structural or functional terms, are no exception, especially when (as here) there is no “general quality” shared by the claimed genus (*Id.*). Undue experimentation, if required to identify which of the claimed species possess utility, renders them non-enabled. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Under these standards,

every (remaining) claim is non-enabled. Within each is an unknown number of “active mutant” PH20 polypeptides with 2 to 42 substitutions. Pet., 17-21, 69-71. But the only procedure the disclosure describes for determining which of the 10⁵⁹+ polypeptides in each claims’ scope are “active mutants” (or have any utility) requires producing and testing each one. Pet., 71-74. The scale of experimentation to do so is not only undue—it is impossible. Pet. 74-77. Because at least the “active mutant” subgenera in each claim’s scope are not enabled, the claims are unpatentable.

Claims defining a “vast genus of chemical compounds” in structural (rather than functional) terms also are not exempt from the written description requirement. While written description problems are “especially acute with genus claims that use functional language to define the boundaries of a claimed genus,” *all* genus claims require a disclosure establishing that “the applicant has invented species sufficient to support a claim to a genus.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1349 (2010) (*en banc*). Written description for chemical compounds (*e.g.*, modified PH20 polypeptides) also “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.” *Regents of Univ. Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-1567 (Fed. Cir. 1997). And simply defining the boundaries of the genus (*Ariad*, 598 F.3d at 1349, 1350), providing laundry lists of possible substitutions (*Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570-71 (Fed. Cir. 1996)) or listing desired

attributes of an enzyme is insufficient (*Novozymes et al., v. DuPont Nutrition Biosciences et al.*, 723 F.3d 1336, 1349 (Fed. Cir. 2013)).

The Petition correctly demonstrated that the disclosure shared by the '731 Application and '520 Patent does not describe the vast majority of polypeptides being claimed: it describes *no examples* (prophetic or actual) of position 324-substituted PH20 polypeptides of varying lengths with *multiple* substitutions. Pet., §§ V.A.1. What Halozyme identifies in response are not descriptions of these distinct species of multiply-modified PH20 polypeptides—they are laundry lists of possible changes, optional combinations, and mathematically defined boundaries of genera. POPR, 39-45; EX1001, 14:24-17:64. None are “an adequate substitute for describing a variety of materials constituting the genus.” Pet., 52-59, 69-77; *Ariad*, 598 F.3d at 1349-50; *Regents*, 119 F.3d 1559 at 1567-68.

Halozyme's reliance on *In re Entresto*, 125 F.4th 1090 (Fed. Cir. 2025) is misplaced. *Entresto* considered claims to a pharmaceutical composition with two compounds that together formed a particular complex. Unremarkably, the Federal Circuit held the disclosure did not need to describe the later-discovered complex that forms if it adequately described the composition with those two compounds in it. *Id.* at 1097-99. It did not hold, as Halozyme contends, that the written description need not describe *the compounds being claimed*—the issue presented here.

Halozyme's criticism of Merck's explanation why the claims are directed to

“active mutant” modified PH20 polypeptides is also baseless. POPR, 2-6, 9, 28-32. The Petition stated the claim terms were expressly defined, quoted the patent’s definition of “modified PH20 polypeptides” (Pet., 17-18, *contra* POPR, 17-19), and identified *other* claim requirements—inclusion of specific position 324 substitutions—the disclosure associates with only one of two mutually exclusive embodiments (Pet., 22-26). Regardless, the Petition *also* explained why the claims were unpatentable even if not so limited. *See* Pet., §V.C.

Halozyme cannot seriously dispute that to be patentable, the claimed PH20 polypeptides must have a credible utility. While “active mutants” do, many modified PH20 polypeptides do not. The Petition also provided *evidence* (*i.e.*, scientific publications) that *human* PH20 proteins do not have “contraceptive” utility—the only one alleged for “inactive mutants.” Pet., 81-83. In response, Halozyme cites EX2009, contending it provides a “‘strong rationale’ with recent data...” that contraception with “anti-sperm contraceptive vaccines, like PH20, was an ‘exciting proposition’ and a ‘viable alternative to other modalities of contraception.’” POPR, 55-56. But EX2009 does not mention *PH20*, provides no “recent data” about it, and said the guinea pig model “may not be [a] suitable model[]for a vaccine to be tested in humans.” EX2009, 8. Regardless, the disclosure does not identify *which* “inactive mutants” have this implausible utility—it identifies none—and discovering which do (if any) requires making and testing 10⁵⁹+ mutants using procedures nowhere

identified in the disclosure. Pet., 83-84; EX1003, ¶¶ 112-113; *Idenix Pharms. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019).

Boehringer I, not *Boehringer II*, also controls here. POPR, 35-37. First, the functional characteristics required by disclaimed dependent claims 3-5, 16, and 31-35 required an antecedent basis in claim 1, and claim 1 ***still claims*** all such “active mutants.” *Allergan Sales, LLC v. Sandoz, Inc.*, 2:12-CV_00207-JRG, 2013 WL 4854786, *6 (E.D. Tex. Sept. 5, 2013). Second, as in *Boehringer I*, dependent claims 27-30 ***still impose*** activity requirements—they claim pharmaceutical compositions that combine a modified PH20 polypeptide with a “therapeutically active agent.” The disclosure’s description of those compositions states that they are formulated “so that the components, ***particularly the PH20 ... remain active*** or are ***stable***” “(i.e., [PH20] ***retains*** activity...)” EX1001, 32:24-39 (emphases added). Like *Boehringer I*, the disclosure here fails to “explain what, if any, structural features exist (e.g., remain) in sequences that vary by as much as” 5-9 % and remain “active mutants” and is just a research plan. Pet., 34, 52-66, 78-80.

II. Halozyme Mischaracterizes Merck’s Analysis of PGR Eligibility

Employing a reading it describes as “illogical” (POPR, 12), Halozyme contends the Petition only considered “the ’731 application as of 2011, rather than the ’731 application’s December 28, 2012 filing date” (POPR, 1, 32-33). But the Petition explained that the ’731 Application incorporated by reference two earlier-filed

provisionals and identified what the former added. Pet. 5-6. It also did not restrict the § 112(a) analysis to December 2011—it said the claims are not entitled to the “December 28, 2012” benefit date of the ’731 Application, while “the obviousness grounds use” the December 2011 priority date being claimed. Pet, 5-6, 15-16.

More directly, the Petition (and Dr. Hecht) documented *what is not described or discussed* in the common disclosure of the ’731 Application and ’520 Patent, such as numerous types of modified PH20 polypeptides, including active PH20 polypeptides still being claimed. Pet, §§V.A-B. Tellingly, Halozyme does not dispute the *factual* accuracy of the Petition’s or Dr. Hecht’s analysis of the common disclosure. Instead, Halozyme advances flawed *legal* responses—that such descriptions are unnecessary under *Entresto* (POPR, 41-45) or that describing the boundaries of genera and listing optional combinations is sufficient (POPR 39-43). It also mischaracterizes *Reiffin* as turning on the date of an intervening application. But the error in *Reiffin* was (unlike here) that the intervening application’s disclosure was never assessed. 214 F.3d 1342, 1345-46 (Fed. Cir. 2000). The § 112(a) grounds thus rest upon *omissions* of the ’731 Application’s disclosure, which are not “cured” by the passage of time. EX1003, ¶ 6 (citing 2024 Nobel Prize paper explaining computer-based protein structure predictions could not match experimentally-determined accuracy until 2018-2020). Finally, Merck’s experts properly framed their opinions using a date immediately prior to the claimed benefit date. EX1002,

359-64, 24-27. *Ariad*, 598 F.3d at 1355 (“written description analysis occurs ‘as of the filing date sought’”); *Reiffin*, 214 F.3d at 1346; Pet., 5.

III. Halozyme Mischaracterizes Dr. Park’s Opinions

Dr. Park was not told to limit his analysis to position 324. POPR, 6-9, 74, 84-85. He said 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, ¶ 15), that he assessed *all* non-essential residues of PH20₁₋₄₄₇ to “develop [his] unbiased scoring system” (*id.*, ¶102), “conducted [his] analysis in a manner that did not focus on any particular position” (*id.*, ¶ 103), and then was asked to *report* opinions he *had formed* about position 324 (*id.* ¶¶ 103-104).

Halozyme’s criticisms about scripts Dr. Park used are also baseless. POPR, 76-77, 82. First, the PyMol scripts were *produced* to Halozyme, used “built-in functions in PyMol,” and cited webpages that explained their functions. EX1004, ¶¶ 177-179, Appendix E-1, E-2; EX1067, 47-48. Second, while Dr. Park used perl scripts to compile the 88 unique sequences he analyzed (POPR, 76-77), his multiple sequence alignment was based on the 88 sequences, not intermediate files used to filter results from a public database (many of which were provided to Halozyme). EX1053; EX1054; EX1055; EX1056; EX1057. Dr. Park explained why he ran the perl scripts, how they function, and how he created the MSA. EX1004, ¶¶ 155-160.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 8th day of July, 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by electronic mail on the following counsel:

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