UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ITM ISOTOPE TECHNOLOGIES MUNICH SE,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

Case PGR2025-00012
U.S. Patent No. 11,938,201

PATENT OWNER'S BRIEF IN SUPPORT OF DISCRETIONARY DENIAL

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Dr. Henry VanBrocklin in Support of Patent Owner Discretionary Denial Brief
2002	Declaration of Dr. Henry VanBrocklin in Support of Patent Owner Preliminary Response
2003	*Curriculum vitae* of Dr. Henry VanBrocklin
2004	Krippendorff *et al.*, "Mechanism-Based Inhibition: Deriving K_I and k_{inact} Directly from Time-Dependent IC_{50} Values," *Society for Biomolecular Sciences* (Mar. 2009) ("Krippendorff")
2005	Šácha *et al.*, "iBodies: Modular Synthetic Antibody Mimetics Based on Hydrophilic Polymers Decorated with Functional Moieties," *Wiley-VCH Verlag GmbH & Co.* (Jan. 2016) ("Šácha")
2006	Meletta *et al.*, "Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging," *Molecules* (Jan. 2015) ("Meletta")
2007	Dvořáková *et al.*, "Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein: Supporting Information," *Journal of Medicinal Chemistry* (Sept. 2017) ("Dvořáková SI") Accessed Apr. 26, 2025 at: https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767
2008	Tassa *et al.*, "Binding Affinity and Kinetic Analysis of Targeted Small Molecule-Modified Nanoparticles," *American Chemical Society* (Dec. 2009) ("Tassa")
2009	Tweedle, "Adventures in multivalency, the Harry S. Fischer memorial lecture CMR 2005; Evian, France," *Wiley InterScience* (Feb. 2006) ("Tweedle")

Exhibit No.	Description
2010	Carlucci *et al.*, "Preclinical Evaluation of a Novel ^{111}In-Labeled Bombesin Homodimer for Improved Imaging of GRPR-Positive Prostate Cancer," *Molecular Pharmaceutics* (Apr. 2013) ("Carlucci")
2011	Sikkandhar *et al.*, "Theranostic Probes for Targeting Tumor Microenvironment: An Overview," *International Journal of Molecular Sciences* (May 2017) ("Sikkandhar")
2012	Brennen *et al.*, "Rationale Behind Targeting Fibroblast Activation Protein–Expressing Carcinoma-Associated Fibroblasts as a Novel Chemotherapeutic Strategy," *American Association for Cancer Research* (Feb. 2012) ("Brennen")
2013	McLuckey & Stephenson, "Ion/Ion Chemistry Of High-Mass Multiply Charged Ions," *Mass Spectrometry Reviews* (Dec. 1998) ("McLuckey")
2014	ITM Location and Contact Information, accessed Apr. 26, 2025 at: https://www.itm-radiopharma.com/contact
2015	Johns Hopkins University Factbook, May 2023, accessed Apr. 26, 2025 at: https://www.jhu.edu/assets/uploads/2018/12/johnshopkinsfactbook.pdf
2016	Johns Hopkins University Research Statistics, Research.com, accessed Apr. 26, 2025 at: https://research.com/university/johns-hopkins-university#:~:text=Overview,publications%20per%20scientist%20of%20337.80.&text=Please%20note%20that%20the%20research,%2C%20MAG%20profile%2C%20and%20LinkedIn
2017	About Us, Research.com, accessed Apr. 26, 2025 at: https://research.com/about-us
2018	WO 2010/108125 A2 to Pomper *et al.*

TABLE OF AUTHORITIES

Cases

Other Authorities

I. INTRODUCTION

Per the Office's Interim Processes for PTAB Workload Management, dated March 26, 2025 ("Interim Processes Memo"), Patent Owner Johns Hopkins University ("JHU") submits this brief explaining the applicable bases for discretionary denial of institution by the Director. Interim Processes Memo, 2. This brief is supported by a declaration from Dr. Henry VanBrocklin, a professor at the University of California, San Francisco, and an expert in radiopharmaceuticals and imaging with 35 years of experience in the field. EX2001, ¶¶4−15. As discussed herein, multiple factors identified in the Interim Process Memo justify discretionary denial here.

First, ITM relies on art and arguments that are the same or substantially the same as those previously considered by the Office, and has not shown that the Office erred in a manner material to the patentability of the challenged claims—failing the *Advanced Bionics* framework. Thus, "another forum has already adjudicated the [] patentability of the challenged patent claims" and "[t]he strength of the unpatentability challenge" is weak on the merits. Interim Process Memo, 2−3. *Second*, ITM uses the wrong "prism or lens" through which the claimed invention must be viewed by a person of ordinary skill in the art ("POSA"), when advancing each of the Petition's Grounds of unpatentability. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). ITM also extensively relies on conclusory

testimony from a declarant that does not possess the requisite skill of a POSA, further showing its unpatentability challenge is weak on the merits. Interim Process Memo, 2−3. *Third*, discretionarily denying ITM's weak petition would serve to protect domestic economic and national interests over those of a foreign actor. The Petition thus does not warrant taxing the finite resources of the Board by instituting review.

II. THE PETITION RELIES ON THE SAME ART AND ARGUMENTS CONSIDERED DURING PROSECUTION, AND THE PETITION FAILS TO IDENTIFY A MATERIAL ERROR.

The Interim Memo expressly states that its discretionary considerations—including "[w]hether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims"—are "consistent" with the *Advanced Bionics* framework for discretionary denial under § 325(d). Interim Process Memo, 2. Because ITM's petition presents the same or substantially the same art and arguments that were previously presented to the Office in Grounds I through V, yet fails to identify any material error committed by the Office, its petition fails under the two-part test of *Advanced Bionics* with respect to these Grounds. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7–11 (P.T.A.B. Feb. 13, 2020).

ITM's failures under *Advanced Bionics* with respect to Grounds I through V provide a sufficient basis for the Director to discretionarily deny ITM's whole

Petition, especially in view of the considerations set forth in the Interim Process Memo.

A. Grounds I and II Fail the *Advanced Bionics* Framework.

Ground I relies on "Jansen I and/or Jansen II taken in view of Zimmerman and Pomper." Pet., 26. Ground II relies on "Dvořáková in view of Pomper." *Id.* The Director should exercise its discretion to deny institution based on these Grounds (and Grounds III−V, as discussed below) because they present the same or substantially the same art and arguments previously presented to the Office, and ITM has not demonstrated any material error as to the patentability of the challenged claims.

1. Grounds I and II Rely on the Same or Substantially the Same Art Considered and Overcome During Prosecution.

As the Petition acknowledges, "prior art references Dvořáková, Jansen I, Jansen II, and Zimmerman were considered during prosecution." Pet., 100; EX2001, ¶¶30−31, 36. In fact, the Examiner raised and discussed each of Dvořáková, Jansen I, Jansen II, and Zimmerman to reject the then pending claims. EX1004, 1177−1182 (raising a rejection under § 102 over Dvořáková and under § 103 over Jansen I (as US 2014/0357650; *see* EX1007, (65)), Jansen II, and Zimmerman); EX2001, ¶¶30−31, 34−35. Thus, part one of the *Advanced Bionics* framework is met as to Dvořáková (EX1008), Jansen I (EX1007), Jansen II (EX1010), and Zimmerman (EX1009).

The Examiner also considered Pomper (EX1006). EX2001, ¶¶30−31, 37−40. Pomper was cited in an IDS that the Examiner signed and indicated that she considered the reference. EX1004, 1171 (Cite No. 4, WO 2010/108125, which is the PCT counterpart of Pomper); EX2001, ¶¶31, 37−38. This is sufficient to meet the first prong of the *Advanced Bionics* framework as to Pomper. *See Keysight Techs., Inc. v. Centripetal Networks, Inc.*, IPR2022-01421, Paper 14 at 5 (P.T.A.B. Aug. 24, 2023). Indeed, "the first part of the *Advanced Bionics* framework does not require that an Examiner provide a discussion, analysis, or other findings on the applicability of the relevant material contained in an IDS" *Id.* (internal quotations omitted); *see also Stone Basket Innovations, LLC v. Cook Med. LLC,* 892 F.3d 1175, 1179 (Fed. Cir. 2018) ("[W]hen prior art is listed on the face of a patent, the examiner is presumed to have considered it.") (citation omitted).

The '201 patent also incorporates Pomper by reference in its entirety. EX1001, 17:45−53 (incorporating US 2012/0009121 (Pomper) by reference); EX1004, 153; EX2001, ¶¶39−40. This is also sufficient to meet the first prong of the *Advanced Bionics* framework as to Pomper. *Celltrion, Inc. v. Regeneron Pharm., Inc.*, IPR2023-00462, Paper 11 at 17–20 (P.T.A.B. July 20, 2023) (finding the same art previously presented where the art was cited in the specification and incorporated by reference).

Pomper is also cumulative to Zimmerman (EX1009). *See Advanced Bionics* at 9–10 (*Becton, Dickinson* factor (b), "the cumulative nature of the asserted art and the prior art evaluated during examination", "broadly provide[s] guidance as to whether the art presented in the petition is the 'same or substantially the same.'"); EX2001, ¶¶30−31, 41−43. ITM argues that Pomper discloses that "low molecular weight inhibitors may have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies." Pet., 2, 46, 56, 61–62; EX2001, ¶41. Zimmerman, which was raised by the Examiner when rejecting the pending claims during prosecution, EX1004, 1179−1182, however, *also* purportedly discloses low molecular weight radiopharmaceuticals, EX1009, ¶¶2, 7, FIG. 7, as ITM's declarant Dr. Martin readily admits and relies on: "Zimmerman is directed to '*[s]mall molecule inhibitors* of seprase [FAP-α] [] *for use as therapeutic medicines or as radiopharmaceuticals* useful in diagnostic imaging and in the therapeutic treatment of diseases characterized by overexpression of seprase [FAP-α]."[1] EX1002, ¶118;[2] *see also* Pet., 38, 51, 53–55; EX2001, ¶41.

[1] As Dr. VanBrocklin explains, a POSA would understand that a "small molecule" would mean a compound of low molecular weight. EX2001, ¶41.

[2] Emphasis added throughout unless otherwise indicated.

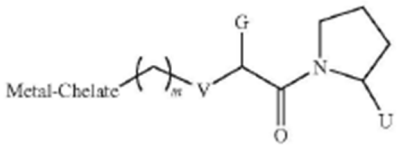
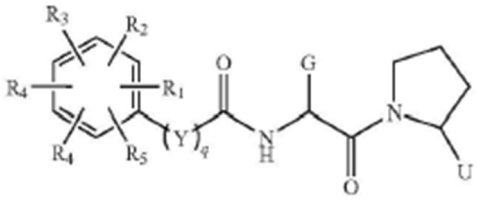
ITM, moreover, admits that the "Examiner recognized [the] teachings and motivations in the prior art" to "design and prepare *a low molecular weight compound* with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent." Pet., 46; EX2001, ¶¶42−43. Pomper's alleged disclosures of "low molecular weight radiopharmaceuticals," therefore, is cumulative to Zimmerman with respect to the alleged disclosure of low molecular weight compounds. EX2001, ¶¶42−43.

ITM further argues that Pomper "discloses suitable linkers that can be used to couple the inhibiting moiety and the optical or radiolabeled moiety." Pet., 55; EX2001, ¶¶41−43. Here, once again, ITM admits that Zimmerman also allegedly discloses "a linker having bi-functionalization adapted to form a chemical bond with B and A" that "meets the parameters of the claimed linker, L." Pet., 52−53; EX2001, ¶¶42−43. ITM does not explain why Pomper's linkers offer anything beyond Zimmerman's already considered linkers. EX2001, ¶41. Thus, Pomper is cumulative to Zimmerman in their disclosures of linkers. EX2001, ¶41.

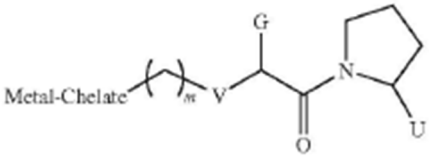
The tables below demonstrate the cumulative nature of Pomper compared to Zimmerman and how ITM makes substantially the same arguments the Examiner advanced during prosecution. EX2001, ¶¶42−43.

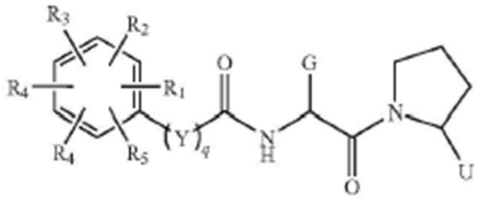
ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
"Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis." EX1002, ¶125; EX1006, Abstract, ¶12.	"This invention relates in general to small molecule inhibitors of seprase that can be used as ***therapeutic agents*** through inhibition of seprase's enzymatic activity, or as ***radiopharmaceuticals*** that bind to seprase and ***therefore enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues*** that express seprase." EX1009, ¶2. "Seprase is expressed in epithelial ***cancers*** and has been implicated in extracellular matrix remodeling, tumor growth, and metastasis." EX1009, ¶3.

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	"The expression of seprase on ***tumors*** makes it an attractive target to exploit for ***noninvasive imaging as well as targeted radiotherapy***." EX1009, ¶5. "The complexes or compounds, may be used in accordance with the methods also described herein, by those skilled in the art, e.g., by specialists in nuclear medicine, ***for diagnostic imaging of tissue*** which expresses seprase, and therapeutic treatment of diseases which are characterized by overexpression of seprase." EX1009, ¶136. Formula I:

ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	 Formula II:  "Zimmerman et al. (US2010/0098633Al) discloses radiopharmaceuticals useful in ***diagnostic imaging and therapeutic treatment of disease*** comprising [Formulas I and II] wherein U is -$B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; Vis a bond, etc.; the metal is a metallic moiety include [sic] a radionuclide for PET, SPECT; chelate is a chelating

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	moiety that coordinates with the radionuclide; Y is -CH_2-, etc.; and R_1-R_5 may comprise radiohalogen, etc. (p1−2, [0008−0028]; p3, [0048−0049]; p6, [0087−0099]; p9, [0111−0117]; p13,)" EX1004, 1180−1181.
"These compounds include a PSMA inhibitor used to treat cancer that is linked with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping." EX1002, ¶125; EX1006, ¶¶31−34, 279.	"Small molecule inhibitors of seprase are provided for use as therapeutic medicines or as radiopharmaceuticals useful in ***diagnostic imaging and in the therapeutic treatment*** of diseases characterized by overexpression of seprase. The radiopharmaceuticals include complexes or compounds that contain a functionalized proline moiety which is capable of ***selectively inhibiting*** seprase, and ***a radionuclide*** adapted for

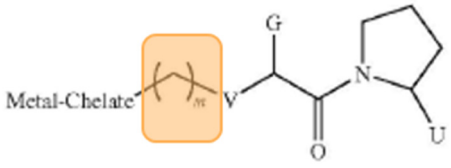
ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	radioimaging and/or radiotherapy." EX1009, ¶7. "In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . [**m**]**etal represents a metallic moiety including a radionuclide**[.]" EX1009, ¶¶8–19. "In another aspect, a compound of general Formula II, its enantiomer,

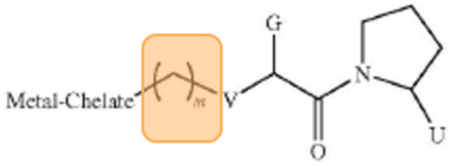
ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . R_1, R_2 , R_3, R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino; with the proviso that at least one of R_1, R_2 , R_3, R_4 and R_5 is a halogen ***(including radiohalogen***).” EX1009, ¶¶21–28. “Zimmerman et al. teaches of radiohalogenation of ***FAP inhibitors*** for

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	the advantage of ***diagnostic imaging and therapeutic treatment of diseases***." EX1004, 1181.
"These imaging agents 'offer better contrast between target tissues and non-target tissues,' 'greater cellular retention,' and 'low molecular weight.'" EX1002, ¶125; EX1006, ¶12.	"The expression of distinct proteins on the surface of tumor cells offers the opportunity to diagnose and characterize disease by probing the phenotypic identity and biochemical composition and activity of the tumor. Radioactive molecules that ***selectively bind to specific tumor cell surface proteins*** allow for the use of noninvasive imaging techniques, such as molecular imaging or nuclear medicine, for detecting the presence and quantity of tumor associated proteins . . . . [T]herapy may be realized through the use of

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	radiopharmaceuticals that are not only capable of imaging disease, but also are capable of delivering a therapeutic radionuclide to the diseased tissue. ***The expression of seprase on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.*** Furthermore, since seprase has both dipeptidyl peptidase and endopeptidase activity, and DPP-IV exhibits only dipeptidyl peptidase activity, ***selective seprase inhibitors would be useful to reduce unwanted side effects***." EX1009, ¶¶5–6. "***Small molecule inhibitors*** of seprase are provided for use as therapeutic

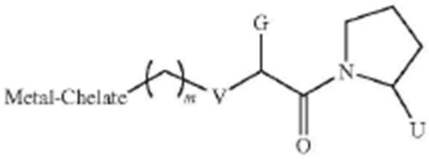
ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	medicines or as ***radiopharmaceuticals*** useful in ***diagnostic imaging*** and in the therapeutic treatment of diseases characterized by overexpression of seprase." EX1009, ¶7. Zimmerman contains explicit reference to selectivity and references the compounds as "***small molecule***," EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Pomper also discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety." EX1002, ¶125; EX1006, ¶12.	"In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided where . . . m is an integer ranging from 0 to 6[.] EX1009, ¶¶8–19.

ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	Formula I:  (linker annotation added) "Zimmerman et al. (US2010/0098633Al) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising [Formulas I and II]." EX1004, 1180.

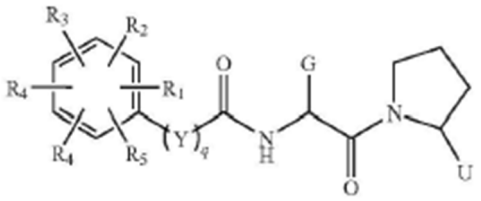
ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	Formula I:  (linker annotation added)
"Pomper also teaches the benefits of low molecular weight compounds. Pomper discusses how 'antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically.'" EX1002, ¶126; EX1006, ¶8.	"This invention relates in general to ***small molecule inhibitors of seprase that can be used as therapeutic agents*** through inhibition of seprase's enzymatic activity, or as radiopharmaceuticals that bind to seprase and therefore ***enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues that express seprase***." EX1009, ¶2.

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	"***Small molecule inhibitors*** of seprase are provided for use as therapeutic medicines or as ***radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases*** characterized by overexpression of seprase." EX1009, ¶7. Zimmerman contains explicit reference to selectivity and references the compounds as "***small molecule***," EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Pomper also discusses how low molecular weight inhibitors have 'shown promise in preclinical	"This invention relates in general to small molecule inhibitors of seprase that can be used as therapeutic agents

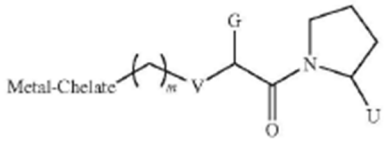
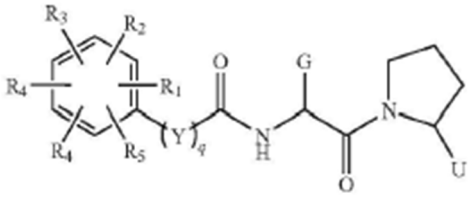
ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
imaging studies.'" EX1002, ¶126 (citing EX1015 and EX1016); EX1006, ¶242.	through inhibition of seprase's enzymatic activity, or as radiopharmaceuticals that bind to seprase and therefore ***enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues that express seprase***." EX1009, ¶2. "Small molecule inhibitors of seprase are provided for use as therapeutic medicines or as ***radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases*** characterized by overexpression of seprase." EX1009, ¶7.

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	Zimmerman contains explicit reference to selectivity and references the compounds as "***small molecule***," EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Zimmerman and Pomper disclose radiolabeled functional groups suitable for PET imaging, SPECT imaging, or radiotherapy." EX1002, ¶129.	"In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . [**m**]**etal represents a metallic moiety including a radionuclide**[.]" EX1009, ¶¶8–19.

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	"'Radionuclide' refers to molecule that is capable of generating a detectable image that can be detected either by the naked eye or using an appropriate instrument, ***e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT)***." EX1009, ¶49. In another aspect, a compound of general Formula II, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable

ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	salt is provided:  where . . . R_1, R_2 , R_3, R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino; with the proviso that at least one of R_1, R_2 , R_3, R_4 and R_5 is a halogen ***(including radiohalogen***)." EX1009, ¶¶21–28. "'***Radiohalogen***,' as used herein, refers to those ***radionuclides*** that are also halogens (i.e. F, Br, I, or At)." EX1009, ¶49.

ITM's Arguments Based on Pomper	**Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination**
	"Zimmerman et al. (US2010/0098633Al) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising [Formulas I and II] wherein U is -$B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; Vis a bond, etc.; the metal is a metallic moiety include [sic] a radionuclide for ***PET, SPECT***; chelate is a chelating moiety that coordinates with the radionuclide; Y is-CH_2-, etc.; and R_1-R_5 may comprise radiohalogen, etc." EX1004, 1180−1181.

ITM's Arguments Based on Pomper	Same Art (Zimmerman) or Arguments (Examiner's Statements) Made During Examination
	 

As the table above demonstrates, Pomper is cumulative of Zimmerman, and ITM's reliance on Pomper does not provide anything beyond what the Examiner already raised and considered. EX2001, ¶43. Accordingly, the first prong of *Advanced Bionics* is met with respect to all art forming Grounds I and II.

2. Petitioner Fails to Establish Material Error with Respect to the Office's Prior Consideration of the Art in Grounds I and II.

ITM carries the burden of demonstrating material error. "If a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute []

review." *Advanced Bionics* at 8−9. Mere disagreement with the Office's prior determinations is an insufficient basis for institution. "If *reasonable minds can disagree* regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.*

ITM has failed to meet its burden to show that the Examiner erred in a manner material to patentability in allowing the challenged claims. One of ITM's proffered errors is in the Examiner's "evaluation of the prior art" because the Examiner allegedly did not apply Pomper during prosecution. Pet., 100; EX2001, ¶¶44−45. ITM's position that the Examiner should have rejected the claims over Pomper is a mere disagreement, not a material error, as discussed below.

Pomper was squarely before the Examiner and is also cumulative to Zimmerman. EX2001, ¶¶37−43. Yet even though reasonable minds may disagree as to whether or not the Examiner should have raised Pomper, "it cannot be said that the Office erred in a manner material to patentability." *Advanced Bionics* at 9. This is because the Examiner did not overlook or misapprehend any prior art teachings the Petition relies on—those same disclosures were already found in Zimmerman, as shown in the tables above. EX2001, ¶45. *Advanced Bionics* at 9. The Examiner raised Zimmerman, and JHU overcame it. EX1004, 1179−1184; EX2001, ¶36.

ITM further argues that the Examiner "erroneously" withdrew the obviousness rejection over Dvořáková, Jansen I and II, and Zimmerman based on "a flawed showing of unexpected results." Pet., 100. Here, the only evidence that ITM cites to support this allegation is Dr. Martin's declaration. *Id.* But Dr. Martin's testimony is conclusory and unsupported on this point. EX1002, ¶¶16, 133–135; EX2001, ¶¶45−46. Indeed, Dr. Martin's declaration merely regurgitates the conclusory assertion it purports to support, *compare* Pet., 47–48, *with* EX1002, ¶¶133–135; EX2001, ¶¶45−46, citing no evidence, as shown in the following chart.

Petition's Statements	**Dr. Martin's Declaration's Statements**
"But **Dr. Pomper's assertion of unexpected results is based on only 11 examples, and is certainly insufficient to represent the thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad language**	"In my opinion, given the broad scope of the claims, **which cover a countless number of compounds, even if these results were surprising, 11 examples are not sufficient to represent the full scope of the very broad claims.** Each of the 11 new examples, along with the two examples XY-FAP-01 and XY-FAP-02-[In] in the '201 patent

Petition's Statements	Dr. Martin's Declaration's Statements
used in the claims. EX1002 at ¶133. These alleged unexpected results were the sole basis given by the Examiner for allowing the prima facie obvious claimed invention over the applied prior art. EX1004 at 1308 (Notice of Allowance)." Pet., 47.	specification, includes the same FAP inhibitor (A) structure. **Meanwhile, as discussed in Section VII.B, the limitations of R_{3x} of the FAP inhibitor (A) themselves have a vast number of possibilities. Neither the additional examples nor the specification, provide any indication as to effect of varying any one of the substituents on the FAP inhibitor (A) structure**." EX1002, ¶133.
"That was legally improper, for Dr. **Pomper's presented evidence of alleged unexpected results was not even remotely commensurate with the extremely broad scope of the claims, and the claimed invention remains obvious in light of that**	"Furthermore, while the structures of the linkers (L) and optical dyes or radiolabeling groups (B) vary in the 11 provided examples, **it is certainly insufficient to represent the thousands, if not millions or more, possible linkers, optical dyes,**

Petition's Statements	Dr. Martin's Declaration's Statements
applied art. See EX1002 at ¶134 . . . ." Pet., 47−48.	**radiolabeling groups, and combinations thereof encompassed by the broad functional language used in the claims . . . . Thus, the Pomper declaration does not provide evidence of unexpected results commensurate with the scope of the vary large, if not limitless, scope of the FAP inhibitor (A) genus described in the claims**. Therefore, in my opinion, the evidence of unexpected results presented during prosecution should be given little or no weight, and is certainly insufficient to overcome the strength of the prior art's teachings." EX1002, ¶¶134−135.

Dr. Martin's testimony adds nothing beyond the attorney arguments it parrots and, therefore, is entitled to little to no weight on this point. *Xerox Corp. v. Bytemark,*

Inc., IPR2022-00624, Paper 9 at 15 (P.T.A.B. Aug. 24, 2022) ("the cited declaration testimony is conclusory and unsupported, adds little to the conclusory assertion for which it is offered to support, and is entitled to little weight"); 37 C.F.R. § 42.65(a).

In assessing material error, the Director should also consider "the *extent* to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection." *Advanced Bionics* at 10−11 (stating that *Becton, Dickinson* "factor[] (c) . . . relate[s] to whether the petitioner has demonstrated a material error by the Office"). Here, Dvořáková, Jansen I, Jansen II, and Zimmerman were extensively considered during examination. EX2001, ¶¶35−36. They were the bases of rejection raised by the Examiner. EX1004, 1177−1182; EX2001, ¶36. This is equally applicable to Pomper because it is cumulative of Zimmerman. EX2001, ¶¶41−43.

Given that the art in Grounds I and II was *extensively* evaluated during examination, the Examiner did not overlook or misapprehend any prior art teachings, and ITM relies on conclusory testimony, ITM's allegations of material error do not clearly and convincingly demonstrate that the Office erred in a manner material to patentability.

B. Grounds III−V Fail the *Advanced Bionics* Framework

Grounds III and IV allege that claims 1−3 lack enablement and written description in the ’201 patent. Ground V alleges claims 1−3 are indefinite. The Director should exercise its discretion to deny institution based on Grounds III−V (and Grounds I and II, as discussed above) because they present the same arguments previously presented to the Office, and ITM has not demonstrated any error material to patentability of the challenged claims.

1. The Examiner considered definiteness of the phrase “low molecular weight.”

For Ground V (indefiniteness), ITM contradicts itself in arguing against the exercise of discretionary denial. On the one hand, ITM states that “the prosecution history does not reflect that the Examiner ever appreciated or considered the § 112 issues” discussed in Ground V. Pet., 100. Yet, on the other hand, according to ITM, “[t]he phrase ‘low molecular weight’ was further discussed during prosecution.” *Id.*, 93–94; EX1004, 1214, 1197, 1272; EX2001, ¶¶32, 47. And ITM states that the Notice of Allowance “indicated that the claims were allowed because of the addition of the phrase ‘low molecular weight’ and the purportedly unexpected results.” Pet., 22.

Indeed, during prosecution, JHU provided a declaration by Dr. Pomper explaining how the term “low molecular weight” should be understood in the context of the claimed invention as approximately 50−1,500 Da. EX1004,

1196−98, 1213−1215; EX2001, ¶¶47−48. JHU also argued there was support in the specification for the claimed "low molecular weight" compounds and how they differed from "polymers" having "high relative molecule mass." EX1004, 1214 (citing 1:28−34, 2:1−7, 8:26−29, 9:1−2, 45:12−14 of the as-filed specification). EX2001, ¶48. *See Google LLC, v. Ecofactor, Inc.*, IPR2022-00535, Paper 7 at 13 (P.T.A.B. Aug. 1, 2022) (holding that the same arguments were previously before the Office when patent owner "presented arguments concerning support for [a] claim limitation during examination"). The Examiner and JHU additionally discussed this phrase during an Examiner's interview, with JHU explaining that "low molecular weight is defined as compounds under ~1500Da." EX1004, 1237; EX2001, ¶48. ITM does not dispute any of the foregoing. Pet., 12−22.

That the Examiner entered the amendment to add "low molecular weight" when allowing the claims after JHU pointed to support in the specification also indicates the Examiner considered the phrase and found compliance with each of the provisions of § 112, including definiteness. EX1004, 1303−1309.

For Ground III (enablement) and IV (written description), the Examiner is presumed to have considered "each claim . . . for compliance with every statutory requirement for patentability," including those under § 112. M.P.E.P. §2103 (2024). The Examiner, therefore, should be presumed to have considered enablement and written description for the challenged claims during prosecution

and found them compliant because enablement and written description rejections were never raised. The Examiner, moreover, as discussed above, also entered amendments to the pending claims, again suggesting the claims were complaint with § 112. Finally, the Examiner is presumed to have "reviewed [the application] to make certain that the whole application meets all formal and substantive (i.e., statutory) requirements and that the language of the claims is enabled by, and finds adequate descriptive support in, the application disclosure as originally filed," when the application was ready for allowance. M.P.E.P. §1302.01 (2024).

Part I of the *Advanced Bionics* framework, therefore, is satisfied with respect to Grounds III−V.

2. ITM has not identified any material error with respect to Grounds III and IV and fails to show material error in the Examiner's definiteness analysis of "low molecular weight" for Ground V.

ITM has made no effort to demonstrate an error material to patentability with respect to Grounds III and IV. Nor does ITM make any effort to demonstrate material error in relation to Ground V. EX2001, ¶49. Instead, ITM erroneously concludes that the Examiner did not "appreciate[] or consider[]" definiteness. Pet., 100; EX2001, ¶49. But ITM's position is merely a disagreement with the Examiner's allowance in view of JHU's arguments during prosecution. But, again, "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to

patentability." *Advanced Bionics* at 9. ITM, therefore, has failed to demonstrate that the Office erred in a manner material to the patentability of the challenged claims with respect to Grounds III−V.

In view of Sections II.A.−II.B., ITM has (1) failed to establish that the art it relies on in Grounds I and II and the arguments it relies on in Grounds III−V were not previously before the Office; and (2) failed to establish that the Office erred in a manner material to patentability of the challenged claims. The Director should exercise her discretion and deny institution under § 325(d). *Advanced Bionics* at 7−11.

III. THE PETITION'S CHALLENGES ARE PARTICULARLY WEAK ON THE MERITS AND WARRANT DISCRETIONARY DENIAL.

In addition to the Petition's failures under *Advanced Bionics*, ITM also uses the wrong POSA lens for each of its unpatentability Grounds, and extensively relies on conclusory testimony from a declarant who does not possess the requisite skill of a POSA. EX2001, ¶¶50−60. Those defects render the merits of the Petition's unpatentability Grounds weak, further justifying discretionary denial. *HP Inc., et al. v. Universal Connectivity Techs., Inc.*, IPR2024-01429, Paper 11 at 6, 16, 20−21, 24−25, 28−29 (P.T.A.B. Apr. 16, 2025) (exercising discretion to deny institution where petitioner's unpatentability arguments were "not particularly strong"); Interim Process Memo, 2−3 (identifying the "strength of the unpatentability challenge," and"[t]he extent of the petition's reliance on expert

testimony" as considerations for exercising discretionary denial); *Innovention Toys, LLC v. MGA Ent., Inc.*, 637 F.3d 1314, 1323−24 (Fed. Cir. 2011) ("not harmless" error where invalidity analysis was "based on inappropriate[] level of skill in the art"); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 26−27 (P.T.A.B. Jan. 24, 2019) (petition's unpatentability showing "insufficient" due to reliance on declarant "testimony [that] is itself conclusory"); *Avail MedSystems, Inc. v. Teladoc Health, Inc.*, IPR2022-00444, Paper 10 at 24−28 (P.T.A.B. July 21, 2022) ("it would be inappropriate for us to consider any testimony by [the inexperienced expert] on any issue that is analyzed through the lens of [a POSA]").

A. ITM's Petition Uses an Incorrect POSA Lens that Infects All of the Petition's Grounds.

The level of ordinary skill in the art is "a prism or lens" through which the claimed invention must be viewed. *Okajima*, 261 F.3d at 1355. However, ITM and its declarant, Dr. Martin, use an incorrect POSA lens for their analysis for each Ground—a lens that does not account for the training and practical experience the POSA would have had in imaging or radiotherapy. EX2001, ¶¶51−59.

In determining the level of skill of a POSA, the Federal Circuit has long considered factors such as the "(1) [] educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field" as a guide in determining the

level of ordinary skill in the art. *Env't Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 696–97 (Fed. Cir. 1983); *Okajima*, 261 F.3d at 1355 (the prior art may reflect the appropriate skill level of a POSA). The Federal Circuit has also held that "[t]he patent's purpose" and the prior art may reflect the appropriate skill level of a POSA. *Best Med. Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1353 (Fed. Cir. 2022); *Okajima*, 261 F.3d at 1355.

Here, the '201 patent abstract expressly states that "[i]maging and radiotherapeutics agents targeting fibroblast-activation protein-α (FAP-α) and their use in imaging and treating FAP-α related diseases and disorders are disclosed." EX2001, ¶¶33, 54, 57; EX1001, Abstract. The specification further discusses radiolabeled groups for these agents, and cites numerous references relating to imaging and radiotherapy; it also provides imaging quality testing for its inventive compounds. EX2001, ¶¶55, 55, 57; EX1001, 17:45−30:67, FIGs. 6−8 (providing nuclear imaging data for the disclosed compounds).

ITM also cannot deny that the prior art it uses for alleging obviousness here likewise discusses compounds with radiotherapeutics and imaging applications, and its art provides in vitro imaging quality testing results. *See, e.g.*, EX1009, Abstract; EX1008, 3, 5; EX2001, ¶¶56−57. ITM further concedes that "claimed subject matter of . . . the '201 patent" is the creation of compounds "used in diagnostic imaging and radiotherapeutics." Pet., 1.

As JHU's expert, Dr. VanBrocklin, explains, in view of the patent's and the cited prior art's overall focus on imaging and radiotherapeutic agents described above, POSAs would, critically, have had *multiple years of both formal training and actual, practical experience* in i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques (such as positron emission tomography and single photon emission computed tomography). EX2001, ¶¶58−59. This training and experience would have involved developing and evaluating agents for biomedical imaging or radiopharmaceuticals, and using molecular imaging techniques. *Id.*, ¶59. Indeed, without this training and practical experience, the POSA would not have had the skill to properly understand the image quality testing data for the compounds described in both the specification and in the prior art, discussed above. *Id.*, ¶¶54−57. Nor would the POSA have had the skills required to perform the sorts of tests needed to evaluate the performance of imaging or radiotherapeutic agents targeting FAP, such as the claimed compounds. *Id.*, ¶¶54−57.

However, ITM's declarant, Dr. Martin, states only that POSAs would have had some undefined "*understanding* of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain

features of a molecule that contribute to its affinity and selectivity for a particular drug target." EX1002, ¶95; EX2001, ¶52. Dr. Martin's definition thus fails to take into account the multiple years of *formal training* and *practical experience* in radiopharmaceuticals that the POSA would have, as discussed above. EX2001, ¶¶53−59.

B. ITM's Petition Extensively Relies on Testimony from Dr. Martin, Who Does Not Possess the Skill of a POSA, Rendering His Analysis of the Patentability of the Challenged Claims Weak.

Not only do ITM and Dr. Martin fail to use the correct POSA lens, Dr. Martin himself does not possess the required ordinary skill in the art. As discussed above, a POSA here would have had multiple years of formal training and practical experience in radiotherapeutics or imaging. Yet nothing in Dr. Martin's CV or discussion of his "Qualifications" indicates that he has *any* practical experience in radiotherapeutics or imaging. EX1002, ¶¶4−13; EX1003; EX2001, ¶¶33, 60. As the Federal Circuit has recognized, "an expert must at a minimum possess ordinary skill in the art." *Osseo Imaging, LLC v. Planmeca USA Inc.,* 116 F.4th 1335, 1340 (Fed. Cir. 2024); *see also Avail*, IPR2022-00444, Paper 10 at 24−28. Dr. Martin's testimony should thus be given little to no weight. *See id*.

By contrast, JHU's expert, Dr. VanBrocklin, *does* possess at least the level of skill of a POSA—he has a Ph.D. in Radiopharmaceutical Chemistry and more than two decades of practical experience in molecular imaging and imaging agent

development. EX2001, ¶¶4−15; EX2003. Dr. VanBrocklin also applies the correct lens of a POSA with multiple years of training and practical experience in radiotherapeutics or imaging. Thus, Dr. VanBrocklin's testimony should, at a minimum, be given more weight than Dr. Martin's testimony.

C. ITM's Use of an Incorrect POSA Lens and Reliance on a Declarant Who Does not Possess the Skill of a POSA Shows its Unpatentability Grounds are Weak.

As set forth below, ITM's failure to use the correct POSA lens, and its reliance on a declarant who does not possesses the requisite skill of a POSA, shows that its unpatentability Grounds are weak on the merits, warranting discretionary denial here. *See Innovention*, 637 F.3d at 1323−24; *Avail*, IPR2022-00444, Paper 10 at 24−28.

1. Claim Construction.

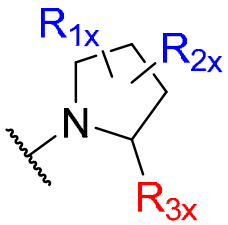
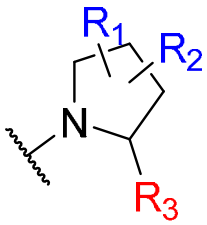
As ITM recognizes, in a PGR proceeding, claim terms are to be construed using the standard under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). Pet., 40. The *Phillips* claim construction standard requires an "inquiry into how a person of ordinary skill in the art understands a claim term." *Phillips*, 415 F.3d at 1313. ITM and its declarant, Dr. Martin, purport to provide a claim construction analysis for two claim terms—"C(O)Alkyl"/"Aryl" and "low molecular weight"—from the perspective of how "a POSA would have understood" those terms. Pet., 40, 42; EX1002, ¶¶98, 102, 105. However, because ITM and Dr. Martin use the

incorrect POSA lens, §III.A., *supra*, their claim construction analysis for these terms from the incorrect perspective is weak on the merits.

For example, ITM and Dr. Martin state that a POSA would have understood that the '201 patent "does not provide any limit" to the number of carbon atoms or rings in the claimed "C(O)Alkyl" and "Aryl" groups, and thus would have understood that the groups are "not limited to any particular length, size or substitution." Pet., 42−44; EX1002, ¶¶110−111. Yet, as explained in JHU's concurrently-filed Patent Owner Preliminary Response ("POPR"),[3] a POSA instead would have understood that the patentee had, in fact, designated *a specific* number of carbons (1 to 6 carbon atoms) or rings (5- or 6-membered aromatic *mono*cycle) for the recited "C(O)Alkyl" and "aryl" within the R_{3x} substituent of "A" *as claimed*. POPR, § III.B; EX2002, ¶¶54−58. In particular, the specification incorporates by reference Jansen I, and states that Jansen I provides "representative" FAP-α inhibitors of the recited structure "A" for "use with the presently disclosed subject matter." EX1001, 8:25−9:29 (citing EX1007); EX2002, ¶¶55−56. The Jansen I "A" FAPi structures share *the same* R_{3x} substituent as the claimed "A" moiety (illustrated below), and Jansen I *defines* the alkyl and aryl groups for use in that R_{3x} substituent as follows: "alkyl groups of this invention comprise from 1 to 6 carbon atoms," and "'aryl' [is] generic for a 5- or 6-

[3] Paper 8 (April 28, 2025).

membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents." EX1007, 6:25−7:22, 22:13−43, 98:45−99:35; EX1001, Certificate of Correction, 1−2; EX2002, ¶¶56−58; POPR, § III.B:

'201 Patent **R_{3x} Substituent in "A" Moiety**	**Jansen I** **R_{3x} Substituent in "A" Moiety**
 R_{3x} = **H, CN, B(OH)$_2$, C(O)alkyl, C(O)aryl, C=CC(O)aryl, C=CS(O)$_2$aryl, CO$_2$H, SO$_3$H, SO$_2$NH$_2$, PO$_3$H$_2$, or 5-tetrazoyl**	 R_3 = **H, CN, B(OH)$_2$, C(O)alkyl, C(O)aryl, C=CC(O)aryl, C=CS(O)$_2$aryl, CO$_2$H, SO$_3$H, SO$_2$NH$_2$, PO$_3$H$_2$, or 5-tetrazoyl**

As another example, ITM and Dr. Martin assert that the meaning of "low molecular weight" "could vary based on the field of study and types of molecules" and the term has "no objective boundaries to a POSA." Pet., 40, 95−96; EX1002, ¶¶105, 184. But, as also explained in the POPR, a POSA reviewing the intrinsic record would have instead understood that the term is used in the claims according to its well-understood, ordinary meaning in the field—namely, compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons—especially given the specification's incorporation of Pomper describing a variety of "low molecular weight" targeting compounds for "imaging [and] therapy" with molecular weights up to about 1,586 Daltons. POPR, § III.C.1; EX1001, 17:45−54;

EX1006, Abstract, ¶12; EX1004, 1197−1198; EX2002, ¶¶59−64. A POSA also would have reasonably understood the boundaries of whether a compound of formula B-L-A was of "low molecular weight" or not (and thus whether or not it would fall under the scope of the claims), given that "low molecular weight" compounds are those with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons, and are thus of significantly less molecular weight than other higher molecular weight compounds like antibodies and polymers. POPR, § III.C.2; EX2002, ¶65.

2. Grounds I and II: Obviousness.

The question for obviousness is "whether the combination [of prior art] was obvious to a person with ordinary skill in the art," and includes an evaluation of whether a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention" and "would have had a reasonable expectation of success in doing so." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367−68 (Fed. Cir. 2016). Yet, because ITM and Dr. Martin use the incorrect POSA lens, § III.A, B, *supra*, their assertions that the prior art would have taught and motivated a POSA to prepare the claimed compounds with a reasonable expectation of success are weak on the merits.

For example, for obviousness Ground I ("Jansen I and/or Jansen II [] in view of Zimmerman and Pomper"), ITM and Dr. Martin assert that a POSA would have selected and combined Jansen's genus of "A" FAPis with Zimmerman's non-"A" FAPi compounds of Formula I *with* linkers "L" and radiolabeled groups "B" for modification to create the claimed B-L-A compounds with a reasonable expectation of success. Pet., 44, 46, 50−51, 56; EX1002, ¶¶113−114, 118−119, 124−128; EX2002, ¶87. However, as explained in the POPR, Zimmerman discloses FAPi compounds of *two* different formulas—Formula I with linkers "L" (the ones ITM and Dr. Martin select) and Formula II *without* linkers "L." POPR, §§ IV.A, IV.B; EX2002, ¶¶79−86; EX1009, ¶¶8–28. ITM and Dr. Martin never mention or address these compounds of Formula II *without* linkers, nor do they mention or address Zimmerman's data showing that compounds of Formula II *without* linkers exhibited overwhelmingly better FAP targeting properties. POPR, §§ IV.A, IV.B; EX2002, ¶¶84−86 EX1009, ¶185, Table 2. Thus, contrary to ITM's and Dr. Martin's assertions, Zimmerman instead teaches a POSA *towards* selecting compounds of Formula II *without* linkers "L" for further modification and development. *Id*.

As another example, for Ground II, ITM and Dr. Martin rely on Dvořáková's *high molecular weight* iBody compound, that used multiple FAP inhibitors, multiple dye units, and a higher molecular weight linker, to assert that a

POSA would have been motivated to synthesize low molecular weight versions of iBody to create the claimed *low molecular weight* B-L-A compounds by "using fewer [FAP] inhibitor and ATTO488 [dye] units and using a linker with a lower molecular weight." Pet., 61−62; EX1002, ¶140; EX2002, ¶98. Yet, as explained in the POPR, Dvořáková would have taught a POSA that iBody exhibited beneficial FAP targeting and imaging properties *because* it used multiple such moieties and a higher molecular weight linker, causing iBody to have high molecular weight. POPR, § IV.D; EX2002, ¶¶99−105; EX1008, Abstract, 8386−8388, 8391, FIG. 2 (b). Thus, a POSA would *not* have been motivated to "us[e] fewer" moieties or a different, lower molecular weight linker, Pet., 61, to arrive at the claimed low molecular weight compounds with a reasonable expectation of success, because the POSA would have expected that using fewer such moieties or a different linker could destroy the compound's beneficial properties. *Id*.

3. Ground III: Enablement.

The enablement inquiry evaluates whether "the patent's specification [] enable[s] a person skilled in the art to make and use" the full scope of the claimed invention without unreasonable or undue experimentation. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). For enablement Ground III, ITM and Dr. Martin assert that the '201 patent specification "requires a POSA to engage in an iterative, trial-and-error process,"

including "countless lengthy, sometimes challenging" undue experimentation to discover what B and L moieties "will work and what will not." Pet., 75−76, 80−81, 84; EX1002, ¶¶167−176; EX2002, ¶¶122−130. However, because ITM and Dr. Martin use the incorrect POSA lens, §§III.A, B, *supra*, their assertions that a POSA would have to perform undue or unreasonable experimentation to make and use the claimed genus of B-L-A compounds are weak on the merits.

For example, as the POPR details, ITM and Dr. Martin fail to explain why or how the specification would have required the POSA to engage in "countless lengthy, sometimes challenging" experimentation to discover what B and L moieties would work or not; indeed they fail to point to even a single allegedly inoperable embodiment. POPR, §§ VI.B.2, VI.B.3; EX2002, ¶¶127−130; Pet., 73−86; EX1002, ¶¶158−176. ITM and Dr. Martin also do not consider or address that POSAs with multiple years of training and practical experience in imaging or radiotherapeutics would have had ample knowledge and guidance, including from the multitude of columns of examples and incorporated references provided by the specification, for selecting B and L moieties for use in the claimed low molecular weight compounds of formula B-L-A. POPR, §§ VI.B.2, V.B.3; EX2002, ¶¶113−118, 124−130; EX1001, cols. 16−30, Example 1, Example 2.

4. Ground IV: Written Description.

The written description analysis evaluates whether the specification reasonably conveys to a POSA that the inventor had possession of the claimed subject matter. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006) (written description is "judged from the perspective of one of ordinary skill in the art"). For written description Ground IV, ITM and Dr. Martin assert that it would have been "readily apparent that Patent Owner did not have possession of the claimed invention" because the specification fails to "provide sufficient blaze marks" or disclosures "permitting a POSA to determine" which B and L moieties would be "suitable" for imaging/radiotherapy and have "bi-functionalization adapted to form a chemical bond with B and A," as claimed. Pet., 87−90; EX1002, ¶¶177−178; EX2002, ¶112. However, because ITM and Dr. Martin use the incorrect POSA lens, § III.A., B, *supra*, their assertions that a POSA would not have been able to determine which B and L moieties would be suitable for imaging/radiotherapy and have bi-functionalization, are weak on the merits.

For example, as the POPR explains, ITM and Dr. Martin fail to point out any "B" or "L" moieties that would not be suitable for the recited B-L-A compounds, and they again fail to point to even a single inoperative embodiment. POPR, § V.B.2; EX2002, ¶118; Pet., 87−90; EX1002, ¶¶177−178. The patent specification also provides multiple working examples of the claimed compounds,

and provides many pages of example B and L moieties for use in the claimed compounds, including two pages relating to L moieties and eight pages relating to B moieties; the specification further incorporates by reference a multitude of other references that provide even further examples of such moieties for use in the inventive compounds. POPR, §§ V.A.2, V.B.2; EX2002, ¶¶113−118; EX1001, cols. 16−30, Example 1, Example 2. Thus, POSAs with the requisite training and experience in radiotherapeutics or imaging reviewing the specification's extensive disclosures of B and L moieties would thus have readily ascertained from the specification's disclosures the B and L moieties that would be suitable in the recited compounds. EX2002, ¶¶113−118. POSAs would thus have likewise readily understood from the specification that the '201 patent inventors possessed the recited subject matter. *Id,* ¶¶113−118.

5. Ground V: Indefiniteness.

The definiteness requirement evaluates whether the patent "inform[s], with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 898−99 (2014). For indefiniteness Ground V, ITM and Dr. Martin assert that "[a] POSA would understand that" low molecular weight is a "relative term" that "could vary based on the specific field of study and types of molecules" "and has no objective

boundaries to a POSA"; thus, "the claims lack reasonable certainty and are therefore indefinite." Pet., 40, 96; EX1002, ¶¶105, 184.

However, because ITM and Dr. Martin use the incorrect POSA lens, §III.A, B, *supra*, their assertions that "low molecular weight" is a relative term with no objective boundaries to a POSA are weak on the merits. For example, as discussed above in Section III.C.1, a POSA would instead have understood that "low molecular weight" *does* have objective boundaries, and specifically means compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *Supra*.

D. ITM Extensively Relies on Dr. Martin's Conclusory Testimony, Further Showing its Unpatentability Grounds are Weak on the Merits.

As exemplified below, ITM's Petition often cites and relies on Dr. Martin's declaration specifically to support its unpatentability assertions, but Dr. Martin himself mostly parrots the language of the Petition essentially verbatim without much (if any) further explanation of his own:

Claim construction

ITM's Petition	Dr. Martin's Declaration
"**In other words, Patent Owner defined a particular nomenclature for situations where it wished to**	"**In other words, Patent Owner defined a particular nomenclature for situations where it wished to**

ITM's Petition	Dr. Martin's Declaration
specify that an alkyl group was limited to a particular length or ranges of lengths. EX1002 at ¶108. An example of this nomenclature can be found **in both claims 1 and 3,** wherein Patent Owner specified that **the R_{1x} and R_{2x} substituents can be chosen from a group that includes, for example, an alkyl chain containing between 1 and 6 carbon atoms, i.e.,** '**C_{1-6}alkyl**.' EX1001, Certificate of Correction, claims 1, 3; EX1002 at ¶109." Pet., 43.	**specify that an alkyl group was limited to a particular length or ranges of lengths.** Based on this definition, a POSA would understand the alkyl group of the —C(O)alkyl to be limited to the number of carbons designated in the term itself. For example, **in both claims 1 and 3, R_{1x} and R_{2x} substituents can be chosen from a group that includes an alkyl chain containing between 1 and 6 carbon atoms, i.e.,** '**C1-6alkyl.**' Id., Certificate of Correction, claims 1, 3." EX1002, ¶¶108−109.
"**Similarly, the definitions provided in the '201 patent explain that the term 'aryl,' identified among the several options at the R3x position in the claimed structure of the A**	"**Similarly, the definitions provided in the '201 patent explain that the term 'aryl,' identified among the several options at the R3x position in the claimed structure of the A**

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moiety, is 'an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently.' EX1001 at 42:64−67; EX1002 at ¶111. **Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C═C—C(O)aryl, and —C═C—S(O)2aryl groups likewise should not be limited to any particular length, size or substitution**. EX1002 at ¶111." Pet., 44.	**moiety, is 'an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently**.' Id. at 42:64−67. **Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C═C—C(O)aryl, and —C═C—S(O)2aryl groups likewise would have been understood by a POSA as not limited to any particular length, size or substitution**." EX1002, ¶111.

Obviousness (Grounds I and II)

ITM's Petition	Dr. Martin's Declaration
"**While neither Jansen I nor Jansen II discloses that the FAP inhibitor**	"**While neither Jansen I nor Jansen II discloses that the FAP inhibitor**

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may be attached via a linker to 'any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy,' it was well known in the art as of the earliest effective filing date to functionalize FAP inhibitors **with radiolabeled groups for optical imaging purposes and to use a linker between the two moieties**." Pet., 50.	**may be attached via a linker to 'any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy, it was well known in the art as of the earliest effective filing date to functionalize** protein targeting moieties with radiolabeled agents or optical agents for imaging and therapy purposes. Furthermore, it was known to specifically use FAP inhibitors **with radiolabeled functional groups and to provide a linker between the two moieties**." EX1002, ¶¶117−118.

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"In summary, **a POSA at the time of filing the '201 patent application would have been motivated to prepare the FAP-α inhibitor described in Jansen I and/or Jansen II**. EX1002 at ¶127. **A POSA also would have been motivated to attach the FAP-α inhibitor of Jansen I and/or Jansen II to a radiolabeled compound via a linker for diagnostic imaging based on Zimmerman and Pomper, which** teach **the advantages of low molecular weight compounds, diagnostic imaging, and therapeutic treatment of diseases, to form the compound of claim 1 of the '201 patent, with a reasonable expectation of success**." Pet., 56.	"**A POSA at the time of filing the '201 patent application would have been motivated to prepare the FAP-α inhibitor described in Jansen I and/or Jansen II**. **A POSA also would have been motivated to attach the FAP-α inhibitor of Jansen I and/or Jansen II to a radiolabeled compound via a linker for diagnostic imaging based on Zimmerman and Pomper, which** touts **the advantages of using low molecular weight compounds**, radiolabeled compounds in **diagnostic imaging, and therapeutic treatment of diseases, to form the compound of claim 1 of the '201 patent, with a reasonable expectation of success**." EX1002, ¶127.

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"[A] POSA would have readily understood how the molecular weight of Dvořáková's compounds could be lowered. Id. For example, a POSA would have recognized that a low molecular weight version of iBody 1 could be synthesized by using fewer inhibitor and ATTO488 units and using a linker with a lower molecular weight. EX1002 at ¶140. **Pomper discloses several such linkers as suitable, including, '[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms,'** are suitable. EX1006 at ¶¶102, 129; EX1002 at ¶140. And, **based on Pomper's teachings about the benefits of a low molecular**	"**A POSA would have also readily understood how the molecular weight of Dvořáková's compounds could be lowered. For example, a POSA would have recognized that a low molecular weight version of iBody 1 could be synthesized by**, for example, reducing the number of FAP-targeting and ATTO488 groups, **using a linker with a lower molecular weight, and eliminating the biotin groups. Pomper discloses several linkers with a lower molecular weight as suitable, including, '[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms.'** EX1006 at ¶¶102, 129. **Based on Pomper's teachings about**

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weight compound, a POSA would have reasonably expected a low. molecular weight version of iBody 1 to work for the desired purpose. EX1002 at ¶140. **Thus, the art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and a POSA would have had a reasonable expectation that such compounds would work for their desired purpose**. EX1002 at ¶141." Pet., 61−62.	**the benefits of a low molecular weight compound, a POSA would have reasonably expected a low molecular weight version of iBody 1 to work for the desired purpose**. **Thus, the art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and a POSA would have had a reasonable expectation that such compounds would work for their desired purpose."** EX1002, ¶¶140−141.

Enablement & Written Description (Grounds III and IV)

ITM's Petition	Dr. Martin's Declaration
"**The '201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions or why other compounds do not**." Pet., 76.	"**The '201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions, or why other compounds do not**." EX1002, ¶167.
"Moreover, **the '201 patent does not describe which features—structural or otherwise—would cause a compound to perform the two claimed functions**." Pet., 80.	"Further, **the '201 patent does not describe which features—structural or otherwise—would be needed for the compound to perform the claimed functions** for the B moiety, i.e., be 'suitable for' optical imaging, PET imaging, SPECT imaging, or radiotherapy, or for the linker moiety, i.e., 'bi-functionalization adapted to form a chemical bond with B and A.'" EX1002, ¶171.

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"**There are only two working examples and the '201 patent does not describe which features—structural or otherwise—would cause a compound to perform the two claimed functions**." Petition at 83.	"**There are only two working examples, and the '201 patent does not describe which features—structural or otherwise—would cause a compound to perform the two claimed functions.**" EX1002, ¶176.
"The patent contains **only two working examples**—XY-FAP-01 and XY-FAP-02—**and does not even describe why or how these two compounds perform the claimed functions, or why other compounds do not**." Pet., 90.	"Despite using this broad functional language, the '201 patent provides **only two working examples** falling within the scope of the claims **and does not even describe why or how these two compounds perform the claimed functions, or why other compounds do not**." EX1002, ¶178.

Indefiniteness (Ground V)

ITM's Petition	Dr. Martin's Declaration
"[T]he term 'low molecular weight' would be relative to the field of study and the type of experiments to be performed. EX1002 at ¶184. **Each of the references provided in Patent Owner's explanation are related to the field of metabolomics or the scientific study of metabolites. Id. Yet, there is no mention of metabolomics anywhere in the '201 patent specification. Id. Furthermore, the '201 patent specification specifically states that 'the injected compound is not metabolized by the body prior to excretion.'** Id.; EX1001 at 35:66−67 (emphasis added). **Therefore, these references are unrelated to the '201**	"[T]he term 'low molecular weight' would be interpreted differently by scientists in various fields. … Notably, **each of the references provided in Patent Owner's explanation is related to the field of metabolomics or the scientific study of metabolites. Yet, there is no mention of metabolomics anywhere in the '201 patent specification. Furthermore, the '201 patent specification specifically states that 'the injected compound is not metabolized by the body prior to excretion.'** EX1001 at 35:66−67 (emphasis added). **Therefore, these references are unrelated to the '201 patent, which discusses imaging and**

ITM's Petition	Dr. Martin's Declaration
patent, which discusses imaging and radiotherapeutics agents, and a POSA would not define 'low molecular weight' in the context of the '201 patent relative to the field of metabolomics." Pet., 95−96.	**radiotherapeutics agents**, further undercutting the weight a POSA would give this statement when attempting to determine the meaning of 'low molecular weight' in the '201 patent." EX1002, ¶184.
"[T]he '201 **patent specification itself discloses several examples of moiety B that have a molecular weight greater than 1,500 Da** by themselves. Id. at ¶185. **For example, embodiments of moiety B are described as including fluorescent dyes such as VivoTag-680 (now named IVISense 680) (molecular weight 1,856 g/mol), AlexaFluor790 (molecular weight about 1,750 g/mol), and IRDye 700DX (molecular**	"The **patent specification itself provides several examples** of compounds **that would have a molecular weight greater than 1,500 Da** but would otherwise fall within the scope of the claims. **For example, moiety B is described as including fluorescent dyes such as VivoTag-680 (now named IVISense 680) (molecular weight 1,856 g/mol), AlexaFluor790 (molecular weight about 1,750 g/mol), and IRDye**

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weight about 1,954 g/mol). EX1001 at 25:19−25, 26:19−24; EX1012; EX1013; EX1014. EX1002 at ¶185. **If any of these fluorescent dyes are including as moiety B in the claimed compounds, the molecular weight of the compound would well exceed the 'typical' range of about 50 to about 1,500 Da, especially when combined with the FAP-α targeting moiety, A, and the linker, L,** which would each contribute **additional weight** to the combined molecule. EX1002 at ¶185. **These contradictory disclosures further demonstrate the ambiguity** and indefiniteness **of the term 'low molecular weight.'"** Pet., 96.	**700DX (molecular weight about 1,954 g/mol)**. EX1001 at 25:19−25, 26:19−24; EX1012; EX1013; EX1014. **If any of these fluorescent dyes are included as moiety B in the claimed compounds the molecular weight of the compound would well exceed the 'typical' range of about 50 to about 1,500 Da, especially considering the addition of the FAP-α targeting moiety, A, and the linker, L**, and the **additional weight** those components would impart. **These contradictory disclosures further demonstrates the ambiguity** of the '201 patent's usage **of the term 'low molecular weight.'"** EX1002, ¶187.

Dr. Martin's testimony "adds little to the conclusory assertion[s] for which is offered to support" and thus is "entitled to little weight." *Xerox*, IPR2022-00624, Paper 9 at 15; *see also Deeper*, IPR2018-01310, Paper 7 at 26−27 ("This conclusory analysis set forth in the Petition . . . , by itself, renders Petitioner's showing insufficient. But even if we were to go beyond the Petition and also consider the cited [expert] testimony . . . , Petitioner's showing would still be insufficient because that cited testimony is itself conclusory."). Accordingly, ITM's claim construction arguments and each of its unpatentability Grounds I−V (obviousness, enablement, written description, and indefiniteness) that heavily rely on such conclusory testimony are weak on the merits.

ITM's extensive reliance on conclusory testimony from Dr. Martin also suggests that any challenge from ITM to the '201 patent is better resolved in an Article III court. *See* FAQs for Interim Processes for PTAB Workload Management, Question 21, *available at* https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management?utm_campaign=subscriptioncenter&%20utm_content=&utm_medium=email&utm_name=&utm_source=govdelivery&utm_term= (last visited Apr. 26, 2025).

IV. DISCRETIONARILY DENYING TRIAL WOULD PROTECT DOMESTIC ECONOMIC AND NATIONAL INTERESTS AGAINST THOSE OF A FOREIGN PETITIONER.

Compelling domestic economic and national interests favor the Director exercising its discretion to deny institution. Interim Processes Memo, 2. ITM has its corporate headquarters and production facilities located in Munich, Germany. EX2014. JHU, in contrast, is a premier academic and research institution located in Baltimore, Maryland, that is America's first research university and whose innovations developed here in the United States benefit the public health and welfare. EX2015, 3, 5.

As of 2021, at least 368 of JHU's numerous researchers ranked as top scholars, according to Research.com, "a leading educational platform that helps students find the best schools, academic opportunities, and career paths." EX2016; EX2017, 1. JHU is Maryland's largest private employer, with JHU "and its affiliates directly and indirectly account[ing] for more than $12.6 billion in economic output in Maryland, and 102,404 jobs. Including operations in Washington, D.C., and Florida, [JHU] estimate[s] a total economic impact of nearly $13.9 billion and more than 114,000 jobs," as of fiscal year 2019. EX2015, 3. Twenty-nine Nobel Prize winners have been associated with JHU over the years, along with MacArthur fellows, presidential honorees, National Academies members, and Academy of Arts and Sciences members. *Id.*, 7. In fiscal year 2022,

JHU had 3,692 active patents; "these active patents held by Johns Hopkins today could become lifesaving medical devices and therapeutic treatments tomorrow." *Id.*, 13.

Indeed, the challenged patent is one such patent. The challenged patent has been licensed to Neuraly Inc., Bracco S.p.A., Blue Earth Diagnostics Ltd., and Z-Alpha, Inc., who are implementing the '201 patent's novel compounds to create radiotherapeutics for use in cancer diagnostics and treatment. *See* Paper 7, 1. Not discretionarily denying ITM's petition for the reasons discussed in §§ II and III above would allow a foreign actor's interests—in the vehicle of a weak petition that harasses JHU and would tax the Board's limited resources—to trump domestic economic and national interests that are served by JHU's research and development activities that benefit patients and communities through partnerships with other businesses based on the university's patented innovations. Indeed, the patents JHU duly obtains allow JHU to collaborate with businesses and are important to facilitate JHU's ongoing innovation.

***

In sum, because ITM, *first*, relies on art and arguments that are the same or substantially the same as those previously considered by the Office, and has not shown that the Office erred in a manner material to the patentability of the challenged claims, and *second*, uses the wrong POSA lens for its unpatentability

Grounds, and further extensively relies on conclusory testimony from a declarant that does not possess the requisite skill of a POSA, its unpatentability challenges are weak on the merits. *Third*, discretionarily denying the Petition would favor domestic economic and national interests over the interests of a foreign actor who has advanced a weak petition. The Petition thus does not warrant taxing the Board's finite resources for review, and it should be discretionarily denied. *See* Interim Process Memo, 2−3.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Patent Owner's Brief In Support of Discretionary Denial complies with the type-volume limitation of 14,000 words, comprising 10,365 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

2. This Patent Owner's Brief In Support of Discretionary Denial complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Respectfully submitted,

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

I certify that the above-captioned **PATENT OWNER'S BRIEF IN SUPPORT OF DISCRETIONARY DENIAL** and associated Exhibits 2001−2018 were served in their entireties on April 28, 2025, upon the following parties via electronic mail:

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