

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.
Petitioner

v.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Patent Owner

Case PGR2022-00037
U.S. Patent 11,078,265

**PETITION FOR POST-GRANT REVIEW
OF U.S. PATENT NO. 11,078,265**

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

| | | |
|------|--|----|
| I. | INTRODUCTION | 1 |
| II. | REQUIREMENTS FOR POST-GRANT REVIEW (37 C.F.R. § 42.204) | 4 |
| A. | Grounds for Standing (37 C.F.R. § 42.204(a)) | 4 |
| B. | Identification of Challenged Claims (37 C.F.R § 42.204(b)(1))..... | 4 |
| C. | Specific Statutory Grounds (37 C.F.R. § 42.204(b)(2))..... | 4 |
| III. | BACKGROUND OF '265 PATENT | 4 |
| A. | State of the Art | 4 |
| 1. | Before April 25, 2013, the stability of a liquid antibody formulation was unpredictable, and remains so today..... | 5 |
| (a) | Physical/chemical degradation and instability | 6 |
| (b) | Aggregation and other sources of instability..... | 7 |
| (c) | Liquid antibody formulations and instability | 8 |
| 2. | There were many excipients and stability characteristics to consider when developing liquid antibody formulations..... | 9 |
| (a) | Detergents | 9 |
| (b) | Buffers and self-buffering | 10 |
| (c) | Tonicity agents..... | 13 |
| (d) | Other excipients | 14 |
| 3. | Excipient-antibody interactions are unpredictable, cannot be predicted from antibody structure, and affect stability..... | 15 |
| (a) | Antibody concentration | 16 |
| (b) | Excipient-antibody interactions..... | 16 |
| (c) | Antibody structure is not predictive of stability..... | 18 |
| (d) | Post-translational modifications | 19 |
| (e) | Product storage effects..... | 20 |
| 4. | The process of testing antibody formulations for stability is labor intensive and requires large amounts of antibody. | 21 |
| B. | The '265 Patent | 24 |
| 1. | Challenged Claims | 24 |
| 2. | The Specification | 25 |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| | | |
|------|--|----|
| 3. | Prosecution History..... | 28 |
| C. | Person of Ordinary Skill in the Art (“POSA”)..... | 33 |
| IV. | CLAIM CONSTRUCTION (37 C.F.R. § 42.204(B)(3))..... | 33 |
| A. | “wherein the formulation is stable”..... | 34 |
| 1. | “wherein the formulation is stable” encompasses at least a subgenus of formulations that are “stable following storage in a syringe for 8 weeks at 40° C,” as recited in claim 14..... | 34 |
| 2. | “wherein the formulation is stable” also encompasses a subgenus of formulations that are stable following storage at “4° C. for at least 4 months,” as indicated in Example 9. | 36 |
| B. | “liquid aqueous pharmaceutical formulation” | 37 |
| C. | “comprising” | 37 |
| V. | DISCRETIONARY DENIAL IS NOT JUSTIFIED..... | 38 |
| A. | The examiner withdrew the written description rejection after BI’s mischaracterization of the <i>Fresenius</i> patent and decision. | 39 |
| 1. | BI’s analogy to the patent in <i>Fresenius</i> was misleading. | 39 |
| (a) | The claims in <i>Fresenius</i> expressly excluded excipients and the specification limited the variety of excipients... .. | 40 |
| (b) | The ’039 patent describes the systematic testing of 89 formulations compared to an FDA-approved product. .. | 42 |
| (c) | The outcome in <i>Fresenius</i> turned on the Board’s rejection of the petitioner’s claim construction..... | 44 |
| 2. | Claims 7 and 19 do not require a specific detergent..... | 45 |
| 3. | It was material error to allow the challenged claims. | 45 |
| B. | Enablement was neither presented to, nor considered by, the Office and should not be presumed to have been considered. | 47 |
| VI. | ELIGIBILITY FOR POST-GRANT REVIEW (AIA § 3(N)(1))..... | 48 |
| A. | The provisional lacks written description for issued claim 14 and pending claim 44 (as presented on February 12, 2021). | 49 |
| B. | The provisional does not enable the full scope of issued claim 14 and pending claim 44 (as presented on February 12, 2021). | 49 |
| VII. | GROUND AND EVIDENCE (37 C.F.R. § 42.204(B)(4)–(5))..... | 50 |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| | | |
|-----|---|----|
| A. | GROUND 1: CLAIMS 7–10, 14–16, 19–22, AND 27–28 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION. | 50 |
| 1. | Claims 7 and 19..... | 51 |
| (a) | The claims encompass a broad genus of antibody formulations, recited in generic and functional terms. | 51 |
| (b) | The specification does not describe a representative number of species within the genus of formulations..... | 53 |
| (c) | The specification does not describe any “common structural feature” correlative of stability..... | 58 |
| (d) | The little known about anti-IL23p19 antibody formulations cannot bridge the disclosure gaps. | 62 |
| 2. | Claim 14 (and once-pending claim 44)..... | 62 |
| 3. | Claims 8 and 20..... | 64 |
| 4. | Claims 9 and 21..... | 66 |
| 5. | Claims 10 and 22..... | 67 |
| 6. | Claims 15 and 27..... | 68 |
| 7. | Claims 16 and 28..... | 69 |
| B. | GROUND 2: CLAIMS 7–10, 14–16, 19–22, AND 27–28 ARE UNPATENTABLE FOR LACK OF ENABLEMENT. | 70 |
| 1. | Claims 7 and 19..... | 71 |
| (a) | The breadth of the claims is vast because the claims generically recite a functionally defined genus..... | 71 |
| (b) | The stability of antibody formulations, particularly liquid ones, is unpredictable and requires testing..... | 72 |
| (c) | A POSA, regardless of their qualifications, would not be able to predict formulation stability <i>a priori</i> | 73 |
| (d) | The prior art was not developed and there was no FDA-approved product to serve as a benchmark..... | 73 |
| (e) | The nature of the invention is complex as it involves unpredictable interactions and characteristics..... | 74 |
| (f) | There is insufficient guidance in the specification for how to identify formulations that would be “stable.” | 74 |
| (g) | The specification offers three narrow examples but claims a genus encompassing millions of formulations. | 75 |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| | | |
|-------|---|----|
| (h) | The quantity of experimentation needed for a POSA to practice the full scope of the claims is enormous..... | 75 |
| 2. | Claim 14 (and once-pending claim 44)..... | 76 |
| 3. | Claims 8 and 20..... | 77 |
| 4. | Claims 9 and 21..... | 78 |
| 5. | Claims 10 and 22..... | 79 |
| 6. | Claims 15 and 27..... | 80 |
| 7. | Claims 16 and 28..... | 80 |
| VIII. | MANDATORY NOTICES (37 C.F.R. § 42.8)..... | 81 |
| A. | Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))..... | 81 |
| B. | Related Matters (37 C.F.R. § 42.8(b)(2))..... | 81 |
| C. | Lead and Back-Up Counsel (37 C.F.R. § 42.9(b)(3))..... | 81 |
| D. | Service Information (37 C.F.R. § 42.8(b)(4))..... | 82 |
| E. | Power of Attorney (37 C.F.R. § 42.10(b))..... | 82 |
| IX. | PAYMENT OF FEES (37 C.F.R. §§ 42.203 AND 42.15(A))..... | 82 |
| X. | CONCLUSION..... | 83 |

PETITIONER'S EXHIBIT LIST

| Exhibit No. | Description |
|--------------------|---|
| 1001 | Nabozny, G.H., et al., "Anti-IL-23 Antibodies," U.S. Patent No. 11,078,265 B2 (filed Apr. 25, 2013; issued Aug. 3, 2021) ("the '265 patent") |
| 1002 | Declaration of Alexander M. Klibanov, Ph.D. ("Klibanov Decl.") |
| 1003 | <i>Curriculum Vitae</i> of Alexander M. Klibanov, Ph.D. |
| 1004 | File History of U.S. Patent No. 11,078,265 ("Prosecution History") |
| 1005 | U.S. Provisional Patent Appl. No. 61/642,032 (filed on May 3, 2012) |
| 1006 | M. Manning and R. Payne, "Stable Aqueous Formulations of Adalimumab," U.S. Patent No. 10,155,039 B2 (filed Oct. 31, 2017; issued Dec. 18, 2018) |
| 1007 | Chi, E.Y., et al., "Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation," <i>Pharm. Research</i> , 20: 1325–36 (2003) |
| 1008 | A.L. Daugherty and R.J. Mersny, "Formulation and Delivery Issues for Monoclonal Antibody Therapeutics," <i>Adv. Drug Delivery</i> , 58: 686–706 (2006) |
| 1009 | Emami, F., et al., "Drying Technologies for the Stability and Bioavailability of Biopharmaceuticals," <i>Pharmaceutics</i> , 10: 1–22 (2018) |
| 1010 | Cui, Y. et al., "Monoclonal Antibodies: Formulations of Marketed Products and Recent Advances in Novel Delivery," <i>Drug Dev. & Industr. Pharmacy</i> , 43: 519–30 (2017) |
| 1011 | Capelle, M.A.H., et al., "High Throughput Screening of Protein Formulation Stability: Practical Considerations," <i>European J. of Pharm. & Biopharm.</i> , 65: 131–48 (2006) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|--------------------|--|
| 1012 | S. Frokjaer and D.E. Otzen, “Protein Drug Stability: A Formulation Challenge,” <i>Nature Reviews Drug Discovery</i> , 4: 298–306 (2005) |
| 1013 | Manning, M.C., et al., “Stability of Protein Pharmaceuticals: An Update,” <i>Pharm. Research</i> , 27: 544–75 (2010) |
| 1014 | Wang, W., et al., “Antibody Structure, Instability, and Formulation,” <i>J. Pharm. Sci.</i> , 96: 1–26 (2007) |
| 1015 | S. Nema and R.J. Brendel, “Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions,” <i>PDA J. of Pharm. Sci. & Tech.</i> , 65: 287–332 (2011) |
| 1016 | Gokarn, Y.R., et al., “Self-Buffering Antibody Formulations,” <i>J. of Pharm. Sci.</i> , 97: 3051–66 (2008) |
| 1017 | Shire, S.J., et al., “Challenges in the Development of High Protein Concentration Formulations,” <i>J. Pharm. Sci.</i> , 93: 1390–402 (2004) |
| 1018 | Karow, A.R., et al., “Buffer Capacity of Biologics—From Buffer Salts to Buffering by Antibodies,” <i>AIChE J.</i> , 29: 480–92 (2013) |
| 1019 | Label for Humira® (adalimumab), Rev. 11/2015, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125057s394lbl.pdf (last accessed April 25, 2013) |
| 1020 | Label for Humira® (adalimumab), Rev. 6/2016, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125057s397lbl.pdf (last accessed April 25, 2013) |
| 1021 | Label for Humira® (adalimumab), Rev. 10/2016, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125057s400lbl.pdf (last accessed April 25, 2013) |
| 1022 | Label for Humira® (adalimumab), Rev. 4/2017, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s401lbl.pdf (last accessed April 25, 2013) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|--------------------|---|
| 1023 | Bauer, J., et al., “Rational Optimization of a Monoclonal Antibody Improves the Aggregation Propensity and Enhances the CMC Properties Along the Entire Pharmaceutical Process Chain,” <i>MABS</i> , 12: e1787121 (2020) |
| 1024 | Bahrenburg, S., et al., “Buffer-Free Therapeutic Antibody Preparations Provide a Viable Alternative to Conventionally Buffered Solutions: From Protein Buffer Capacity Prediction to Bioprocess Applications,” <i>Biotechnology J.</i> , 10: 610–22 (2015) |
| 1025 | Goldberg, D.S., et al., “Formulation Development of Therapeutic Monoclonal Antibodies Using High-Throughput Fluorescence and Static Light Scattering Techniques: Role of conformational and Colloidal Stability,” <i>J. Pharm. Sci.</i> , 100: 1306–15 (2011) |
| 1026 | Luo, Q., et al., “Chemical Modifications in Therapeutic Protein Aggregates Generated under Different Stress Conditions,” <i>J. Biological Chem.</i> , 286: 25134–44 (2011) |
| 1027 | Shi, S., et al., “Biophysical Characterization and Stabilization of the Recombinant Albumin Fusion Protein sEphB4–HAS,” <i>J. Pharm. Sci.</i> , 101: 1969–84 (2012) |
| 1028 | Deechongkit, S., et al., “Physical and Biophysical Effects of Polysorbate 20 and 80 on Darbepoetin Alfa,” <i>J. Pharm. Sci.</i> , 98: 3200–17 (2009) |
| 1029 | Lee, H.J., et al., “Molecular Origins of Surfactant-Mediated Stabilization of Protein Drugs,” <i>Adv. Drug Delivery Reviews</i> , 63: 1160–71 (2011) |
| 1030 | Le Brun, V., et al., “A Critical Evaluation of Self-Interaction Chromatography as a Predictive Tool for the Assessment of Protein–Protein Interactions in Protein Formulation Development: A Case Study of a Therapeutic Monoclonal Antibody,” <i>European J. Pharm. & Biopharm.</i> , 75: 16–25 (2010) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|-------------|---|
| 1031 | Hartl, J., et al., “Characterizing Protein–Protein-Interaction in High-Concentration Monoclonal Antibody Systems with the Quartz Crystal Microbalance,” <i>Phys. Chem. Chem. Phys.</i> , 19: 32698–707 (2017) |
| 1032 | W. Wang, “Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals,” <i>Int’l J. Pharm.</i> , 185: 129–88 (1999) |
| 1033 | D. Shukla and B.L. Trout, “Understanding the Synergistic Effect of Arginine and Glutamic Acid Mixtures on Protein Solubility,” <i>J. Physical Chem. B</i> , 115: 11831–39 (2011) |
| 1034 | Zheng, K., et al., “The Impact of Glycosylation on Monoclonal Antibody Conformation and Stability,” <i>mAbs</i> , 3: 568–76 (2011) |
| 1035 | R.J. Sola and K. Griebenow, “Effects of Glycosylation on the Stability of Protein Pharmaceuticals,” <i>J. Pharm. Sci.</i> , 98: 1223–45 (2009) |
| 1036 | T.J. Kamerzell and C.R. Middaugh, “The Complex Inter-Relationships Between Protein Flexibility and Stability,” <i>J. Pharm. Sci.</i> , 97: 3494–517 (2008) |
| 1037 | Mahler, H.C., et al., “Protein Aggregation: Pathways, Induction Factors and Analysis,” <i>J. Pharm. Sci.</i> , 98: 2909–34 (2009) |
| 1038 | Sharma, V.K., et al., “The Formulation and Delivery of Monoclonal Antibodies,” <i>Therapeutic Monoclonal Antibodies: From Bench to Clinic</i> , 675–709 (2009) |
| 1039 | D. Otzen, “Protein-Surfactant Interactions: A Tale of Many States,” <i>Biochimica et Biophysica Acta</i> , 1814: 562–91 (2011) |
| 1040 | BIOCHEMISTRY 107-150 (Reginald H. Garrett and Charles M. Grisham eds., 2nd ed. 1999) |
| 1041 | J.Y. Zheng and L.J. Janis, “Influence of pH, Buffer Species, and Storage Temperatures on Physicochemical Stability of a Humanized Monoclonal Antibody LA298,” <i>Int’l J. Pharm.</i> , 308: 46–51 (2006) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|--------------------|---|
| 1042 | EXCIPIENT DEVELOPMENT FOR PHARMACEUTICAL, BIOTECHNOLOGY, AND DRUG DELIVERY SYSTEMS 291–307 (Ashok Katdare and Mahesh V. Chaubal eds., 2006) |
| 1043 | Hawe, A., et al., “Forced Degradation of Therapeutic Proteins,” <i>J. Pharm. Sci.</i> , 101: 895–913 (2012) |
| 1044 | Boulet-Audet, M., et al., “High-Throughput Thermal Stability Analysis of a Monoclonal Antibody by Attenuated Total Reflection FT-IR Spectroscopic Imaging,” <i>Analytical Chem.</i> , 86: 9786–93 (2014) |
| 1045 | Wong, J.J.H., et al., “Simultaneous High-Throughput Conformational and Colloidal Stability Screening Using a Fluorescent Molecular Rotor Dye, 4-(4-Dimethylamino)styryl)- <i>N</i> -Methylpyridinium Iodide (DASPMI),” <i>J. Biomolecular Screening</i> , 21: 842–50 (2016) |
| 1046 | Lahlou, A., et al., “Mechanically-Induced Aggregation of the Monoclonal Antibody Cetuximab,” <i>Annales Pharmaceutiques Françaises</i> , 67: 340–52 (2009) |
| 1047 | Label for Humira® (adalimumab), Rev. 12/2011, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125057s0276lbl.pdf (last accessed April 25, 2013) |
| 1048 | Label for Prolia® (denosumab), Rev. 6/2010, <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125320s0000lbl.pdf (last accessed April 25, 2013) |
| 1049 | Declaration of Dr. Patrick Garidel, European Patent Appl. No. 17208896.5, executed Aug. 1, 2019 |
| 1050 | Sigma-Aldrich Research Chemicals Catalog (2008–2009) |
| 1051 | Kamerzell, T.J., et al., “Protein–Excipient Interactions: Mechanisms and Biophysical Characterization Applied to Protein Formulation Development,” <i>Advanced Drug Delivery Reviews</i> , 63: 1118–59 (2011) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|--------------------|---|
| 1052 | van Berkel, P.H.C., et al., “N-Linked Glycosylation Is an Important Parameter for Optimal Selection of Cell Lines Producing Biopharmaceutical Human IgG,” <i>AChE</i> , 25: 244–51 (2009) |
| 1053 | E. Higgins, “Carbohydrate Analysis Throughout the Development of a Protein Therapeutic,” <i>Glycoconj J.</i> , 27: 211–25 (2010) |
| 1054 | A.L. Demain and P. Vaishnav, “Production of Recombinant Proteins by Microbes and Higher Organisms,” <i>Biotechnology Advances</i> , 27: 297–306 (2009) |
| 1055 | HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (R.C. Rowe et al. eds., 6th ed. 2009) |
| 1056 | Eu, B., et al., “Direct Visualization of Protein Adsorption to Primary Containers by Gold Nanoparticles,” <i>J. Pharm. Sci.</i> , 100: 1663–70 (2011) |
| 1057 | Sacha, G.A., et al., “Practical Fundamentals of Glass, Rubber, and Plastic Sterile Packaging Systems,” <i>Pharm. Dev. & Tech.</i> , 15: 6–34 (2010) |
| 1058 | M. Perkins, “Recombinant Albumin Facilitates Formulation Design of Stable Drug Products,” <i>BioPharm Int’l</i> , 25: 40–44 (2012) |
| 1059 | B.L. Erstad, “Osmolality and Osmolarity: Narrowing the Terminology Gap,” <i>Pharmacotherapy</i> , 23: 1085–86 (2003) |
| 1060 | R.G. Strickley and W.J. Lambert, “A Review of Formulations of Commercially Available Antibodies,” <i>J. Pharm. Sci.</i> , 110: 2590–608 (2021) |
| 1061 | Nony, P., et al., “Impact of Osmolality on Burning Sensations During and Immediately After Intramuscular Injection of 0.5 ml of Vaccine Suspensions in Healthy Adults,” <i>Vaccine</i> , 19: 3645–51 (2001) |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Exhibit No. | Description |
|--------------------|---|
| 1062 | Rouet, R., et al., “Stability engineering of the human antibody repertoire,” <i>FEBS Letters</i> , 588:269-277 (2014) |
| 1063 | Amendments Received Before Examination, EP Appl. No. 17208896.5, filed Nov. 28, 2018 |
| 1064 | Amended Claims with Annotations, EP Appl. No. 17208896.5, filed Nov. 28, 2018 |

I. INTRODUCTION

Petitioner Sandoz Inc. (“Petitioner”) requests post-grant review (“PGR”) of claims 7–10, 14–16, 19–22, and 27–28 of U.S. Patent No. 11,078,265 (“the ’265 patent”) (EX1001), assigned to Boehringer Ingelheim International GMBH (“BI”).

The challenged claims recite a vast genus of liquid antibody formulations “comprising” an anti-IL23p19 antibody and a generic list of excipients not limited by type or concentration (e.g., “a detergent,” “a tonicity agent,” and “optionally ... a buffer”). The challenged claims recite this genus in classically functional terms—not based on what the antibody formulation is, but based on whether it is “stable.”

Yet whether a given antibody formulation will be “stable,” and under what conditions, is an elusive and unpredictable characteristic. This is in part because, as BI itself argued during prosecution of the ’265 patent, “antibodies possess ‘unique and somewhat unpredictable solution behavior.’” EX1004, 6824 (emphasis in original) (quoting EX1014). And as BI again argued when seeking to overcome an obviousness rejection made against similar claims in a European counterpart to the ’265 patent, it would be “impossible” to predict “how or which parameters of the thousands of possible combinations would indeed be successful for the provision of a stable antibody formulation.” EX1064, 3. As BI argued to the European Patent Office in its remarks: “[T]he provision of a stable antibody formulation is – even

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

with the existing knowledge on possible parameters, excipients and working equipment – still *a full blown research program.*” *Id.*, 3 (emphasis added).

While the challenged claims broadly encompass millions, if not billions, of anti-IL23p19 antibody formulations, the nearly 200-column specification devotes a mere five columns—and at best three narrow examples—to the claimed subject matter. Such minimal disclosure falls far short of what the law requires to satisfy the written description and enablement requirements of 35 U.S.C. § 112(a).

The specification of the '265 patent does not disclose either a representative number of species or any structural features (i.e., the combination of antibody and excipients) common to members of this massive and diverse formulation genus. Rather, it would be necessary to prepare, test, and analyze individual formulations by performing stability studies—a process that is labor-intensive, time-intensive, and without shortcuts. A vast distance separates BI’s whiteboard from the reality of possessing what is encompassed by these broad, functional claim limitations.

Not only is the field of formulating antibodies highly unpredictable, but the state of the art from 2012 to 2013 was undeveloped. During that timeframe, there was no FDA-approved anti-IL23p19 antibody, let alone an FDA-approved liquid pharmaceutical formulation of it. This contrasts sharply with the PTAB decision denying institution in PGR2019-00064 (“*Fresenius*”) that BI misleadingly told the examiner was “clearly applicable” to its own claims and specification. EX1004,

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

7668. The claims at issue in *Fresenius* were significantly narrower than BI's, and the specification at issue in *Fresenius* included the results of stability testing for 89 different adalimumab formulations, analyzed after systematically varying multiple excipients and concentrations, modeling formulation-stability relationships, and comparing stability to the FDA-approved adalimumab formulation of Humira®.

It was material error to credit BI's mischaracterization of *Fresenius* and to withdraw the written description rejection without requiring BI to narrow the scope of the challenged claims. For example, despite expressly requesting that BI amend the independent claims to recite a specific detergent, the examiner allowed them *without* the requested amendment. And it was error never to reject these claims for lack of enablement, an issue first presented to the Office in this petition. These and other oversights likely occurred due to the extended length of prosecution—which spanned over five years—as well as BI's repeated practice of pursuing new claim sets after receiving a Notice of Allowance by requesting continued examination.

Petitioner challenges only the broadest claims of the '265 patent to correct these errors. PGR should therefore be instituted and the challenged claims found unpatentable for lack of written description and enablement under § 112(a).

II. REQUIREMENTS FOR POST-GRANT REVIEW (37 C.F.R. § 42.204)

A. Grounds for Standing (37 C.F.R. § 42.204(a))

The '265 patent issued on August 3, 2021. This petition is filed not later than nine months after the date of the grant of the '265 patent. 35 U.S.C. § 321(c).

As shown below (*infra* § VI) the '265 patent is eligible for PGR because it issued from an application “that contains or contained at any time . . . a claim” having an effective filing date after March 16, 2013. AIA § 3(n)(1).

Petitioner hereby certifies that it is not barred or estopped from requesting a PGR challenging these claims based on the grounds identified in the petition.

B. Identification of Challenged Claims (37 C.F.R § 42.204(b)(1))

Petitioner challenges claims 7–10, 14–16, 19–22, and 27–28.

C. Specific Statutory Grounds (37 C.F.R. § 42.204(b)(2))

| Ground | Claims | Statutory Basis |
|---------------|---------------------------|---|
| Ground 1 | 7–10, 14–16, 19–22, 27–28 | 35 U.S.C. § 112(a) Lack of Written Description |
| Ground 2 | 7–10, 14–16, 19–22, 27–28 | 35 U.S.C. § 112(a) Lack of Enablement |

III. BACKGROUND OF '265 PATENT

A. State of the Art

The state of the art from May 3, 2012 to April 25, 2013 is described below, supported by the declaration of Alexander Klibanov, Ph.D. (EX1002), cited herein.

1. Before April 25, 2013, the stability of a liquid antibody formulation was unpredictable, and remains so today.

Before April 25, 2013, which includes May 3, 2012, the art taught that “[t]he formulation of protein drugs is a difficult and time-consuming process, mainly due to the complexity of protein structure and the very specific physical and chemical properties involved.” EX1011, 131; EX1002, ¶23. One challenge associated with formulating antibodies was that they “are only marginally stable and are highly susceptible to degradation, both chemical and physical.” EX1007, 1325; EX1002, ¶¶24, 70. It was also understood that “[a]lthough antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior.” EX1014, 1. Developing stable antibody formulations was thus regarded as difficult, time-consuming, and unpredictable. EX1002, ¶¶23–27, 99–107.

As to formulation stability, the art described that “antibodies ... experience a variety of instabilities.” EX1014, 21; EX1002, ¶24. Antibodies were known to “come [with] a series of technical challenges ... to maintain sufficient stability,” particularly at high concentrations. EX1008, 686. This remains true even today. As recently as 2020, BI researchers explained that formulating “purified protein to ensure long-term storage stability and optimal routes of administration ... can be challenging because the diversity and inherent structural complexity of biologicals

and their individual interplay with excipients necessitate an individual evaluation and ‘trial-and-error’-based stabilization for the molecule of choice.” EX1023, 2.

BI’s researchers further observed that, when formulating antibodies, “a universal strategy for ... stabilization is excluded by the diversity of antibody drug candidates ... making the identification of the most appropriate additive(s) a time-consuming, resource-intensive, trial and error process.” *Id.*, 9; EX1002, ¶¶36–37.

(a) Physical/chemical degradation and instability

Antibody formulations are susceptible to physical degradation by a variety of pathways, each of which can lead to instability, including protein unfolding, undesirable adsorption to surfaces, and aggregation. EX1002, ¶¶23–26. The art taught that antibodies in particular were subject to degradative effects including oxidation, deamination, aggregation, fragmentation and other forms of chemical modification . EX1002, ¶¶25, 28–29, 32–37; EX1014, 8. It was also known that antibodies could be degraded when exposed to heat, freezing, light, pH extremes, agitation, shear-stress, metals, and organic solvents. EX1002, ¶28; EX1007, 1325.

Moreover, “[t]he conformational stability of a [monoclonal antibody], or its ability to maintain its native, folded state, can be impacted by pH, ionic strength, added excipients, and protein concentration.” EX1025, 1306; EX1002, ¶¶28, 70.

Thus, antibody formulations were known to be susceptible to instability due to multiple sources of degradation and external factors. EX1002, ¶¶28–29, 70–85.

(b) Aggregation and other sources of instability

Antibody “aggregation,” a major factor affecting antibody stability, was known to be “particularly problematic because it is encountered routinely during refolding, purification, sterilization, shipping, and storage processes.” EX1007, 1325; EX1002, ¶25. It was well-understood that “[p]rotein aggregation behaviors, such as onset, aggregation rate, and the final morphology of the aggregated state (i.e., amorphous precipitates or fibrils) ha[d] been found to depend strongly on the properties of a protein’s solution environment, such as temperature, pH, salt type, salt concentration, cosolutes, preservatives, and surfactants.” EX1007, 1325.

The challenges associated with aggregation are and remain elusive because “prevention of aggregation remain[s] largely empirical, due to a lack of insight into the molecular details of the aggregation process.” EX1012, 303; EX1002, ¶26. The difficulty of predicting whether aggregation would occur was also due to “[t]here [being] no single protein aggregation pathway but a variety of pathways, which may differ between proteins and may result in different end states.” EX1037, 2910.

It was also understood “that chemical and physical instabilities [associated with antibody formulations] are interrelated.” EX1013, 561; EX1002, ¶34 For example, “[d]eamidation ha[d] been found to produce species that are more prone to aggregate than the unmodified protein.” EX1013, 562; EX1002, ¶34. The art taught that “[d]eamidation ha[d] also been linked ... to a lower kinetic barrier for

unfolding.” EX1013, 562; EX1037, 2911; EX1002, ¶34. These interrelationships were highly unpredictable. EX1026, 25143; EX1013, 562; EX1002, ¶¶34, 70–85.

Thus, antibody formulation stability was highly unpredictable, not due only to the potential for aggregation, but to other sources of physical instability and the interrelatedness of chemical and physical instabilities. EX1002, ¶¶23–37, 68–97.

(c) Liquid antibody formulations and instability

Intravenous administration (“IV”) and subcutaneous administration (“SC”) were regarded as a conventional routes of delivering antibody therapies. EX1017, 1390; EX1017, 1390; EX1002, ¶63. Both require liquid formulation. EX1002, ¶63.

Yet “[l]iquid antibody formulations” were known to be especially “prone to oxidation, deamidation, aggregation and fragmentation” due to the presence of water. EX1008, 694; EX1002, ¶30; EX1014, 9, 12–14. Developing a stable liquid antibody formulation was therefore far from straightforward because “water is a *big problem* for stabilizing antibody-based drugs.” EX1008, 694 (emphasis added). It was reported in 2018 that “liquid formulations of proteins are more susceptible to unfavorable physiochemical degradation.” EX1009, 1; EX1002, ¶¶30–31.

Aggregation of liquid antibody formulations was known to be a significant problem at high antibody concentrations, which are typical of SC formulations. EX1002, ¶¶26, 33, 63–65; EX1017, 1391; EX1011, 133; EX1010, 519, 521.

2. There were many excipients and stability characteristics to consider when developing liquid antibody formulations.

There were a variety of excipients to consider, in combination with a range of antibody concentrations, when developing a liquid antibody pharmaceutical formulation. EX1002, ¶¶35, 38–63, 66–67, 70–85, AppxB; EX1014, 14–17; EX1038, 685–87. The categories and species of excipients are discussed below.

(a) Detergents

Detergents were known to be “[o]ne of the main excipients often used in antibody formulations.” EX1014, 16; EX1002, ¶39. Detergents (or surfactants or surface-active compounds) while “usually effective in reducing shaking/stirring-induced aggregation” were known to have a “negative effect during long-term storage.” EX1014, 16–17; EX1002, ¶39. Detergents were also known to contain residual levels of peroxides that can cause oxidation of the antibody. EX1002, ¶39.

It was known in the art that developing a liquid antibody formulation that included a detergent would involve testing various different detergents at various concentrations. EX1002, ¶¶40–44. The concentration of the detergent used could act beneficially to prevent aggregation but it could also act detrimentally to cause destabilization. *Id.*, ¶¶40–41, 43–46. Detergents, including polysorbates, were understood to have varying properties depending on their concentration in solution. *Id.* These dynamics between aggregation and stability could depend, not just on the absolute detergent concentration, but on the detergent-to-protein ratio. *Id.*, ¶46.

During the relevant timeframe, there were numerous detergents used in injectable products that had already been approved by the U.S. Food & Drug Administration (“FDA”), including: Cremophor EL, desoxycholate sodium, lecithin, polyoxyethylated fatty acid, polysorbate 80 (Tween 80), polysorbate 20 (Tween 20), PEG 40 castor oil, PEG 60 castor oil, poloxamer 188 (Pluronic F68), sodium dodecyl sulfate, and Triton X-100. EX1015, 291; EX1002, ¶47, AppxB. Still other detergents were known in the art, not limited to detergents used in FDA-approved in injectable products, and would have been considered when developing a liquid antibody formulation—e.g., alpha-tocopherol (Ex 1055, 31), cetrimide (*id.*, 152), lauric acid (*id.*, 383), myristyl alcohol (*id.*, 456). EX1002, ¶47, AppxB.

(b) Buffers and self-buffering

The challenged claims encompass the use of any buffer at any concentration. *Infra* § VII.A.1. The choice regarding which buffer and at what concentration was vast, and the consequences significant. EX1002, ¶¶48–52. In general, buffers are used in formulations to resist changes in pH. *Id.*, ¶48. For injectable products, the “[s]election of a buffer concentration (which contributes to the ionic strength of the formulation) and a buffer species is important” (EX1015, 294) and for monoclonal antibodies “different buffer species affect the physicochemical stability” (EX1051, 1122). EX1002, ¶¶48–50. It was also known that the choice of buffer could affect chemical degradation of antibodies, with different buffers having different effects

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

on the same antibody. EX1014, 16; EX1002, ¶¶48–50. It was known that the effects of different buffers, and buffer concentrations, could affect both deamidation and aggregation, and that those effects would vary depending on pH and temperature. EX1002, ¶¶48–50. Thus, it was understood that buffers used in “pharmaceutical formulation must satisfy numerous requirements.” EX1016, 3052; EX1002, ¶48.

During the relevant timeframe, there were numerous buffers and buffer systems used in FDA-approved injectable products. EX1015, 295; EX1002, ¶51, AppxB. Dual-buffering systems (using more than a single buffer in a formulation) would also have been considered, as dual-buffer systems had already been used with other FDA-approved antibody formulations like Humira®. *Id.*, ¶52, AppxB.

While the independent challenged claims make the buffer *optional*, as of 2013, the FDA had yet to license any bufferless liquid formulation of an antibody. EX1002, ¶205. And even today, only one antibody in a buffer-less formulation has been licensed by FDA, namely, adalimumab. *Id.*, ¶¶53–56; EX1060, 2592, 2601.

Although some antibodies formulated at high concentrations were known to have self-buffering activity “prediction of the buffering capacity of an antibody” was understood to be “nontrivial” and would depend on having many parameters characterized. EX1016, 3062; EX1016, 3051–52; EX1002, ¶¶53–56. Consistent with this, researchers at BI acknowledged the difficulty of predicting whether an

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

antibody would self-buffer, stating in a March 2013 publication: “The prediction of buffering power by antibodies is not straightforward.” EX1018, 489; EX1002, ¶54.

Importantly, it was also understood that self-buffering does not equate to stability. EX1002, ¶55. Knowledge of an antibody’s ability to self-buffer would not alleviate concerns about potential excipient-excipient and excipient-antibody interactions. *Infra* § VII.A.1.b. Indeed, BI’s researchers recommended that “case to case assessments” of self-buffering antibody formulations were “still advisable and extended data on the stability of self-buffering formulations [was] awaited from future studies.” EX1018, 491. BI also recognized that limitations on self-buffering formulations included “[r]estriction in the suitable pH range[,] as it needs to be covered by sufficient buffer capacity of the protein of interest” and “[p]otential instability of the protein of interest in absence of buffer excipient.” *Id.* Even in 2015, BI researchers observed there was “very little data on the quality attributes and stress stability of [antibodies] in self-buffering solution.” EX1024, 611.

Thus, self-buffering—should it exist—was not understood to be equivalent to stability, nor was it regarded as a panacea for the challenges and unpredictability generally associated with making stable antibody formulations. EX1002, ¶¶53–56.

(c) Tonicity agents

Tonicity agents are used to provide “isotonicity” to a formulation, such that it is “suitable for injection.” EX1042, 296; EX1002, ¶57. The art gives as examples of tonicity agents “polyols, salts, and amino acids.” EX1042, 296; EX1002, ¶57.

Polyols were understood to be “a class of excipients that includes sugars (e.g., mannitol, sucrose, and sorbitol), and other polyhydric alcohols (e.g., glycerol and propylene glycol)” and were used as used as stabilizing excipients and/or isotonicity agents in liquid protein formulations. EX1042, 300; EX1002, ¶59.

Salts, while useful as tonicity agents, were understood to “affect the physical stability of proteins in a variety of ways.” EX1042, 298. Indeed, the art taught that “[t]he mechanisms by which salts affect protein stability are protein specific and may vary significantly as a function of solution pH.” EX1042, 299; EX1002, ¶58.

And the amino acids histidine, glutamic acid, glycine, proline, serine, and alanine had been shown to function as tonicity agents. EX1042, 299; EX1002, ¶60.

There were a variety of tonicity agents used in antibody formulations, with varying effects. EX1002, ¶¶61–62. For example, replacing NaCl with mannitol or trehalose in a rhuMab anti-CD20 formulation affected chemical stability. EX1014, 16. Replacing NaCl with mannitol and benzyl alcohol was shown to protect against oxidation. EX1014, 16; EX1002, ¶61. And, as illustrated in one case, “sucrose has

been shown to promote agitation-induced aggregation of an IgG1 antibody.”

EX1014, 16; EX1002, ¶61. These effects were not predictable. *Id.*, ¶¶62, 70–85.

During the relevant timeframe, there were numerous tonicity agents used in injectable FDA-approved products, including for example: alanine, arginine, asparagine, aspartic acid, calcium chloride, glucose, glycerin, imidazole, inositol, lactose, magnesium chloride, magnesium sulfate, maltose, mannitol, potassium chloride, proline, serine, sodium chloride, sodium succinate, sodium sulfate, sodium cholesteryl sulfate, sorbitol, sucrose, threonine, and trehalose. EX1015, 296; EX1002, ¶62, AppxB. Other tonicity agents were also known in the art and would have been considered. EX1002, ¶¶57–62. It was understood that developing a liquid antibody formulation that included a tonicity agent would involve testing different tonicity agents across a range of concentrations. *Id.*; EX1013, 557.

(d) Other excipients

Other excipients, all of which had been used in antibody formulations, were understood to affect stability. EX1002, ¶¶66–67. For example, the art taught that “[a] rather wide spectrum of agents can reduce protein aggregation rate: urea, guanidinium chloride, amino acids (in particular glycine and arginine), various sugars, polyalcohols, polymers (including polyethylene glycol and dextrans).” EX1008, 693; EX1002, ¶66. The art noted that antibody formulations “commonly used antioxidants, such as thiosulfate and methionine, are effective in inhibiting

antibody oxidation.” EX1014, 16. The art also explained that preservatives such as benzyl alcohol, methylparaben, and propylparaben, had been used as stabilizers in antibody formulations. *Id.*, 17. Chelators (e.g., EDTA) had shown an ability to slow degradation of monoclonal antibodies. EX1013, 548–49; EX1002, ¶¶66.

Each excipient would have been understood to affect the stability of a liquid antibody formulation to which it was added, including as to the excipient-excipient and excipient-antibody interactions discussed below. EX1002, ¶¶67, 70–85.

3. Excipient-antibody interactions are unpredictable, cannot be predicted from antibody structure, and affect stability.

It was also understood that the physical and chemical properties of antibody formulations would be unpredictable due to interactions among components of the formulation, the antibody, and the storage container over time. EX1002, ¶¶70–98.

The effects of excipients on an antibody’s stability in a liquid formulation result from physical and chemical interactions that arise from: (i) the formulation’s excipients and the antibody; and (ii) excipient-excipient interactions, including those discussed above (*supra* § III.A.2). EX1002, ¶¶70–85. The art taught that “[o]ptimization of each of these [formulation] parameters is often complicated *due to the interactions between them.*” EX1025, 1306 (emphasis added); EX1002, ¶70.

Thus, it was known that the behavior and properties of any component of a formulation would be interrelated with the behavior and properties of the other components of the formulation, including the antibody. *Id.*, ¶¶70–85. It was also

known that excipient-excipient interactions and excipient-antibody interactions were unpredictable, requiring empirical analysis to determine whether a given formulation would be stable under a given set of conditions. *Id.*, ¶¶85, 99.

(a) Antibody concentration

It was known that antibody formulation stability was significantly affected by the concentration of the antibody in formulation. EX1002, ¶¶26–28, 33, 63–65; EX1014, 14–15 (“[C]oncentration-dependent protein aggregation is the greatest challenge to developing high-concentration protein formulations.”); EX1017, 1393; EX1002, ¶¶63–65. It was known that high antibody concentrations could result in aggregation and thereby cause instability. EX1002, ¶¶ 26–28, 63–65. Another challenge with high-antibody-concentration formulations was viscosity, which could complicate administration by injection. *Id.*, ¶¶64–65; EX1017, 1397.

(b) Excipient-antibody interactions

Maintaining an antibody in the appropriate shape and conformation in a formulation involved balancing interactions among the antibody and excipients. EX1002, ¶¶70–85; EX1032, 145 (“Many factors can disrupt this delicate balance.”).

It was known that the conformational stability of an antibody (meaning its ability to maintain its native, folded state) “can be impacted by pH, ionic strength, added excipients, and protein concentration.” EX1025, 1306. This made achieving

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

formulation stability highly unpredictable, even when armed with the antibody's primary, secondary, tertiary, and quaternary structures. EX1002, ¶¶70–85.

Many excipient-antibody interactions were known to affect formulation stability. For example, it was known that polysorbate 20 and 80, both detergents used in antibody formulations, could bind to proteins and effect changes in protein secondary and tertiary structures. EX1002, ¶¶73, 76–77; EX1028, 3214; EX1029, 1164. As another example, in 2010, researchers at BI investigated the influence of buffer composition, salt concentration, and amino acids on a monoclonal antibody. EX1030, 17–20. In that study, BI's own researchers observed that: "The presence of buffer can be essential in order to stabilize protein formulations, since buffer inhibits a change of pH in solution, which is a crucial factor for protein stability." EX1030, 20. BI acknowledged, after 2013, that the effects of interactions between components of, and a protein within, a formulation are unpredictable, explaining: "Understanding protein-excipient interactions is a challenge." EX1031, 32698. BI also reiterated that the ways in which different buffers can interact with antibodies vary widely based on the particular buffer used and its concentration. *Id.*, 32699.

These interactions were known to affect stability significantly depending on the concentration of a given excipient as well as depending on temperature and ionic strength of the solution. EX1002, ¶¶70–85. For example, the art observed: "[I]t is important to understand the impact of excipient combinations on stability,"

in part, because “[w]hen excipient combinations are used, the stability is difficult to predict because the excipients may not always result in additive effects due to different modes of interaction.” EX1025, 1310. Thus, merely identifying a few specific combinations of excipients and antibody at specific concentrations that yield a stable formulation would not predict whether *different* combinations of excipients, at different concentrations, having their *own* unique excipient-excipient and excipient-antibody interactions, would also yield stable formulations because the interactions are unpredictable and require testing. EX1002, ¶¶24, 29, 36–37, 85, 99. Accordingly, developing stable liquid antibody formulations was not a straightforward task, but a highly unpredictable, trial-and-error endeavor. *Id.*

(c) Antibody structure is not predictive of stability.

An antibody’s primary, tertiary, and quaternary structures are not sufficient to predict an excipient’s effects on stability in a liquid formulation. EX1002, ¶¶87–93. Even though only a portion of an antibody’s primary sequence differs significantly from another antibody within the same class, a formulation that is stable for one antibody is not predictive of whether the same combination of excipients would also be stable for another antibody. *Id.*, ¶¶29, 36. Rather, “[e]ach protein is unique both chemically and physically and therefore will exhibit unique stability behavior.” EX1007, 1326; *see also* EX1011, 132 (“Practical experience has shown that there are no general stabilization approaches for proteins and that

for each protein a customized formulation needs to be developed.”); EX1002, ¶36. Moreover, having a few stable liquid formulations for a given antibody would not be enough to identify *all* stable formulations for the same antibody. EX1002, ¶¶36, 249. Rather, empirical stability testing is required to assess stability in part because each degradation pathway could be affected by, e.g., antibody polypeptide-chain flexibility and unpredictable alterations in the antibody’s structure. *Id.*, ¶¶88–93.

Thus, it was understood that, in an antibody formulation, the antibody alone is not solely responsible for formulation stability, even within a target pH range. *Id.*, ¶¶68–98. The stability profile was understood to vary significantly based on the specific combination of formulation components, including excipients, and stability testing would be required to determine that profile. *Id.*, ¶¶36–37, 68–99.

(d) Post-translational modifications

It was also known that an antibody’s post-translation modifications could significantly affect its stability. EX1002, ¶91. Post-translational modifications, such as glycosylation, were known to have effects on antibody stability in liquid pharmaceutical formulations. EX1014, 8; EX1034, 568; EX1002, ¶¶86–93.

For example, the art reported that “[c]hanges in a product’s glycosylation pattern may significantly alter its intrinsic properties and stability, thereby adding challenges for downstream process development.” EX1034, 568; *see also* EX1035, 1226, 1237. It was also known that an antibody’s glycosylation status could vary

depending on cell culture conditions and cell type used to express the antibody. EX1052, 244–45, 248; EX1053, 211. Antibodies produced in prokaryotic cells would not be expected to be glycosylated at all and the glycosylation profile of antibodies expressed in mammalian cells was often heterogeneous. EX1054, 299; EX1002, ¶93. Glycosylation status could even vary from one mammalian cell type to another, even within clones generated from the *same* host cell. EX1002, ¶93.

Thus, it was understood that even among antibodies sharing the same primary amino acid sequence, there could be significant differences in post-translational modification that could affect formulation stability. *Id.*, ¶¶87–93.

(e) Product storage effects

Antibodies were also known to encounter issues related to “adsorption” on the surface of the product storage container. *Id.*, ¶¶94-98; EX1013, 555. The art taught: “Surface adsorption can significantly reduce the antibody concentration in a solution.” EX1014, 11. Not only was adsorption to containers known to lead to loss of protein in solution, but “[a]dsorption itself is a physical instability, as it changes the physical state of the protein”—meaning the formulation could be destabilized by storage container materials. EX1013, 555. Adsorption presented significant issues with instability for liquid antibody formulations having both relatively high *and* relatively low antibody concentrations. EX1002, ¶¶94–98.

It was also known that “[a] variety of leached materials from rubber, glass and metal components can cause instability in prefilled syringes, including issues with silicone oil.” EX1013, 556; EX1002, ¶97. By 2013, it was understood that “[s]ilicone oil ... ha[d] ... been implicated in aggregation of monoclonal antibodies in pre-filled syringes.” EX1029, 1163. And while “[a]n extensive study on the effect of silicone oil on protein aggregation found that high concentrations were needed to have an effect[,] ... the problem persists.” EX1013, 556; EX1002, ¶97.

4. The process of testing antibody formulations for stability is labor intensive and requires large amounts of antibody.

The stability of an antibody formulation is not predictable *a priori* and must be determined experimentally in each instance, with testing performed under the specific conditions for which a stable formulation is sought. EX1002, ¶¶99–107.

The art recognized that “[e]xtensive studies are required to fully characterize the physical and chemical properties of a new biopharmaceutical drug.” EX1011, 132. As part of those characterizations, antibody formulations would be tested in an attempt to uncover, to the extent possible, the important excipient-antibody and excipient-excipient interactions. EX1025, 1307. Yet it was still possible that “[a] particular formulation may have no immediately apparent effect on physical or chemical stability,” and such effect would only manifest over time. EX1011, 133.

Thus, to determine stability, liquid antibody formulations would need to be subjected to stability testing. EX1011, 133; EX1002, ¶99. “[A]ccelerated stability

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

studies [were] usually conducted.” EX1014, 17. It was understood, however, that accelerated studies were not predictive of stability under other conditions. EX1002, ¶¶100–105. Rather, different conditions (e.g., different temperatures, durations, light intensities, mechanical stresses, etc.) could affect aggregation, oxidation, deamidation, isomerization, and other degradative modifications differently. *Id.*, ¶¶101–103. Consequently, each set of conditions would have be tested. *Id.*

The art recognized that “[t]he formulation of protein drugs is a difficult and time-consuming process” (EX1011, 131; EX1025, 1306) and that screening of liquid antibody formulations for stability “require[d] large amounts of protein.” EX1025, 1306; EX1002, ¶104. Researchers had tried to develop high-throughput methods for investigating multiple different antibody formulations. EX1002, ¶105. But such high-throughput techniques have, to this day, never come to fruition in terms of shortening the time needed to assess antibody formulations for stability. *Id.*, ¶106. As late as 2016, BI’s own researchers noted that the “need for a more high-throughput method of conformational stability screening [had] been partially met,” but suffered from “extensive background interference from surfactants.” EX1045, 842–43; EX1002, ¶106. Regardless, even after using such supposed high-throughput techniques, analyzing a formulation would still have required “further evaluate[ing] [identified formulations] using traditional stability studies.” EX1025, 1314; EX1002, ¶105. Thus, despite focused attempts to accelerate the formulation

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

screening process, the art was, and remains today, dependent upon extensive stability testing on a formulation-by-formulation basis. EX1002, ¶¶37, 94–107.

This testing required the production of large quantities of antibody, which is itself a complex process. *Id.*, ¶37, 97–107. This would be particularly burdensome when testing formulations having a relatively high antibody concentration. *Id.*

With regard to the stability assays themselves, each formulation would be tested for stability over multiple weeks, with testing performed for various lengths of time, at multiple different temperatures, and under a range physical conditions (e.g., light intensity, mechanical stress, agitation, packaging). *Id.*, ¶¶100, 107. Each tested formulation would then need to be individually analyzed (e.g., using SDS, IEF, HPLC, MS, etc.) to determine whether or not it was stable under each set of conditions and, if so, how stable. *Id.*, ¶107. This process of preparing, testing, and analyzing each formulation would then often be repeated to ensure that there was confidence that the results of the testing were significant and not anomalous. *Id.*

Thus, from start to finish, each formulation would be tested under specific conditions, the process for which would typically take at least several weeks, if not months, per formulation, typically followed by months of initial, intermediate, and real-time testing. *Id.* There was not then—nor is there today—any means to reduce the significant amount of time, labor, and resources needed to perform this type of

stability testing. *Id.*, ¶¶103–107. As a consequence, the process of testing even one antibody formulation for stability would be both time-intensive and laborious. *Id.*

B. The '265 Patent

The '265 patent issued from a “transitional” application, U.S. Application No. 13/870,061 (“the '061 application”). EX1001, Item (21). The '061 application was filed April 25, 2013, and claims priority to U.S. Provisional Application No. 61/642,032, filed May 3, 2012. EX1001, Item (60); *see also* EX1002, ¶3. The '265 patent states that it relates to “anti-IL-23p19 binding compounds, in particular new humanized anti-IL-23p19 antibodies, pharmaceutical compositions and therapeutic and diagnostic methods and compositions for using the same.” EX1001, Abstract.

1. Challenged Claims

The challenged claims recite a broad genus of formulations comprising an anti-IL23p19 antibody, namely: “[a] liquid aqueous pharmaceutical formulation *comprising* (a) an anti-IL23p19 antibody ..., (b) *a detergent*, and (c) *a tonicity agent*, wherein the anti-IL23p19 antibody comprises a light chain amino acid sequence shown as SEQ ID NO:174 and a heavy chain amino acid sequence shown as SEQ ID NO:176, wherein the formulation is *stable*, isotonic, has a pH *in the range of 5.5 to 6.5*, and wherein the formulation *optionally* comprises a buffer.” EX1001, 189:62–190:28, 190:60–67 (emphasis added). The “anti-IL23p19 antibody” that “comprises a light chain amino acid sequence shown as SEQ ID

NO:174 and a heavy chain amino acid sequence shown as SEQ ID NO:176” is referred to in the specification as “Antibody A,” also used herein. EX1002, ¶110.

2. The Specification

In contrast to the broad scope of the claims, the corresponding disclosure is extremely limited. In a specification spanning almost 200 columns, essentially only columns 89 through 94 discuss formulating anti-IL-23p19 antibodies—of which only about three columns are focused on “Pharmaceutical Compositions.” EX1001, 92:22–94:36 (Examples 11 and 12); EX1002, ¶126–134. The vast majority of the patent is focused on the anti-IL-23p19 antibodies themselves. EX1002, ¶¶118–119.

While the clear majority of the specification does not discuss anti-IL-23p19 antibody *formulations*, “Example 11” lists three “[p]harmaceutical [c]ompositions” comprising Antibody A and particular excipients. EX1001, 92:22–94:12; EX1002, ¶¶126–129. Example 11 identifies the formulation components and concentrations for each component for “Formulation 1,” “Formulation 2,” and “Formulation 3.” EX1001, 92:29–42, 92:56–93:9, 93:26–36; *see also* EX1002, ¶¶126–127, 130.¹

“**Formulation 1**” is identified in Example 11 as having 10 mg/ml anti-IL-23p19 antibody, 25 mM succinate buffer (the buffer), 125 mM sodium chloride

¹ During prosecution of the European counterpart to the ’265 patent, BI stated that Formulations 2 and 3 contain Antibody A. EX1049, 1; EX1002, ¶130.

(the tonicity agent), and 0.20 g/L polysorbate 20 (the detergent). EX1001, 92:28–55; EX1002, ¶¶127–128. Example 11 states: “The pH of formulation 1 is typically in the range of pH 6.0 to 7.0, for example pH 6.5. This formulation is particularly suitable for intravenous administration.” EX1001, 92:44–46.

Assuming that Formulation 1 is “stable” and has a pH between 5.5 and 6.5, Formulation 1 is within the scope of challenged claims 19–22 and 27–28. EX1002, ¶133. Formulation 1 is not within the scope of challenged claims 7–10 and 14–16 because those claims require an anti-IL-23p19 antibody at a concentration of “90 mg/ml,” which Formulation 1 lacks. EX1002, ¶133.

“**Formulation 2**” is identified in Example 11 as having 90 mg/ml anti-IL-23p19 antibody, 4.4 mM succinate buffer (the buffer), 225 mM sorbitol (the tonicity agent), and 0.20 g/L polysorbate 20 (the detergent). EX1001, 92:56–93:25; EX1002, ¶127. Example 11 states: “The pH of formulation 2 is typically in the range of pH 5.5 to 6.5 This formulation is particularly suitable for subcutaneous administration.” EX1001, 93:10–12.

Assuming that Formulation 2 is “stable” and has a pH between 5.5 and 6.1, Formulation 2 is within the scope of the challenged claims. EX1002, ¶134.

“**Formulation 3**” is identified in Example 11 as having 90 mg/ml anti-IL-23p19 antibody, 240 mM sorbitol (the tonicity agent), and 0.20 g/L polysorbate 20 (the detergent). EX1001, 93:26–94:12; EX1002, ¶127. Example 11 states: “The pH

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

of formulation 3 is typically in the range of pH 5.5 to 6.5 This formulation is particularly suitable for subcutaneous administration.” EX1001, 94:1–4.

Assuming that Formulation 3 is “stable” and has a pH between 5.5 and 6.1, Formulation 3 is within the scope of challenged claims 7–9, 14–16, 19–21, and 27–28. EX1002, ¶135. Formulation 3 is not within the scope of claims 10 and 22 because those claims require a buffer, which Formulation 3 lacks. *Id.*, ¶135.

“**Example 9**” discloses that anti-IL-23p19 “[p]roteins were resuspended in a final buffer containing 20 mM Sodium Citrate and 115 mM NaCl, pH 6.0 and are stable at 4° C. for at least 4 months and with solubility up to 100 mg/ml in this buffer.” EX1001, 89:62–90:55; EX1002, ¶137. Example 9 does not refer to the re-suspended protein as a “pharmaceutical formulation.” EX1001, 89:62–90:55; EX1002, ¶¶138–139. But even if Example 9 were considered a pharmaceutical formulation, and even if it were considered “stable,” it still does not fall within the scope of any challenged claim because it lacks a “detergent.” EX1002, ¶139.

Despite the challenged claims encompassing a broad genus of formulations using functional limitations, the specification does not disclose or exemplify (in language, through data, or by example) any other detergents, tonicity agents, or buffers, either as to type or concentration. EX1002, ¶¶120–125. As shown above, certain of the examples do not fall within the scope of certain challenged claims. Indeed, Example 9 is not within the scope of *any* challenged claim. *Id.*, ¶138–139.

Example 12 does not disclose any distinct antibody formulations, but lists the results of a single accelerated stability test for Formulations 2 and 3 “stored at 40° C. for 8 weeks in a syringe.” EX1001, 94:14–36; EX1002, ¶¶130–132.

3. Prosecution History

Beginning with the first rejection issued on May 6, 2015, BI faced a series of obviousness rejections (e.g., EX1004, 6801–6816). In response, BI argued that the claimed formulations would not have been obvious, for example, because: “[T]he identification of suitable formulation conditions for a specific monoclonal antibody remains challenging and cannot be determined from its amino acid sequence.” EX1062, 271; EX1004, 6824; EX1002, ¶277. In support of this assertion, BI cited the publication “Wang et al., J. Pharm Sci. 96(1): 1-26 (2007)” (“Wang 2007”) (EX1014, 1) for the proposition that “antibodies possess ‘*unique* and somewhat *unpredictable* solution behavior.’” EX1004, 6824 (emphasis in the original).

A few months later, on November 28, 2018, BI emphasized this point in defense of substantially similar claims in a European counterpart sharing the same specification as the ’265 patent. EX1002, ¶145. In Europe, BI cited Wang 2007 to argue that making stable antibody formulations is a highly unpredictable endeavor:

Antibodies can be instable both for physical and chemical reasons. Physical reasons can be e.g. denaturation, aggregation or surface adsorption. Chemical instabilities can be e.g. disulfide formulation/exchange, no-reducible cross-linking,

deamidation, isomerization, oxidation, formation of acidic or basic species, C-terminal clipping, fragmentation and the Maillard reaction It becomes immediately clear that there are a whole lot of different parameters which can and will affect the stability of an antibody formulation. Just as one example: it might be considered to be obvious to change one buffer against another buffer – however, it is immediately apparent from reading this review by [Wang 2007], that this would have various effects. This then would have to be counter-acted by other excipients, but could also be counter-acted by e.g. changing the pH of the formulation, or the protein concentration, or, by addition, or deletion of preservatives, or the choice of processing equipment, or the choice of the product containers or the choice of the shaking or shearing which takes place during formulation procedures, or any combination of the above. Every parameter which is changed will in all likelihood have an effect which might or might not make further changes necessary. *Therefore, any prediction with any reasonable expectation of success how or which parameters of the thousands of possible combinations would indeed be successful for the provision of a stable antibody formulation, is impossible. Therefore, the provision of a stable antibody formulation is – even with the existing knowledge on possible parameters, excipients and working equipment – still a full blown research program.*

EX1063, 3 (emphasis added).²

In the context of prosecution of the '265 patent in the United States, BI eventually overcame the obviousness rejection by amending then-pending claim 1 to include the limitation “the osmolarity of said pharmaceutical composition is 300 +/- 30 mOsmol/kg.” EX1004, 7047–48. After receiving a Notice of Allowance, BI then filed multiple Requests for Continued Examination (“RCE”) adding, among other claims, claims 37 and 49, which issued as claims 7 and 19 of the '265 patent. EX1004, 7247–7255. Some of these claims, including claim 44 (issued as claim 14) added the limitation that the “liquid aqueous pharmaceutical formulation of claim 37 ... is stable following storage in a syringe for 8 weeks at 40°C.” *Id.*, 7254.

The examiner rejected these new claims for lack of written description. *See, e.g.*, EX1004, 7283–7284. In response, BI argued that its claims and specification were analogous to the claims and specification of the patent in *Fresenius Kabi*

² The Federal Circuit has recognized the relevance of statements made by the patentee in the context of prosecuting foreign counterparts. *See, e.g., Tanabe Seiyaku Co. v. U.S. Int’l Trade Comm’n*, 109 F.3d 726, 733 (Fed. Cir. 1997).

BI’s statements about Wang 2007 are admissions and—in the context of this challenge—also statements against interest. Fed. R. Evid. 801(d)(2), 804(b)(3).

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

USA LLC v. Coherus Bioscience, Inc., PGR2019-00064, Paper 10 (P.T.A.B. Mar. 19, 2020)—U.S. Patent No. 10,155,039 (“the ’039 patent”). EX1004, 7379–7380.

Citing *Fresenius*, BI argued: “[T]his decision found a similar claim with only one exemplified embodiment in the specification possessed sufficient written description, even though the claim arguably encompassed ‘millions of possible species.’” EX1004, 7379–7380 (quoting *id.*, 7395). As shown below, however, the claims and specification of the ’039 patent are vastly different from the claims and specification of the ’265 patent. *Infra* § V.A.1. Moreover, the phrase “millions of possible species” in the *Fresenius* decision was not a quote from the *Board’s* own analysis in the decision, but a quote from the *petitioner’s* argument. EX1004, 7395.

BI also provided the examiner with a table, not present in the ’265 patent’s specification, which BI argued: “[S]ummarizes the information from Examples 9, 11, and 12 of the specification, which show that the claimed pH, osmolality, and stability can be achieved using the recited components” EX1004, 7380.

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| | Formulation #1 | Formulation #2 | Formulation #3 | Example 9 |
|--------------------------|-----------------------|-----------------------|-----------------------|------------------|
| Buffer | Succinate | Succinate | None | Citrate |
| Tonicity Modifier | NaCl | Sorbitol | Sorbitol | NaCl |
| Surfactant | PS20 | PS20 | PS20 | No Surfactant |
| pH | 6.0-7.0(6.5) | 5.5-6.5(5.8) | 5.5-6.5(5.8) | 6.0 |
| Osmolarity | Isotonic | Isotonic | Isotonic | Isotonic |
| Stability | Stable | Stable | Stable | Stable |

EX1004, 7380.

After the examiner maintained the rejection, an examiner interview was conducted on January 22, 2021. The examiner interview summary noted that “[a] discussion was held regarding the 112(a) rejection over claims 37 and 49” and “[t]he Attorney explained the relevancy of PGR-2019-00064 to the instant case.” EX1004, 7656. The summary also notes: “The Attorney stated that examples 9, 11 and 12 provide examples of *various formulations* that fall within the scope of the claims and have the claimed functional characteristics.” *Id.* (emphasis added). The summary notes: “The Attorney stated that anti-IL-23p19 antibody recited in the claims is self-buffering, and this characteristic contributes to the stability of the antibody *in the various formulations.*” *Id.* (emphasis added). And the summary concludes with noting: “The Attorney proposed amending the claims to state that

the formulation includes a tonifier and a buffer” and that “[t]he Examiner also suggested amending the claims to recite the specific detergent (polysorbate).” *Id.*

BI subsequently amended claims 37 and 49 to include the limitations “and (c) a tonicity agent,” and “wherein the formulation optionally comprises a buffer.” *Id.*, 7661–62. These amendments resulted in a Notice of Allowance on March 24, 2021—five years and ten months after the first office action. *Id.*, 7678–85.

Despite being found allowable, claims 37 and 49 (issued as claims 7 and 19) still did not recite the specific detergent—as the examiner had requested during the interview—and the “buffer” was only identified as “optional[.]” *Id.*, 7661–62.

C. Person of Ordinary Skill in the Art (“POSA”)

A POSA tasked with developing pharmaceutical formulations of antibodies, such as those claimed in the ’265 patent, would have had an advanced degree in biology, biochemistry, pharmaceuticals, or a related discipline. EX1002, ¶21.

A POSA would also have had at least two years of experience in the development or manufacture of therapeutic protein formulations. *Id.*, ¶21. A higher level of education could substitute for less experience or vice versa. *Id.*

IV. CLAIM CONSTRUCTION (37 C.F.R. § 42.204(b)(3))

The applicable claim construction standard is articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). 37 C.F.R. § 42.200(b).

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

Under 37 C.F.R. § 42.204(b)(3), Petitioner identifies how the challenged claims are to be construed without waiver of any argument that the challenged claims are unpatentable based on arguments and evidence supported by the record, should the Board adopt any construction different from those proposed below.

A. “wherein the formulation is stable”

All of the challenged claims require a pharmaceutical formulation that is “stable.” EX1002, ¶¶160–161. The ’265 patent does not define the term “stable.” But claim 14 further recites that “stable” encompasses formulations that are “stable following storage in a syringe for 8 weeks at 40° C.” EX1001, 190:43–45.

1. “wherein the formulation is stable” encompasses at least a subgenus of formulations that are “stable following storage in a syringe for 8 weeks at 40° C,” as recited in claim 14.

Claim 14 depends from claim 7. Because independent claims are presumed to be broader than, and encompass, the subject matter in dependent claims, at least claim 7 must be construed to encompass stability under the conditions recited in claim 14. *Phillips*, 415 F.3d at 1314–15 (citing *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004)). “By definition, an independent claim is broader than a claim that depends from it, so if a dependent claim reads on a particular embodiment of the claimed invention, the corresponding independent claim must cover that embodiment as well.” *Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022). This is so because, “[o]therwise, the

dependent claims would have no scope and thus be meaningless.” *Id.* Thus, the term “stable” in claim 7 should be construed to encompass at least a subgenus of formulations that are “stable following storage in a syringe for 8 weeks at 40° C.”

Independent claim 19 mirrors claim 7, except that claim 19 does not specify a concentration of Antibody A. Owing to this similarity, usage of the term “stable” in claim 7 relative to dependent claims 14 also informs the meaning of “stable” in claim 19. *Phillips*, 415 F.3d at 1314 (“Other claims of the patent in question ... can also be valuable sources of enlightenment as to the meaning of a claim term.”).

Consistent with this claim differentiation, the specification states that “the pharmaceutical compositions disclosed herein” are “stable ... for example when stored for 8 weeks at 40° C.” EX1001, 84:20–26. Additionally, during prosecution BI represented to the examiner that Example 12 “show[s] that the claimed pH, osmolality, and *stability* can be achieved using the recited components.” EX1004, 7380 (emphasis added). Example 12 provides the results of accelerated stability testing when the “compositions are stored at 40° C. for 8 weeks in a syringe in the case of formulations 2 and 3.” EX1001, 94:14–36; EX1002, ¶130–132, 164.

Thus, the specification and prosecution history confirm that “stable”—as recited in claims 7 and 19—should be construed to encompass at least a subgenus of formulations that are stable following storage in a syringe for 8 weeks at 40° C.

2. **“wherein the formulation is stable” also encompasses a subgenus of formulations that are stable following storage at “4° C. for at least 4 months,” as indicated in Example 9.**

The scope of the term “stable” is also informed by Examples 9, 11, and 12 of the '265 patent. During prosecution, BI represented to the examiner that Examples 9, 11, and 12 “show that the claimed pH, osmolality, and *stability* can be achieved using the recited components.” EX1004, 7380 (emphasis added). While the protein solution of Example 9 does not contain a detergent, and thus falls outside the scope of the challenged claims, BI’s prosecution statements are evidence that BI intended for “stable” to include stability under the conditions of Example 9. *Phillips*, 415 F.3d at 1317 (“Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.”). Example 9 discloses that the antibody showed minimal aggregation after storage at “4° C. for at least 4 months.” EX1001, 90:51–91:10, Tbl. 18. Thus, “stable,” as recited in claims 7 and 19, should further be construed to encompass a second subgenus of formulations that are stable following storage at “4° C. for at least 4 months,” as BI argued.

This intrinsic evidence is consistent with how a POSA would understand the term “stable” as used in the context of the challenged claims. EX1002, ¶¶163–166.

In sum, the term “stable” should be construed to encompass a subgenus of formulations that are stable under conditions of dependent claim 14 (“following storage in a syringe for 8 weeks at 40° C”). Consistent with BI’s statements during

prosecution, “stable” should also be construed to encompass a second subgenus of formulations that are stable following storage at “4° C. for at least 4 months.”

B. “liquid aqueous pharmaceutical formulation”

The preambles of claims 7 and 19 recite a “liquid aqueous pharmaceutical formulation comprising ...” EX1001, 189:62–189:63, 190:60–61. The body of both claims recite “wherein *the formulation* is stable, isotonic, has a pH in the range of 5.5 to 6.5.” EX1001, 189:63–190:27, 190:61–66 (emphasis added). The preambles thus provide antecedent basis for limitations in the body of the claims, making them limiting. *Eaton Corp. v. Rockwell Int’l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003). The preambles also “recite[] essential structure that is important to the invention or necessary to give meaning to the claim,” confirming that they are limiting. *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006).

C. “comprising”

Independent claims 7 and 19 recite the term “comprising” as a transition between the preamble and the body of each claim. “‘Comprising’ is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.” *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also In re Davis*, 80 U.S.P.Q. 448, 450 (B.P.A.I. 1948) (“comprising” leaves the “claim open for the inclusion of unspecified ingredients even in major amounts”).

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

This is consistent with how a POSA would understand the claims, because a POSA would consider additional excipients—not limited to those recited—if asked to design formulations meeting the requirements of the claims. EX1002, ¶170.

V. DISCRETIONARY DENIAL IS NOT JUSTIFIED.

There is no basis to discretionarily deny institution. This is the first petition filed by the Petitioner challenging any claim of the '265 patent and there is no co-pending litigation that would reach a result before the Board issues a final decision.

The Board applies a two-part framework to determine whether denial under § 325(d) is appropriate. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential). As shown in detail below, both factors show that § 325(d) denial is not warranted.

And none of the factors in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017) (precedential), favor denial of institution under § 325(d). Because no prior art grounds are being raised in this petition, *Becton, Dickinson* factors (a), (b), (c), (d), and (e) do not favor denial.

As to factor (f) (“the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments”), as shown below, the petition presents significant new evidence and arguments, including the declaration of Alexander M. Klibanov, Ph.D., Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology (“M.I.T.”). EX1002.

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

New evidence is also presented in support of this petition that was not previously presented to the Office. For example, BI's contradictory remarks during prosecution of the European counterpart (EX1063) and the '039 patent that was at issue in *Fresenius* (EX1006). Dr. Klivanov's declaration also cites new evidence about the state of the art, including BI's own publications (e.g., EX1018, EX1030, EX1031, EX1045, EX1023, EX1024). These new arguments and evidence warrant reconsideration of the decision during prosecution to issue the challenged claims.

A. The examiner withdrew the written description rejection after BI's mischaracterization of the *Fresenius* patent and decision.

While the examiner issued a written description rejection, it was material error for the examiner to allow the challenged claims without further amendment.

1. BI's analogy to the patent in *Fresenius* was misleading.

It was material error to allow the challenged claims without requiring BI to amend them to encompass only formulations supported by the specification. BI induced this error by representing to the examiner that the claims and specification in *Fresenius* were analogous to those of the '265 patent, repeatedly stressing to the examiner that "the PTAB's analysis in the institution decision of PGR2019-00064 is *clearly applicable here* and it is noteworthy that the PTAB found *a similar claim*, which was exemplified by only a single formulation in that specification[,] was sufficiently described under 35 U.S.C. §112(a)." EX1004, 7668 (emphasis added). It was material error to credit BI's mischaracterization of *Fresenius*.

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

(a) The claims in *Fresenius* expressly excluded excipients and the specification limited the variety of excipients.

The claims in *Fresenius* involved adalimumab formulations. EX1002, ¶150; EX1006, 87:33–88:44. Adalimumab is a recombinant monoclonal antibody known commercially as Humira®. EX1002, ¶150. The '039 patent prefaces its disclosure by stating that “[v]arious formulations of adalimumab are known in the art,” but that “[t]here is still need for stable liquid formulations of adalimumab that allow its long term storage without substantial loss in efficacy.” EX1006, 1:66–2:3.

The adalimumab formulation of claim 1 of the '039 patent, which BI argued was analogous to claims 7 and 19 of the '265 patent, requires a specific surfactant (polysorbate 80) and expressly *excludes* “i) mannitol [tonicity agent], ii) citrate and phosphate buffers, and iii) sodium chloride [tonicity agent].” EX1002, ¶¶151–156; EX1006, 87:33–41. Importantly, these excipients are excluded because they were found (based on extensive experimentation that is described in the '039 patent) to adversely affect stability. *Id.* While claim 1 recites adalimumab, a buffer, and a sugar, the '039 patent limits (again based on extensive experimentation described in the patent) the variety of suitable excipients for use in the claimed formulations:

- The buffer is “*selected from the group consisting of citrate, phosphate, succinate, histidine, tartrate and maleate . . . wherein said buffer does not comprise a combination of citrate and phosphate.*” EX1006, 2:9–61 (emphasis added); EX1002, ¶156.

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

- The sugar should be “*selected from the group consisting of mannitol, sorbitol and trehalose,*” but “as between mannitol and sorbitol, ... a distinct stabilization advantage in using sorbitol or trehalose instead of mannitol, unless mannitol is used at concentrations in excess of about 200 mM” because “[a]t concentrations below about 200 mM, mannitol has been found to be a poorer stabilizer than sorbitol or trehalose.” EX1006, 5:28–39 (emphasis added); EX1002, ¶156.
- The ’039 patent explains that there was “a distinct and surprising thermal stabilization advantage in selecting [polysorbate 80] instead of [polysorbate 20].” EX1006, 5:40–44; EX1002, ¶156.

The Board in *Fresenius* cited such details to support its determination that claim 1 of the ’039 patent had adequate written description. EX1004, 7397–98. Yet none of these details apply to the claims of the ’265 patent. Claims 7 and 19 of the ’265 patent generically recite *any* detergent, *any* tonicity agent, and *any* buffer (or no buffer) and are open-ended (“comprising”) as to other components (including “wherein the formulation *optionally comprises* a buffer”). And unlike the ’039 patent at issue in *Fresenius*, the ’265 patent does not provide any limitations on the types or concentrations of excipients that should be used. EX1002, ¶¶149–151, 155–158. Quite the contrary. Where the ’265 patent identifies a specific excipient, it expressly states that the excipient, and its concentration, is merely an “example.”

EX1005, 17:14–30, 130:10–132:10; EX1001, 11:51–55 (“*for example* polysorbate 20 (Tween 20), *for example* at a concentration of 0.20 g/l.”) (emphasis added), 60, 12:19–21, 27, 36, 83:31–34, 40, 65–67, 84:6–14, Example 11; EX1002, ¶120.

(b) The ’039 patent describes the systematic testing of 89 formulations compared to an FDA-approved product.

The inventors of the ’039 patent arrived at the specific limitations above by preparing, testing, and analyzing 89 *distinct* adalimumab formulations. EX1002, ¶¶151–156; EX1006, 20:64–59:9. They did so by systematically varying different combinations of excipients at different pHs and different antibody concentrations, using the FDA-approved formulation for Humira® as a baseline. *Id.* They varied the concentration and type of buffer (including by using dual buffer systems), the concentration and type of tonicity agent, the concentration and type of detergent, the concentration and type of stabilizers. *Id.* Overall, the ’039 patent analyzed:

- 14 different buffers or buffer combinations, or no buffer at all, with 5 of the buffers tested at different concentrations;
- 4 different concentrations of mannitol, or no mannitol;
- 4 different concentrations of NaCl or no NaCl;
- 2 different sorbitol or trehalose concentrations or no sorbitol or trehalose;
- 3 different detergents (polysorbate 80, polysorbate 20, Pluronic F-68), with polysorbate 80 and polysorbate 20 tested at 3 different concentrations, or no detergent;

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

- 6 different concentrations of glycine or no glycine;
- 7 different concentrations of arginine or no arginine;
- 2 different EDTA concentrations or no EDTA;
- 2 different methionine concentrations or no methionine;
- 6 different pH values; and
- 2 antibody concentrations.

EX1002, ¶152–53.

The '039 patent discloses the data obtained from the stability testing of these 89 distinct formulations and even used that data to try to model and describe how different buffers, pH levels, excipients, and concentrations would likely affect the stability of additional formulations. EX1002, ¶¶154–156; EX1006, 59:11–67:23.

The Board highlighted this type of disclosure in its assessment that the '039 patent had adequate written description. EX1004, 7397–98. The specification of the '265 patent, by stark contrast, offers nothing remotely close to that level of detail. Rather, regarding formulations within the scope of the challenged claims, the '265 patent discloses at best three examples which collectively offer: a single buffer at two concentrations (succinate at 25mM and 4.4mM); two tonicity agents at respective concentrations (NaCl at 125mM and sorbitol at 225mM and 240mM); and one detergent at one concentration (polysorbate 20 at 0.20 mg/mL). EX1002, ¶147–149; EX1001, 83:10–84:26. Unlike the '039 patent in *Fresenius*, the '265

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

patent does not describe—in language, with data, or by example—excipients that should not be used. EX1002, ¶¶147–149. Unlike the '039 patent, the '265 patent does not limit the universe of possible detergents, buffers, or tonicity agents to a list of suitable types. *Id.* Unlike the '039 patent, the '265 patent does not attempt to benchmark any formulation against an FDA-approved product—nor could the '265 patent because, as of April 25, 2013, there was no FDA-approved anti-IL23p19 antibody, let alone an FDA-approved formulation of Antibody A. *Id.*, ¶¶158. And the '265 patent discloses nowhere near the amount of data necessary to produce a model, such as the modeling disclosed in '039 patent. *Id.*, ¶¶152–153, 157–158.

BI failed to bring these significant differences to the examiner's attention. BI did the opposite by arguing that the specification of the '039 patent is “[j]ust like” that of the '265 patent. EX1004, 7379. Notably, BI did not even present the '039 patent *itself* to the examiner as an exhibit or in an SB-08 form. Consequently, there is no evidence on the face of the '265 patent that the examiner ever considered it.

(c) The outcome in *Fresenius* turned on the Board's rejection of the petitioner's claim construction.

The outcome in *Fresenius* also resulted from the Board's rejection of the petitioner's construction of the term “stable,” one that required a “stringent 5% upper end” of the stability range. EX1004, 7397–98. Premised on its rejection of this narrow construction, the Board reasoned that the petitioner had improperly ignored testing involving other formulations that informed what was required to

achieve a stable formulation (e.g., which excipients should be used). EX1002, ¶156. Ignoring this distinction, BI misleadingly argued that *Fresenius* found that “a single working example” had been sufficient to support the “millions of possible species.” EX1004, 7379. This was a gross mischaracterization of *Fresenius*.

2. Claims 7 and 19 do not require a specific detergent.

The examiner indicated in her interview summary that BI should amend then-pending claims 37 and 49 to recite the specific detergent used in the examples (polysorbate 20), and BI proposed that it would also add a buffer. EX1004, 7656; *supra* § III.B.3. Yet BI did not follow through when it submitted its amendments, which did not specify the detergent and made the buffer “optional” in the amended claims. Consequently, issued claims 7 and 19 do not recite a specific detergent.

As shown below (*infra* §§ VII.A, VII.B), adding these limitations would not have been sufficient to satisfy the requirements of § 112(a); however, not requiring BI to amend the claims *as the examiner had requested* is evidence that the duration and complexity of prosecution—which lasted well over five years and was subject to multiple RCEs adding new claims after allowance—resulted in material error.

3. It was material error to allow the challenged claims.

The examiner also materially erred by allowing the claims based on an insufficient amendment, namely, adding “(c) a tonicity agent” and “the formulation optionally comprises a buffer.” EX1004, 7661–62. Even with this amendment, the

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

challenged claims recite a broad functionally defined genus encompassing millions of potential formulations, while the specification fails to disclose a representative number of species or common structural feature, as required by law. *Infra* § VII.A.

It was material error to overlook or accept BI's mischaracterization that the examples in its summary table and remarks were all within the scope of the claims. The examiner stated that "[t]he Attorney stated that examples 9, 11 and 12 provide examples of *various formulations* that fall within the scope of the claims and have the claimed functional characteristics." EX1004, 7656 (emphasis added). But only Formulations 2 and 3 are within the scope of certain claims, and Example 9 does not fall within the scope of *any* claim. *Supra* § III.B.2. Similarly, the examiner stated "[t]he Attorney stated that anti-IL-23p19 antibody recited in the claims is self-buffering, and this characteristic contributes to the stability of the antibody *in the various formulations*." *Id.* (emphasis added). But there is only *one* example of a formulation lacking any buffer (Formulation 3). EX1002, ¶¶127–132, 232–233. These statements reflect a misunderstanding, likely owing to BI's arguments.

The examiner did not address whether there was support for the optional buffer limitation at antibody concentrations lower than the 90 mg/ml. EX1002, ¶¶53–55, 214, 233. Self-buffering is not the same as stability, is an unpredictable aspect, and requires a relatively high concentration of antibody. *Infra* § VII.A.1.b.

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

This petition presents new evidence and arguments on these issues that warrant reconsideration of the Office's decision to allow the challenged claims.

B. Enablement was neither presented to, nor considered by, the Office and should not be presumed to have been considered.

The Office has not previously considered arguments regarding lack of enablement of any challenged claim, much less the specific arguments raised in this Petition. *Adello Biologics, LLC v. Amgen Inc.*, PGR2019-00001, Paper 13 at 10–11 (P.T.A.B. Apr. 19, 2019). This alone would rule out § 325(d) denial because enablement was not previously presented to the Office. Moreover, enablement is a substantively and materially different requirement than written description. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1345 (Fed. Cir. 2010) (en banc); *see also Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab's Inc.*, 923 F.3d 1368, 1382 (Fed. Cir. 2019) (“[T]he fact that an invention may be enabled does not mean it is adequately described, and vice versa.”). The Office recognizes this distinction. M.P.E.P. § 2103.I (“Where a rejection not based on prior art is proper (lack of *adequate written description, enablement, or utility, etc.*) such rejection should be stated with a full development of the reasons”) (emphasis added). Thus, any rejection for lack of enablement should have been “stated with a full development of the reasons.” *Id.* There was no such rejection.

VI. ELIGIBILITY FOR POST-GRANT REVIEW (AIA § 3(n)(1))

The '265 patent is eligible for PGR because it is not entitled to the pre-AIA filing date of the provisional application to which it claims priority due to a lack of written description and enablement. AIA §§ 3(n)(1), 6(f)(2)(A); *Daiichi Sankyo, Inc. v. Seagen, Inc.*, PGR2021-00030, Paper 17 at 8–10 (P.T.A.B. Apr. 7, 2022).

The AIA's post-grant review provisions apply to patents that “contain[] or contained *at any time* ... a claim to a claimed invention that has an effective filing date” that is on or after March 16, 2013. AIA § 3(n)(1) (emphasis added).

For a claimed invention to be entitled to a “right of priority” or “an earlier filing date” based upon an earlier-filed application, in this case U.S. Provisional Application No. 61/642,032 (“the provisional”), filed May 3, 2012, the earlier-filed application must have been disclosed “in the manner provided by section 112(a).” 35 U.S.C. § 119(e)(1); 35 U.S.C. § 120. As demonstrated below (*infra* §§ VII.A.2, VII.B.2), the provisional does not describe or enable claim 14 as issued in the '265 patent and once-pending claim 44 (first presented as part of the '061 application on March 16, 2020, thereafter amended, and deemed allowable on March 24, 2021 in the form presented by BI on February 12, 2021). EX1004, 7678, 7660–7664.³

³ Once-pending claim 44 eventually issued in the '265 patent as claim 14.

Any statutory disclaimer of claim 14 made under 37 C.F.R. § 42.207(e) would not

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

A. The provisional lacks written description for issued claim 14 and pending claim 44 (as presented on February 12, 2021).

For the reasons specified below, *infra* §§ VII.A.1–2, the provisional to which the '265 patent claims priority, which contains no more disclosure than the '265 patent itself (EX1002, ¶3), does not convey to a POSA that the inventors had possession of the full scope of issued claim 14 and once-pending claim 44 (in the form presented to the Office on February 12, 2021). Because claim 14 and once-pending claim 44 lack written description in the provisional, for the reasons below (*infra* § VII.A.1–2) the '265 patent is eligible for PGR. EX1002, ¶¶271–272, 300.

B. The provisional does not enable the full scope of issued claim 14 and pending claim 44 (as presented on February 12, 2021).

For the reasons specified below, *infra* §§ VII.B.1–2, the provisional does not enable a POSA to practice the full scope of claim 14 and once-pending claim 44 (as presented on February 12, 2021) without undue experimentation. EX1002, ¶¶273–300. Because claim 14 and once-pending claim 44 are not enabled by the provisional (*infra* § VII.B.1–2) the '265 patent is eligible for PGR. EX1002, ¶300.

remove PGR eligibility. *RetailMeNot v. Honey*, PGR2019-00060, Paper 17 at 9–17 (P.T.A.B. Mar. 10, 2020). Once-pending claim 44 cannot be statutorily disclaimed.

VII. GROUNDS AND EVIDENCE (37 C.F.R. § 42.204(b)(4)–(5))

The Board should institute review because “it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a).

A. GROUND 1: CLAIMS 7–10, 14–16, 19–22, AND 27–28 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION.

“To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent.” *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019). “[F]or a claim to a genus, [the] patentee must disclose a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.” *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017). Additionally, “if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus.” *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

As is the case here, “[f]unctionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a

correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus.” *Id.* at 1301. Other factors considered include: “[T]he existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Id.* at 1299. Another factor is “how large a genus is involved and what species of the genus are described in the patent.” *Id.*

1. Claims 7 and 19

Independent claims 7 and 19 recite “stable” liquid aqueous pharmaceutical formulations “comprising” Antibody A, in a concentration of “90 mg/ml” (for claim 7) or *any* concentration (for claim 19), *any* detergent at *any* concentration, *any* tonicity agent at *any* concentration resulting in isotonicity, “optionally” *any* buffer at *any* concentration, having *any* pH between 5.5 and 6.5. EX1002, ¶179.

(a) The claims encompass a broad genus of antibody formulations, recited in generic and functional terms.

The claims define the genus in generic and functional terms: The claims do not specify particular excipients, but recite broad classes of excipients *generically*, encompassing any excipient capable of acting as “a detergent,” “a tonicity agent,” or “a buffer.” EX1002, ¶179. The claims also define the genus *functionally*—as encompassing liquid Antibody A formulations having a pH anywhere between 5.5 and 6.5 that are “isotonic” and “stable.” *Id.*; *supra* § III.B. Also, as shown above, the term “stable” encompasses the conditions recited in claim 14 (“stable following

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

storage in a syringe for 8 weeks at 40°C.”) and the conditions set forth in Example 9 (stable following storage at 4° C. for at least 4 months). *Supra* § IV.A. Thus, the claims define the genus of formulations based on “what a material does, rather than of what it is” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002); *see also Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (“A written description of an invention involving a chemical genus ... ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.”) (*quoting Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)).

The claims encompass millions of potential formulations: Even assuming that the claims do not encompass classes of excipients other than those expressly recited (i.e., ignoring that the claims recite an open-ended “comprising” list, *supra* § IV.C), and considering only the detergents, tonicity agents, and buffers that had been used in FDA-approved injectable products by 2011 (a highly conservative number given that a POSA would have considered other excipients), and assuming only 10 concentrations of each excipient were considered (a highly conservative number, given that a POSA would consider more when analyzing stability)—the number of potential formulations encompassed by claim 7 is **3,052,500**. EX1002, ¶181, AppxB. Making the same assumptions for claim 19, but also considering 10

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

concentrations of the antibody (since concentration is not specified), the number of potential formulations encompassed by claim 19 is **64,102,500**. *Id.*, ¶220, AppxB.

The numbers increase when more concentrations of each component of the formulation are considered, which a POSA would have done to evaluate the effect of component concentration on stability. *Id.*, ¶182. Considering 15 concentrations of each excipient, the number of potential formulations encompassed by claim 7 is **10,271,250** and by claim 19 is **215,696,250**. *Id.*, ¶¶182, 220, AppxB. The numbers further increase if, as the transition “comprising” allows (*supra* § IV.C), a second buffer were added. Then, with each excipient considered at 10 concentrations, the number of potential formulations encompassed by claim 7 would be **305,552,500** and by claim 19 would be **6,416,602,500**. EX1002, ¶¶182, 220–221, AppxB.

A POSA would have considered adding a second buffer for stability, as had been done with other FDA-approved antibody formulations, e.g., Humira®, as the manufacturer could presumably afford to use an improved pH control. *Id.*, ¶183.

Thus, whether calculated using more or less conservative assumptions, the genus is vast, encompassing millions of formulations. *Id.*, ¶¶181–182, 220–221.

(b) The specification does not describe a representative number of species within the genus of formulations.

In contrast to the millions of potential formulations encompassed by the claims, the '265 patent discloses at best three formulations that, assuming each is “stable,” fall within the scope of claim 19 and only two of which fall within the

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

scope of claim 7. *Supra* § III.B. Collectively, these examples disclose two antibody concentrations (10 mg/ml and 90 mg/ml), one buffer at two concentrations (25mM and 4.4mM succinate buffer) or no buffer, two tonicity agents at certain respective concentrations (125mM NaCl and 225mM and 240mM sorbitol), and one detergent at one concentration (0.20 mg/mL polysorbate 20). EX1002, ¶¶120–127.

Given the high unpredictability in the art and the variability associated with excipient-excipient and excipient-antibody interactions, three narrow examples (and only two examples for claim 7) is at best a small “corner of the genus” and is not a representative number of species sufficient to support this broad functionally defined genus. *AbbVie*, 759 F.3d at 1300. This is because the claimed genus is vast, encompassing millions of potential formulations, and because it is diverse in terms of the types of excipients that could be used and the concentrations at which each could be present. EX1002, ¶¶181–182, 220–221; *supra* §§ III.A.2, VII.A.1.a.

BI’s own statements confirm that the art is highly unpredictable. *Supra* § III.A. As BI argued during prosecution of the ’265 patent seeking to overcome an obviousness rejection: “It is ... well known that ‘aggregation remains difficult to control,’ in general, and ‘the identification of suitable formulation conditions for a specific monoclonal antibody remains challenging and cannot be determined from its amino acid sequence.’” EX1004, 6371 (quoting EX1062, 271). Further, as BI argued during examination of the European counterpart: “Every parameter which

is changed will in all likelihood have an effect which might or might not make further changes necessary [T]he provision of a stable antibody formulation is – even with the existing knowledge on possible parameters, excipients and working equipment – still *a full blown research program.*” EX1063, 3 (emphasis added).

The innumerable variables introduced by the breadth of the claims, and the understanding that even subtle changes to any variable could significantly affect excipient-excipient and excipient-antibody interactions and formulation stability (e.g., by affecting aggregation, deamidation, oxidation, isomerization, etc.) (*supra* §§ III.A.1–3; EX1002, ¶¶ 70–85), which could also be affected by conditions (e.g., temperature, pH, humidity), demonstrate why disclosing only a few embodiments make functional claims “inherently vulnerable to invalidity challenge for lack of written description support.” *AbbVie*, 759 F.3d at 1301; *see also Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1125 (Fed. Cir. 2008) (noting that broad genera are typically not adequately supported by “narrow specifications”).

Claims 7 and 19 are particularly vulnerable because they recite that the formulation only “*optionally* comprises a buffer.” As of 2013, the FDA had yet to approve a buffer-less antibody formulation. EX1002, ¶¶56, 206. And even today, only one antibody (adalimumab) has been formulated without a buffer in an FDA-approved product. *Id.*, ¶56; *supra* § III.A.2.b. To the extent Formulation 3 is stable without a buffer and is assumed to self-buffer (as BI advocated during prosecution,

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

EX1004, 7667), the specification does not describe this and self-buffering capacity is not a predictable aspect. EX1002, ¶54; *supra* § III.A.2.b. Accordingly, the '265 patent does not convey possession of such an understanding. EX1002, ¶206.

Self-buffering capacity was also not expected when the antibody is present in low concentrations—as are broadly encompassed by claim 19. EX1002, ¶233. Nor does the specification address that an antibody's capacity to self-buffer refers only to its ability to resist changes in pH, which does not equate to stability. *Supra* § III.B; EX1002, ¶55. Rather, a POSA would have understood that many other aspects of the formulation would affect stability, beyond simply the antibody's ability to resist changes in pH—e.g., the potential for denaturation, aggregation, surface adsorption, deamidation, disulfide formulation/exchange, non-reducible cross-linking, isomerization, oxidation, formation of acidic or basic species, C-terminal clipping, fragmentation, the Maillard reaction. EX1002, ¶¶24–29, 32–36. BI itself listed these as factors that would affect formulation stability in arguments it made in Europe when seeking to overcome obviousness rejections. EX1063, 3.

That all the claims recite “*liquid aqueous* pharmaceutical formulation[s]” increases the unpredictability, as liquid antibody formulations were known to be particularly susceptible to the destabilizing effects of aggregation, deamidation, oxidation, and fragmentation due to the presence of water. EX1002, ¶30; *supra* § III.A.1.c. Because the claims generically recite a “liquid aqueous pharmaceutical

formulation,” they encompass IV *and* SC formulations. EX1002, ¶169. However, parameters favoring stability for an IV formulation were not regarded as predictive of stability for an SC formulation, and vice versa. EX1002, ¶¶63, 229–231.

Also, properly construed, claims 7 and 19 encompass a subgenus of liquid formulations that are stable “following storage *in a syringe* for 8 weeks at 40°C.” *Supra* § IV.A.1. In addition to the unpredictability associated with making stable liquid antibody formulations generally, syringes require silicone oil, and a POSA would have understood that silicone oil present in the syringe could leach over the eight weeks of storage and cause aggregation and instability—particularly in the presence of a detergent (which the claims require). *Id.*; EX1002, ¶¶97, 210–213.

Properly construed, claims 7 and 9 also encompass a second subgenus of formulations that are stable following storage at “4° C. for at least 4 months.” *Supra* § IV.A.2. It was also unpredictable whether a liquid antibody formulation would be stable under these distinct conditions. EX1002, ¶¶24–29, 32–36, 101, 237–239; *supra* § III.A.4. Testing would be required to determine whether a given formulation is stable under those conditions. EX1002, ¶36–37, 99; *supra* § III.A.4.

“With the written description of a genus ... merely drawing a fence around a perceived genus is not a description of the genus. One needs to show that one has ... conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others

to explore the unknown contours of the claimed genus.” *AbbVie*, 759 F.3d at 1300.

Here, three narrow examples are not a representative number of species sufficient to convey possession of the enormous and diverse genus of “stable” anti-IL23p19 antibody formulations being claimed. EX1002, ¶¶214, 229, 240–249; *supra* § III.B.

(c) The specification does not describe any “common structural feature” correlative of stability.

Although the challenged claims recite a genus of formulations defined by a particular function—stability—the ’265 patent fails to describe structural features common to members of the claimed genus that would allow a POSA to visualize which formulations within the massive genus are “stable.” The ’265 patent also fails to correlate any structural feature of any excipient—or any combination of excipients—that make a formulation comprising Antibody A “stable.” To satisfy the written description requirement by disclosing structural features common to a functionally-defined genus, the specification must disclose the combination of structural features that are required to achieve that claimed function. *See AbbVie*, 759 F.3d at 1301; *Nuvo*, 923 F.3d at 1384. The ’265 patent fails entirely to do so.

Unlike the patent in *Fresenius*, the ’265 patent does not limit⁴ the excipients, nor does it identify which excipients (or which excipients at which concentrations)

⁴ To the extent “Example 11” lists Formulations 1–3, these are “[e]xamples of formulations,” and thus not limiting. EX1001, 92:23–94:12 (emphasis added).

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

are common to Antibody A formulations that are “stable.” Rather than describe any structure that distinguishes “stable” formulations, the ’265 patent directs the POSA to conduct stability testing to discover which of the countless formulations covered by the claims would be “stable.” EX1002, ¶¶239–243. But that is exactly the problem. That a POSA must do *further undirected research* to discover new formulations and determine which are “stable” conveys a lack of possession as to which, if any, structures distinguish stable from unstable formulations. *Id.*, ¶243.

By any measure, the ’265 patent fails to describe any correlation between the structure of a liquid antibody formulation comprising Antibody A (the chemical and physical nature of the combined excipient-excipient and excipient-Antibody A interactions in formulation) and the function of that formulation being “stable.”

1. A POSA would know that the primary amino acid sequence of Antibody A would be insufficient to establish a structural feature that correlates with whether a given liquid Antibody A formulation would be stable. EX1002, ¶¶87–93. Merely knowing the antibody’s structure does not adequately inform whether, when the antibody is formulated, deamidation, oxidation, or hydrolysis will occur—let alone the extent to which those effects will occur—as each of those degradation pathways can be affected by antibody polypeptide-chain flexibility and alterations to the antibody’s structure. *Id.*, ¶¶88–90. Further, the extent to which the antibody peptide chain will be flexible and can unfold would also be affected

by excipients. *Id.*, ¶¶89–90. A POSA would have understood that post-translation modifications also affect stability, including glycosylation, and that an antibody’s glycosylation status—e.g., presence, amount, and type—could vary depending on culture conditions and cell type used to express the antibody. *Id.*, ¶¶91–93.

2. A POSA would also know that having a target pH range for a liquid Antibody A formulation would be insufficient to establish a structural feature that correlates with whether a given liquid Antibody A formulation would be stable. *Id.*, ¶245. Rather, the interdependent behaviors and properties of a given antibody formulation would still be unknowable at any given pH within a pH range until tested. *Id.*; EX1014, 15 (“[T]he pH effect on the stability of antibodies depends on the formulation composition, stress conditions, and even antibody concentration.”).

3. For the same reasons noted above, a POSA would know that merely having Antibody A’s primary sequence in conjunction with a target pH range is inadequate to identify a correlation between structure and function. EX1002, ¶246.

4. A POSA would know that the interdependent behaviors and properties of excipients and an antibody in a liquid formulation are highly unpredictable, and that knowing an antibody’s sequence and target pH, in combination with general classes of excipients would not remove that unpredictability. *Id.*, ¶¶70–85, 248; *supra* § III.A. Rather, a POSA would know that the stability of a particular liquid antibody formulation is not predictable *a priori* due to interactions among the

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

formulation components, the antibody itself, and the drug product storage vessel. *Id.*, ¶¶70–98, 247. The '265 patent does not disclose, present, or analyze anything that would convey even a basic understanding of the interdependent behaviors and properties of an Antibody A formulation. *Id.*, ¶¶247–249. The '265 patent does not address the effects of excipient-excipient and excipient-antibody interactions on the stability of an Antibody A formulation. *Id.* The '265 patent does not hint at, let alone describe, the roles or effects of the classes of excipients recited in the claims and how, in combination, they produce a “stable” formulation. *Id.*, ¶¶246–249.

5. Even having the full complement of components and concentrations within Formulations 1–3, along with the relevant passages from the specification, a POSA would find this to be insufficient to identify a structural feature correlative of “stable” formulations across the vast and diverse genus claimed. *Id.*, ¶¶244–249.

The '265 patent's examples and specification collectively disclose only: one exemplary detergent at one exemplary concentration, polysorbate 20 at 0.2 mg/ml; one exemplary buffer, succinate, at a concentration of 50 mM or less; and two tonicity agents with ranges of concentrations, 50–200 mM sodium chloride and 100–300 mM sorbitol. EX1002, ¶¶120–125. The '265 patent makes no attempt to show a correlation between the chemical nature and properties of these specific excipients and concentrations and their interactions with Antibody A, at any pH, that makes a formulation “stable.” *Id.*, ¶¶240–249. And the '265 patent does not

explain, or show, that these limited and specific examples correlate to stability for the countless undisclosed and untested formulations, having different excipients and concentrations, that fall within the scope of these broad claims *Id.*, ¶¶248–249.

In this unpredictable field (*supra* § III.A), merely knowing the amino acid sequence of Antibody A, a target pH range, general classes of excipients, and a few narrow examples of stable formulations does not identify a structure that correlates with the stability of formulations comprising Antibody A. EX1002, ¶¶240–249.

Accordingly, the 256 patent fails to adequately describe the combination of structural features required to achieve the function recited in claims 7 and 19.

(d) The little known about anti-IL23p19 antibody formulations cannot bridge the disclosure gaps.

As BI argued during prosecution, the prior art does not disclose any specific anti-IL23p19 antibody formulations. EX1004, 7656. And the limited disclosure of Formulations 1–3 does not convey how or why those combinations of components are “stable.” EX1002, ¶278; *supra* § III.B. The limited information available as of April 25, 2013 about anti-IL23p19 antibody formulations—whether in the prior art or in BI’s specification—does not give BI a pass on disclosing common structural features or sufficient representative species in its patent. *Amgen*, 872 F.3d at 1373.

2. Claim 14 (and once-pending claim 44)

Issued claim 14 and once-pending claim 44 (as presented on February 12, 2021) depend from issued claim 7 and once-pending claim 37 respectively. Both

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

recite a genus of liquid aqueous pharmaceutical formulations “comprising” a 90 mg/ml concentration of Antibody A, a generically recited list of excipients not limited by type or concentration (“a detergent,” “a tonicity agent,” “optionally” comprising “a buffer”). EX1001, 190:43–45; EX1004, 7661–62; EX1002, ¶268. The recited genus is defined functionally as having a pH between 5.5 and 6.5 and being isotonic and “stable following storage in a syringe for 8 weeks at 40°C.” *Id.*

The limitations regarding conditions under which the formulation is stable, as in claim 14 and once-pending claim 44, do not narrow the number of potential formulations encompassed by claim 7. EX1002, ¶¶180–214. Thus, as with claim 7, whether one calculates using more or less conservative assumptions, the genus of claim 14 encompasses **millions** of potential formulations. *Supra* § VII.A.1.a.

Assuming Formulations 2 and 3 are “stable following storage in a syringe for 8 weeks at 40°C,” there are only two examples within the scope of the claims. Given the unpredictability discussed with respect to claim 7 (*supra* § VII.A.1), two narrow examples are insufficient to describe a representative number of species within this genus, which encompasses millions of diverse formulations. EX1002, ¶¶185–189. And as with claim 7, the ’265 patent does not describe any structural features common to the members of the genus that determine which combinations of excipients, let alone at which concentrations, achieve the functionality of being “stable following storage in a syringe for 8 weeks at 40°C.” EX1002, ¶¶240–249;

supra § VII.A.1.c. As with claim 7, the '265 patent does not establish a correlation between formulation structure and the claimed function for this enormous genus. EX1002, ¶¶240–249; *supra* § VII.A.1.c. Accordingly, while claim 14 is narrower than claim 7 and recites conditions under which the recited genus of formulations must be stable (i.e., “following storage in a syringe for 8 weeks at 40°C”), making liquid anti-IL23p19 antibody formulations that would remain stable in a syringe remained challenging due not only to the general unpredictability of excipient-excipient and excipient-antibody interactions but to the potential for degradation because of interactions with the storage vessel (i.e., a syringe) and the presence of silicone oil. EX1002, ¶¶211–213; *supra* § III.A.3.e. And, as with claim 7, there was little known about anti-IL23p19 antibody formulations. *Supra* § VII.A.1.d.

In sum, claim 14 does not meaningfully narrow the scope of the claimed genus of formulations relative to claim 7. It therefore lacks written description support for substantially the same reasons. EX1002, ¶214; *supra* § VII.A.1.

3. Claims 8 and 20

Claims 8 and 20 depend from claims 7 and 19 respectively and add only that the detergent is “polysorbate 20.” Claims 8 and 20 do not limit the tonicity agent or buffer either by type or concentration, and the buffer remains optional. Assuming, solely for purposes of simplicity, that claims 8 and 20, despite the presence of the transitional term “comprising,” do not encompass classes of excipients other than

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

those expressly recited in the claims, and considering only the tonicity agents and buffers that had already been used in FDA-approved injectable products by 2011, and assuming that only 10 concentrations of each excipient were to be considered, the number of potential formulations encompassed by claim 8 is **277,500** and by claim 20 is **5,827,500**. EX1002, ¶251, AppxB. Considering 15 concentrations of each excipient, the number of potential formulations encompassed by claim 8 is **933,750** and by claim 20 is **19,608,750**. *Id.* If, for the same reasons noted above (*supra* § VII.A.1.a), a second buffer were added, with each excipient considered at 10 concentrations, the number of potential formulations encompassed by claim 8 would be **27,777,500** and by claim 20 would be **583,327,500**. *Id.* Thus, the genus of potential formulations encompassed by claims 8 and 20 is vast. *Id.*, ¶¶251, 253.

At best only two examples fall within the scope of claim 8 and only three within the scope of claim 20. EX1002, ¶254. While claims 8 and 20 recite a specific detergent, adding only “polysorbate 20” is insufficient to narrow the genus to a scope supported by the specification, particularly given that the art taught that polysorbate 20 could have unpredictable effects on stability. *Supra* § III.A.2.a; EX1002, ¶254. Thus, claims 8 and 20 do not meaningfully narrow the scope of the claimed genus relative to claims 7 and 19 and therefore lack written description support for substantially the same reasons. EX1002, ¶255; *supra* § VII.A.1.

4. Claims 9 and 21

Claims 9 and 21 depend from claims 8 and 20 respectively and add that the “polysorbate 20” is present at a concentration of “0.2 mg/ml.” Claims 9 and 21 do not limit the tonicity agent or buffer either by type or concentration, and the buffer remains optional. Assuming, solely for purposes of simplicity, that claims 9 and 21 do not encompass classes of excipients other than those recited—despite the transitional term “comprising”—and considering only the tonicity agents and buffers that had been used in FDA-approved injectable products by 2011, and assuming that only 10 concentrations of each excipient (except polysorbate 20) were considered, the number of potential formulations encompassed by claim 9 is **27,750** and by claim 21 is **582,750**. EX1002, ¶252, AppxB. When considering 15 concentrations of each excipient (except polysorbate 20), the number of potential formulations encompassed by claim 9 is **62,250** and by claim 21 is **1,307,250**. *Id.*, ¶252, AppxB. And if, for the same reasons above (*supra* § VII.A.1.a), a second buffer were added, with each excipient considered at 10 concentrations (except polysorbate 20), then the number of potential formulations encompassed by claim 9 would be **2,777,750** and by claim 21 would be **58,332,750**. EX1002, ¶252; AppxB. Thus, the genus of potential formulations remains vast. *Id.*, ¶¶252, 256.

At best only two examples fall within the scope of claim 9 and only three within the scope of claim 21. *Id.*, ¶257. While claims 9 and 21 recite a specific

detergent in a specific concentration, this remains insufficient to narrow the genus to a scope supported by the specification, particularly given that the art taught that polysorbate 20 could have unpredictable effects on stability. *Id.*; *supra* § III.A.2.a. Additionally, these dynamics could depend, not entirely on the absolute detergent concentration, but also on the detergent-to-protein ratio. EX1039, 568; EX1002, ¶¶43–46. Accordingly, claims 9 and 21 do not meaningfully narrow the scope of the claimed genus relative to claims 8 and 20 and lack written description support for substantially the same reasons. EX1002, ¶258; *supra* §§ VII.A.1, VII.A.3.

5. Claims 10 and 22

Claims 10 and 22 depend from claims 7 and 19 respectively and add that a buffer is required. Claims 10 and 22 do not limit the detergent, tonicity agent, or buffer either by type or concentration. Assuming, solely for purposes of simplicity, that claims 10 and 22 do not encompass classes of excipients other than those recited in the claims, despite the transitional term “comprising,” and considering only detergents, tonicity agents, and buffers that had been used in FDA-approved injectable products by 2011, and assuming that only 10 concentrations of each excipient were considered, the number of potential formulations encompassed by claim 10 is **3,025,000** and by claim 22 is **63,525,000**. EX1002, ¶260, AppxB. Considering 15 concentrations of each excipient, the number encompassed by claim 10 is **10,209,375** and by claim 22 is **214,396,875**. *Id.*, ¶261, AppxB. If, for

the reasons above (*supra* § VII.A.1.a), a second buffer were added, with each excipient considered at 10 concentrations, the number encompassed by claim 10 would be **305,525,000** and by claim 22 would be **6,416,025,000**. *Id.*, ¶¶260–261, AppxB. Thus, the genus of potential formulations encompassed remains vast. *Id.*

At best only one example falls within the scope of claim 10 and only two within the scope of claim 22. *Id.*, ¶¶133–35. While claims 10 and 22 affirmatively require “a buffer,” this is insufficient to narrow the genus to a scope supported by the specification given the variety of buffers and buffer systems that were known in the art and the effects that different buffers and concentrations of buffers were known to have on excipient-excipient and excipient-antibody interactions. *Supra* § III.A.2.b; EX1002, ¶262. Claims 10 and 22 do not meaningfully narrow the scope of the genus relative to claims 7 and 19 and therefore lack written description support for substantially the same reasons. EX1002, ¶262; *supra* § VII.A.1.

6. Claims 15 and 27

Claims 15 and 27 depend from claims 7 and 19 respectively and add that the osmolarity is “300 +/- 30 mOsmol/kg.” These claims do not limit the detergent, tonicity agent, or buffer by type or concentration, and the buffer remains optional.

Assuming the units of claims 15 and 27 are for osmolarity, a POSA would have understood that the limitation means the formulation is isotonic—which does not materially narrow the genus because claims 7 and 19 already recite that the

formulation is “isotonic.” EX1002, ¶¶181, 220, 264; EX1061, 3645–46; EX1016, 3054. The limitation regarding osmolarity therefore does not narrow the number of potential formulations encompassed by claims 15 and 27 relative to claims 7 and 19, from which they depend. EX1002, ¶¶182, 221, 264. As with claims 7 and 19, whether one calculates using more or less conservative assumptions, the genera of claims 15 and 27 encompass **millions** of potential formulations. *Supra* § VII.A.1.

At best only two examples fall within the scope of claim 15 and only three within the scope of claim 27. EX1002, ¶¶133–135. While these claims expressly recite an osmolarity that is “300 +/- 30 mOsmol/kg” this is insufficient to narrow the genus to a scope supported by the specification given that this does not limit the detergent, tonicity agent, or buffer, either by type or concentration thereof. EX1002, ¶264; *supra* § III. Claims 15 and 27 do not meaningfully narrow the scope of the genus relative to claims 7 and 19 and thus lack written description support for substantially the same reasons. EX1002, ¶265; *supra* § VII.A.1.

7. Claims 16 and 28

Claims 16 and 28 depend from claims 7 and 19 respectively and add a pH in the range of 5.5 to 6.1. Claims 16 and 28 do not limit the detergent, tonicity agent, or buffer either by type or concentration, and the buffer remains optional. This pH limitation does not narrow the number of potential formulations encompassed by claims 16 and 28 relative to claims 7 and 19, from which they depend. EX1002,

¶¶181, 220, 267. Therefore, as with claims 7 and 19 from which they depend, and whether one calculates using more or less conservative assumptions, the genera of claims 16 and 28 encompass **millions** of potential formulations. *Supra* § VII.A.1.a.

At best only two examples fall within the scope of claim 16 and only three within the scope of claim 28. EX1002, ¶¶133–135. While claims 16 and 28 slightly narrow the pH range, this is insufficient to narrow the genus to a scope supported by the specification given that the pH requirement does not limit the detergent, tonicity agent, or buffer, either by type or concentration thereof.; EX1002, ¶267; *supra* § III. Claims 16 and 28 do not meaningfully narrow the scope of the genus relative to independent claims 7 and 19 and therefore lack written description support for substantially the same reasons. EX1002, ¶268; *supra* § VII.A.1.

B. GROUND 2: CLAIMS 7–10, 14–16, 19–22, AND 27–28 ARE UNPATENTABLE FOR LACK OF ENABLEMENT.

Under § 112(a), the specification must “enable an ordinarily skilled artisan to make and use the *entire scope* of the claimed invention at the time of filing.” *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) (emphasis added). “A claim is not enabled when, ‘at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.’” *Idenix*, 941 F.3d at 1154. Whether the amount of experimentation is undue considers: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of

working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

It is undue experimentation if “there were at least many, many thousands of candidate compounds, many of which would require synthesis and each of which would require screening.” *Idenix*, 941 F.3d at 1163; *see also Wyeth & Cordis Corp. v. Abbott Lab’ys*, 720 F.3d 1380, 1385–86 (Fed. Cir. 2013) (holding that there was a lack of enablement where “practicing the full scope of the claims would require synthesizing and screening each of at least tens of thousands of compounds”). And the “use of broad functional claim limitations raises the bar for enablement” *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021).

As demonstrated below, the challenged claims violate two cardinal rules of enablement. First, rather than provide guidance, the ’265 patent sends the POSA on an iterative, trial-and-error quest of hypothesizing, formulating, and testing a vast genus of formulations to *figure out* which formulations satisfy the functional claim limitations. Second, the ’265 patent fails to enable the *full scope* of the invention.

1. Claims 7 and 19

(a) The breadth of the claims is vast because the claims generically recite a functionally defined genus.

As shown above (*supra* § VII.A.1.a), claims 7 and 19 generically recite components of a functionally defined genus encompassing several millions, if not

billions, of potential anti-IL23p19 antibody formulations. EX1002, ¶¶181–182, 220–221. Thus, under *Wands* Factor 8, the breadth of the claims is vast. *Id.*, ¶275.

(b) The stability of antibody formulations, particularly liquid ones, is unpredictable and requires testing.

Only through experimentation, not prediction, could a POSA determine whether a particular formulation is “stable.” What makes an antibody formulation stable is highly unpredictable due to excipient-excipient interactions, excipient-antibody interactions, and interactions between the formulation and its container. EX1002, ¶¶70–85; *supra* § III.A. This is particularly the case for liquid antibody formulations, and even more so for those that have high or low concentrations of antibody, such as those encompassed by claim 19. *Supra* §§ III.A.1.c, III.A.3.1. As a result of this unpredictability, stability testing would be needed assess whether a given formulation would be “stable,” including following storage in a syringe for 8 weeks at 40°C or at 4° C for at least 4 months. EX1002, ¶¶99–107; *supra* § III.A.4.

Stability testing is required because this aspect is unpredictable, thus *Wands* Factor 7 weighs strongly against enablement. *Id.*, ¶¶26, 36–37, 99. Further, under precedents such as *Wyeth*, “having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation.” 720 F.3d at 1385. Just as in *Wyeth*, the claims are broad and the specification is narrow. The ’265 patent discloses three formulations, necessitating a research plan to identify

which of millions of untested formulations would be stable. The challenged claims thus improperly encompass the fruits of all that yet-to-be-undertaken research.

(c) A POSA, regardless of their qualifications, would not be able to predict formulation stability *a priori*.

A POSA would have been highly educated yet still unable to determine *a priori* which of the millions of formulations encompassed by the claims would be “stable” as defined in the ’265 patent (*supra* § III.A.4). EX1002, ¶¶26–29, 32–37. Thus, Wands Factor 6 requires specific disclosure, regardless of the level of skill.

(d) The prior art was not developed and there was no FDA-approved product to serve as a benchmark.

Under Wands Factor 5, the prior art was not developed. *Supra* § VII.A.1.d; EX1002, ¶¶278–289. As of 2013, there was no FDA-approved anti-IL23p19 antibody, let alone an FDA-approved formulation of Antibody A. EX1002, ¶278.

When rejecting claims of the ’061 application as obvious during prosecution, the examiner relied on the reference “Barrett” for its disclosure of an anti-IL23p19 antibody for “pharmaceutical use.” EX1004, 6967–78. In response to the rejection, BI argued that Barrett did not disclose any details regarding how to formulate the claimed antibody. *Id.*, 7000–03; EX1002, ¶278. BI also argued that formulating Antibody A would be unpredictable due to the lack of information about how to formulate that *specific* antibody. EX1004, 7001; EX1002, ¶¶26–29, 32–34, 70–85.

Thus, as BI admitted, the prior art offered no background guidance on how to make “stable” formulations of Antibody A. EX1002, ¶¶277–278; *supra* § III.

(e) The nature of the invention is complex as it involves unpredictable interactions and characteristics.

Making stable antibody formulations was, and remains, a complex and unpredictable undertaking, including arriving at formulations that are “stable” as defined in the ’265 patent (*supra* § IV.A). EX1002, ¶¶26–29, 32–34, 70–85. This is especially challenging for *liquid* antibody formulations, and even more so for liquid formulations with high antibody concentrations, such as those encompassed by the claims. *Id.*, ¶¶63–65. Thus, the nature of the invention (Wands Factor 4) shows that the specification must provide guidance. *Id.*, ¶¶26–29, 32–34, 70–85.

(f) There is insufficient guidance in the specification for how to identify formulations that would be “stable.”

The ’265 patent does not provide adequate guidance as to how or why the three formulations it exemplifies are “stable” under any set of conditions. *Supra* § VII.A.1. The ’265 patent does not disclose what variations to those formulations might also be “stable.” EX1002, ¶¶240–249. Simply put, the patent leaves a POSA without guidance to reduce the number of formulations that must be made, tested, and analyzed. Thus, under Wands Factor 3, there is minimal, if any, guidance. In “highly unpredictable technology,” merely disclosing narrow examples with no

further “guidance, direction, or working examples” renders claims non-enabled.

Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372–1374 (Fed. Cir. 1999).

(g) The specification offers three narrow examples but claims a genus encompassing millions of formulations.

The '265 patent discloses only two narrow examples within the scope of claim 7 and only three within the scope of claim 19. *Supra* § III.B. The '265 patent expressly refers to its formulations as “examples,” and all three list only specific formulation components in specific concentrations. EX1002, ¶127. Under Wands Factor 2, the examples are narrow and provide extremely limited information about which of the millions of diverse formulations encompassed by the claims would be “stable,” as defined in the patent (*supra* § IV.A). EX1002, ¶272. Where, as here, “working examples are present but are ‘very narrow, despite the wide breadth of the claims at issue,’” this factor weighs against enablement. *Idenix*, 941 at 1161.

(h) The quantity of experimentation needed for a POSA to practice the full scope of the claims is enormous.

Under Wands Factor 1, the quantity of experimentation required to make and test formulations within the scope of claims 7 and 19 for stability would have been enormous and undue. EX1002, ¶¶180–182, 220–221; *supra* § III.A.4. The process involves an extensive, time-consuming, and laborious trial-and-error undertaking to identify which of the millions—if not billions—of formulations encompassed by claims 7 and 19 are “stable.” EX1002, ¶¶36–37, 99, 180–182, 220–221; *supra* §

VII.A.1. As explained above, it was recognized in the art that “[t]he formulation of protein drugs is a difficult and time-consuming process.” EX1011, 131; EX1002, ¶¶23, 36–37, 99, 104. The art recognized that screening antibody formulations for stability “require[d] large amounts of protein,” and that this would be an especially high burden when testing high antibody concentrations, such as those encompassed by claims 7 and 19. EX1025, 1036; EX1002, ¶¶37, 104, 107; *supra* § III.A.3.

The term “stable” as recited in the claims encompasses stability following storage in a syringe for 8 weeks at 40°C or at 4° C for at least 4 months. *Supra* § IV.A. As detailed above (*supra* § III.A.4), no technique available in 2012, 2013, and even today, would offer a meaningful shortcut to the weeks and months of time, not to mention labor and resources, required to test an antibody formulation for stability under either of those sets of conditions. EX1002, ¶¶36–37, 105, 107.

Accordingly, under Wands Factor 1, practicing the full scope of claims 7 and 19 would require a POSA to perform an enormous amount of labor-intensive, time-consuming, trial-and-error experimentation because a POSA would have to make and test countless formulations. *Id.* This is undue experimentation. *Id.*, ¶290.

2. Claim 14 (and once-pending claim 44)

As shown above (*supra* §§ VII.A.1–2), claim 14 and once-pending claim 44 encompass millions of potential formulations. EX1002, ¶¶181–182, 270. Given the minimal guidance in the specification (two narrow examples) and elsewhere in the

art, a POSA would have had to discover whether potential formulations are stable under the conditions of claim 14 and once-pending 44. *Id.*, ¶¶36–37, 99, 104–105, 107, 300. This would require making large amounts of Antibody A (as the claims require a concentration of “90 mg/ml”) and then producing an impractically large number and variety of diverse formulations. *Id.* The POSA would then have to perform an impractically large number of stability studies, each study involving a process requiring months for a single formulation, or on the order of eight weeks following storage in a syringe at 40°C. *Id.* A POSA would then have to analyze the results to determine whether each formulation was stable. *Id.*; *supra* § III.A.4.

Claim 14 does not meaningfully narrow the scope of the claimed genus of formulations relative to claim 7. Accordingly, it is not enabled for substantially the same reasons as claim 7 discussed above. EX1002, ¶¶291, 295; *supra* § VII.B.1.

3. Claims 8 and 20

While claims 8 and 20 recite a specific detergent, adding “polysorbate 20” is insufficient to materially narrow the genus to a practicable scope. EX1002, ¶296. Claims 8 and 20, like claims 7 and 19 from which they depend, still encompass millions of potential formulations that would need to be made, tested, and analyzed to discover what is “stable” and thus covered by the claims. EX1002, ¶¶250–251; *supra* §§ VII.A.1, VII.A.3–4; III.A.4. As with independent claims 7 and 19, from which they depend, each potential combination of tonicity agent and its respective

concentration, each optional buffer and its respective concentration, as well as the various potential concentrations of Antibody A (for claim 19) would give rise to its own excipient-excipient and antibody-excipient interactions that yield their own behaviors and properties in formulation. EX1002, ¶¶70–85; *supra* §§ III.A.1–3.

Additionally, the heterogeneity of post-translation modifications present in a given batch of Antibody A could impart behaviors and properties that could, in turn, cause the formulation to be unstable. EX1002, ¶¶91–93; *supra* § III.A.3.d.

Because claims 8 and 20 do not meaningfully narrow the scope of the genus encompassed by claims 7 and 19, they are not enabled for substantially the same reasons as claims 7 and 19 discussed above. EX1002, ¶296; *supra* § VII.B.1.

4. Claims 9 and 21

While claims 9 and 21 recite a specific detergent and concentration, this is insufficient to materially narrow the genus to a practicable scope. EX1002, ¶¶250, 252, 256–257, 296. Rather, claims 9 and 21, like claims 8 and 20 from which they depend, still could encompass millions of potential formulations that would need to be made, tested, and analyzed. EX1002, ¶¶252–254; *supra* § VII.A.4. As shown for claims 8 and 20, the same behaviors and properties imparted by each combination of formulation components would apply to claims 9 and 21. *Supra* §§ III.A.1–3.

Because claims 9 and 21 do not meaningfully narrow the scope of the genus encompassed by claims 8, 20, 7, and 19, they are not enabled for substantially the same reasons discussed above. EX1002, ¶296; *supra* §§ VII.B.1, VII.B.3.

5. Claims 10 and 22

While claims 10 and 22 require “a buffer,” generically requiring “a buffer” is insufficient to materially narrow the genus. EX1002, ¶¶259–262, 292. Claims 10 and 22 do not recite any *specific* buffer, leaving a POSA to choose from among numerous buffers, each having its own unpredictable behaviors and properties. EX1002, ¶48–50, AppxB. Indeed, the art expressly cautioned “different buffer species affect the physicochemical stability of human monoclonal antibodies” (EX1051, 1122) and that buffers in “pharmaceutical formulation[s] must satisfy numerous requirements” (EX1016, 3052). EX1002, ¶¶48–50; *supra* § III.A.2.b.

Like claims 7 and 19 from which they depend, claims 10 and 22 encompass millions of potential formulations that would need to be made, tested, and analyzed to discover what is covered by the claims. EX1002, ¶¶260–262; *supra* § VII.A.5.

Because these claims do not meaningfully narrow the scope of the genus encompassed by claims 7 and 19, they are not enabled for substantially the same reasons as claims 7 and 19 discussed above. EX1002, ¶292; *supra* § VII.B.1.

6. Claims 15 and 27

While claims 15 and 27 add that the formulation's osmolarity is "300 +/- 30 mOsmol/kg," requiring an osmolarity within this range does not materially narrow the genus. EX1002, ¶259–260. A POSA would have known that solutions having a higher (or lower) osmolality than 300 mOsm/kg are hypertonic (or hypotonic). *Id.*, ¶263; EX1061, 3645–46; EX1016, 3054. Assuming the units of claims 15 and 27 are for osmolarity, a POSA would have understood that the limitation means that the formulation is isotonic, which does not materially narrow the genus because claims 7 and 19 already recite that the formulation is "isotonic." EX1002, ¶263.

Accordingly, claims 15 and 27, like claims 7 and 19, encompass millions of potential formulations that would need to be made, tested, and analyzed to discover what is covered by claims 15 and 27. EX1002, ¶¶267, 293; *supra* § VII.A.6.

Because these claims do not meaningfully narrow the scope of the genus encompassed by claims 7 and 19, they are not enabled for substantially the same reasons as claims 7 and 19 discussed above. EX1002, ¶¶267, 293; *supra* § VII.B.1.

7. Claims 16 and 28

While claims 16 and 28 add that the formulation has a pH in the range of 5.5 to 6.1, merely requiring a pH within this slightly narrower range is insufficient to materially narrow the genus. EX1002, ¶¶266–267. Rather, claims 16 and 28, like claims 7 and 19 from which they depend, still encompass millions of potential

formulations that would need to be made, tested, and analyzed. EX1002, ¶¶181–182, 220–221, 294; *supra* § VII.A.7. Because claims 16 and 18 do not meaningfully narrow the scope of the genus encompassed by claims 7 and 19, they are not enabled for substantially the same reasons. EX1002, ¶294; *supra* § VII.B.1.

VIII. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

For purposes of 35 U.S.C. § 322(a)(2) and 37 C.F.R. § 42.8(b)(1), and solely for the purpose of the current proceeding, Petitioner identifies the real parties-in-interest as Sandoz Inc. and Sandoz AG.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Under 37 C.F.R. § 42.8(b)(2), Petitioner is unaware of any related matters.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.9(b)(3))

Under 37 C.F.R. § 42.8(b)(3) and 42.10(a), Petitioner appoints **Timothy J. Shea** (Reg. No. 41,306) as lead counsel. Additionally, Petitioner **Pauline M. Pelletier** (*pro hac vice* motion to be filed) and **Christopher M. Gallo** (Reg. No. 70,291) as back-up counsel, at the address: Sterne, Kessler, Goldstein & Fox p.l.l.c., 1100 New York Avenue, N.W., Washington, D.C., 20005, phone number (202) 371-2600, and fax (202) 371-2540.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner consents to electronic service by email at the following addresses:

tshea-PTAB@sternekessler.com, ppelletier-PTAB@sternekessler.com, cgallo-PTAB@sternekessler.com, and PTAB@sternekessler.com.

Petitioner hereby consents to electronic service at the email addresses of lead and backup counsel listed above. Service of any documents via hand delivery may be made at the mailing address of lead and backup counsel listed above.

E. Power of Attorney (37 C.F.R. § 42.10(b))

A Power of Attorney for Sandoz Inc. has been filed concurrently herewith.

IX. PAYMENT OF FEES (37 C.F.R. §§ 42.203 and 42.15(a))

The required filing fee is being submitted herewith. The Office is hereby authorized to charge any fee deficiency, credit any overpayment, or charge any other fees in connection with this proceeding to Deposit Account No. 19-0036.

X. CONCLUSION

For the foregoing reasons, Petitioner requests institution of post-grant review and a final written decision finding challenged claims 7–10, 14–16, 19–22, and 27–28 of U.S. Patent No. 11,078,265 unpatentable for lack of written description under 35 U.S.C. § 112(a) and for lack of enablement under 35 U.S.C. § 112(a).

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/ Timothy J. Shea /

Timothy J. Shea
Registration No. 41,306
Counsel for Petitioner

Date: May 2, 2022

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION,
TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS**

1. Pursuant to 37 C.F.R. § 42.24(d), this Petition complies with the type-volume limitation of 18,700 words, comprising 18,507 words, excluding the parts exempted by 37 C.F.R. § 42.24(a).

2. This Petition 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.

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/Timothy J. Shea/

Timothy J. Shea
Registration No. 41,306
Counsel for Petitioner

Date: May 2, 2022

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.204(a))

The undersigned hereby certifies that on May 2, 2022, true and correct copies of the foregoing **PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 11,078,265** and all associated exhibits were served in their entireties on the following parties via FedEx Express® or Express Mail:

FOLEY & LARDNER LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

*PAIR Correspondence Address for U.S. Pat No.: 11,078,265
(and address Known to Petitioner as Likely to Effect Service)*

The above-listed documents were also served electronically via e-mail on May 2, 2022, on the following signing attorney as likely to effectuate service:

Kristel Schorr
FOLEY & LARDNER LLP
kschorr@foley.com

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

/ Timothy J. Shea /

Timothy J. Shea
Registration No. 41,306
Counsel for Petitioner

Date: May 2, 2022

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

APPENDIX A

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

Claim listing:

| Claim: | Limitation: | Claim Language: |
|---------------|--------------------|---|
| Claim 7 | 7.P | A liquid aqueous pharmaceutical formulation comprising |
| | 7.1 | (a) an anti-IL23p19 antibody in a concentration of 90 mg/ml, |
| | 7.2 | (b) a detergent, and |
| | 7.3 | (c) a tonicity agent, wherein the anti-IL23p19 antibody comprises a light chain amino acid sequence shown as SEQ ID NO:174 and a heavy chain amino acid sequence shown as SEQ ID NO:176, wherein the formulation is stable, isotonic, has a pH in the range of 5.5 to 6.5, and wherein the formulation optionally comprises a buffer. |
| Claim 8 | 8 | The liquid aqueous pharmaceutical formulation of claim 7, wherein the detergent is polysorbate 20 (PS20). |
| Claim 9 | 9 | The liquid aqueous pharmaceutical formulation of claim 8, wherein the PS20 is present at a concentration of 0.2 mg/ml. |
| Claim 10 | 10 | The liquid aqueous pharmaceutical formulation of claim 7, wherein the formulation further comprises a buffer. |
| Claim 14 | 14 | The liquid aqueous pharmaceutical formulation of claim 7, wherein the formulation is stable following storage in a syringe for 8 weeks at 40.degree. C. |
| Claim 15 | 15 | The liquid aqueous pharmaceutical formulation of claim 7, wherein the osmolarity of the formulation is 300 +/- 30 mOsmol/kg. |

*Petition for Post-Grant Review of
U.S. Patent No. 11,078,265*

| Claim: | Limitation: | Claim Language: |
|---------------|--------------------|---|
| Claim 16 | 16 | The liquid aqueous pharmaceutical formulation of claim 7, wherein the formulation has a pH in the range of 5.5 to 6.1. |
| Claim 19 | 19.P | A liquid aqueous pharmaceutical formulation comprising |
| | 19.1 | (a) an anti-IL23p19 antibody, |
| | 19.2 | (b) a detergent, and |
| | 19.3 | (c) a tonicity agent, wherein the anti-IL23p19 antibody comprises a light chain amino acid sequence shown as SEQ ID NO:174 and a heavy chain amino acid sequence shown as SEQ ID NO:176, wherein the formulation is stable, isotonic, has a pH in the range of 5.5 to 6.5, and wherein the formulation optionally comprises a buffer. |
| Claim 20 | 20 | The liquid aqueous pharmaceutical formulation of claim 19, wherein the detergent is polysorbate 20 (PS20). |
| Claim 21 | 21 | The liquid aqueous pharmaceutical formulation of claim 20, wherein the PS20 is present at a concentration of 0.2 mg/ml. |
| Claim 22 | 22 | The liquid aqueous pharmaceutical formulation of claim 19, wherein the formulation further comprises a buffer. |
| Claim 27 | 27 | The liquid aqueous pharmaceutical formulation of claim 19, wherein the osmolarity of the formulation is 300 +/- 30 mOsmol/kg. |
| Claim 28 | 28 | The liquid aqueous pharmaceutical formulation of claim 19, wherein the formulation has a pH in the range of 5.5 to 6.1. |