UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

DECLARATION OF BERNHARDT L. TROUT, Ph.D.

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- A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4 33
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I, Bernhardt L. Trout, Ph.D., hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I understand that the Patent Trial and Appeal Board has granted Amgen Inc.'s ("Amgen") petition to institute this *Inter Partes* Review ("IPR") regarding claims 1-10 of U.S. Patent No. 9,725,504 ("the challenged claims of the '504 patent"). (AMG1001.) I understand from counsel that the '504 patent is owned by Alexion Pharmaceuticals Inc. ("Alexion").

3. This Declaration sets forth my opinions with respect to the challenged claims of the '504 patent, including the documents I considered, and my response to certain opinions set forth in the Declaration of Dr. Joseph P. Balthasar, Ph.D. (AMG1002) as they relate to issues of pharmaceutical formulation and pharmaceutical compositions of monoclonal antibodies.

4. I have been asked whether, from the perspective of a person of ordinary skill in the art ("POSA") prior to March 15, 2007, the pharmaceutical compositions recited in claims 4 and 5 of the '504 patent would have been obvious in view of Hillmen (2004) (AMG1004) and Bell (AMG1005) as asserted in Amgen's Ground 2.

5. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious in view of Hillmen (2004), Bell, and Wang (AMG1028) as asserted in Amgen's Ground 3.

6. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1-5 and 7-10 of the '504 patent would have been obvious in view of Bell, Bowdish (AMG1006), and Evans (AMG1007) as asserted in Amgen's Ground 4.

7. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious in view of Bell, Bowdish, Evans, and Wang as asserted in Amgen's Ground 5.

8. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1-5 and 7-10 of the '504 patent would have been obvious in view of Bell, Evans, and Mueller as asserted in Amgen's Ground 6.

9. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious over Bell, Evans, Mueller, and Wang as asserted in Amgen's Ground 7.

10. Below is a complete Table of the Grounds upon which I will opine in this declaration.

Ground	Claims	Basis	Asserted References
2	4,5	35 U.S.C. § 103(a)	Hillmen (2004) and Bell
3	6	35 U.S.C. § 103(a)	Hillmen (2004), Bell, and Wang
4	1-5, 7-10	35 U.S.C. § 103(a)	Bell, Bowdish, and Evans
5	6	35 U.S.C. § 103(a)	Bell, Bowdish, Evans, and Wang
6	1-5, 7-10	35 U.S.C. § 103(a)	Bell, Evans, and Mueller
7	6	35 U.S.C. § 103(a)	Bell, Evans, Mueller, and Wang

11. I am being compensated at my usual rate for consultation on patent matters of $ 900/hr, plus any additional reasonable expenses. My compensation is in no way dependent on the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

12. I am currently a Professor of Chemical Engineering at the Massachusetts Institute of Technology (MIT). I am also Director of the Society, Engineering and Ethics (SEE) Program at MIT.

13. I received my B.S. and M.S. degrees from MIT (1990) and my Ph.D. from the University of California at Berkeley (1996), all in chemical engineering. I performed post-doctoral research at the Max-Planck Institute for Solid-State Physics in Stuttgart. In 1998, I became an Assistant Professor of Chemical Engineering at MIT. I was promoted to Associate Professor of Chemical Engineering in 2003, and I was promoted to Full Professor of Chemical

Engineering at MIT in 2008. Since 2014, I have held the Raymond F. Baddour, ScD, (1949) Chair as Professor of Chemical Engineering.

14. I am a member of various scientific societies including the American Institute of Chemical Engineers, the American Association of Pharmaceutical Scientists, and the American Chemical Society.

15. I have been a reviewer for several journals including mAbs, Proceedings of the National Academy of Sciences, The Journal of Physical Chemistry, Chemical Physics Letters, Pharmaceutical Research, Journal of the American Chemical Society, Biochemistry, Journal of Pharmaceutical Sciences, Biophysical Journal, The Journal of Organic Chemistry, Analytical Biochemistry, Research Letters in Physical Chemistry, Nature Materials, Molecular Pharmaceutics, Chemical Physics Letters, and Angewandte Chemie.

16. I have given more than 150 invited talks on pharmaceuticals including difficulties associated with antibody formulation and stability, including at the FDA, the American Association of Pharmaceutical Sciences, the Industrial Society of Pharmaceutical Engineering, the American Chemical Society, PEP Talk, and many companies.

17. I have published more than 200 papers in refereed journals and have 18 patents pending or issued.

18. I have over 20 years' experience working with protein formulation and have focused my research on monoclonal antibody formulation since 2004.

19. My current research group at MIT consists of approximately 5 Masters or Ph.D. students, Post-Doctoral Associates, and technical research staff, most of whom focus on antibody formulation research. My research consists of a wide range of areas in pharmaceutical and biopharmaceutical (protein and antibody) development and manufacturing, including formulation and stabilization. Target formulations and manufacturing approaches include both liquid and lyophilized final dosage forms. My research investigates the underlying science of pharmaceutical and biopharmaceutical development and manufacturing and aims to develop new technologies in those areas.

20. My work includes developing approaches to antibody stabilization, developing tools to mitigate antibody aggregation, evaluating monoclonal antibody aggregation, and developing stable antibody formulations. Since starting as a professor at MIT in 1998, I have worked on about 50 or more biologic therapeutics, most of them monoclonal antibodies. The vast majority of this work has been sponsored by industry and includes characterization, formulation, and design of antibodies. My laboratory has elucidated mechanisms of degradation, including aggregation, oxidation, deamidation, and hydrolysis. Current research includes developing approaches for the rational formulation of monoclonal

antibodies and determining key molecular descriptors responsible for various degradation routes in addition to enhanced viscosity.

21. Since 2010, I have been the lead instructor (with a colleague from the FDA and a colleague from industry) of an MIT professional short course entitled, "Formulation and Stabilization of Biotherapeutics." This course is offered annually and mainly consists of professionals in the area of formulation who want to enhance their knowledge in the subject.

22. I also consult and have given invited talks and plenary lectures on topics including stabilizing proteins and antibodies for industry, including for Amgen and Biogen-Idec. I have also lectured at the Biomanufacturing Summit, Cambridge, MA., and have been a consultant for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Overall, my consulting consists of a range of endeavors from technical problem solving to strategy. Much of this consulting is related to formulation of biopharmaceuticals, including mAbs to be commercialized. At least one monoclonal antibody that I have consulted on is now a commercial product, and several others are being commercialized.

23. A full description of my background, awards, and qualifications can be found in my curriculum vitae attached as an appendix to this declaration. My curriculum vitae is attached hereto as Appendix A (ALXN2025.).

III. SUMMARY OF OPINIONS

24. In forming my opinions contained in this Declaration, I have relied on my education, background and experience in antibody formulation. I have also reviewed the ’504 patent, the Balthasar Declaration (AMG1002), the transcript for the October 23, 2019 Deposition of Dr. Joseph Balthasar (ALXN 2032); the Institution Decision (Paper No. 15), and the publications, patents, patent applications and other documents cited in this Declaration.

25. In connection with the opinions and conclusions contained within this Declaration, I have reviewed and considered the documents listed in Appendix B attached to this Declaration, as well as any other documents cited throughout this Declaration.

26. I understand that the documents Bell (AMG1005), or Bell in combination with Wang (AMG1028) are cited in Amgen’s asserted Grounds 2-7 for *inter partes* review of the ’504 patent. Based on my experience and expertise, and the documents and information I have reviewed and considered, I disagree with Dr. Balthasar’s positions that Bell (AMG1005), or Bell in combination with Wang (AMG1028) disclosed the pharmaceutical compositions recited in claims 1-10 of the ’504 patent. I further disagree with Dr. Balthasar’s opinions that a person of ordinary skill in the art (“POSA”) would have been motivated to make and use

the pharmaceutical compositions claimed in the ’504 patent, or that a POSA would have had a reasonable expectation of success in doing so.

IV. LEGAL PRINCIPLES PROVIDED BY COUNSEL

27. I am not an attorney. However, I have been advised of the following legal principles, and they have helped to form my conclusions in this report. I understand that Petitioner has asserted that the challenged claims of the ’504 patent are unpatentable under 35 U.S.C. § 103 as obvious in view of the various prior art combinations I listed in paragraphs 4-9, above.

28. I understand that it is Amgen’s burden to show that the challenged claims are obvious, and that to do this Amgen must show, without the benefit of hindsight, that the claimed invention as a whole would have been obvious to a POSA prior to the date of invention or “priority date.”

29. I understand the Board will consider the following factors when assessing whether Amgen has met its burden to show obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. I have been informed by counsel that objective evidence of non-obviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products

embodying the claimed invention; teaching away from the invention in the prior art; copying of the invention; and industry praise.

30. I understand that, when considering obviousness, I must not use hindsight knowledge of the invention claimed in the ’504 patent. I understand that I must consider only documents or information that would have been available before the priority date. I further understand that I must consider the full scope and content of the prior art that would have been available to a POSA as of March 15, 2007, and that I may not use hindsight to select references from the prior art to be considered in the obviousness analysis. I understand that I must consider the prior art as a POSA would have viewed it as of March 15, 2007, without the benefit of knowing how the invention was successfully achieved.

31. I understand that Amgen must show that, without the benefit of hindsight, a POSA would have been motivated to combine a particular set of prior art references, and that in doing so a POSA would have had a reasonable expectation of success in achieving the claimed invention.

V. PERSON OF ORDINARY SKILL IN THE ART AS OF MARCH 15, 2007

32. I understand from counsel that, for purposes of this proceeding, the ’504 patent is to be read from the perspective of a person of ordinary skill in the art (“POSA”) at the time of invention. I further understand that a POSA is a

hypothetical person who is presumed to know the relevant art at the time of the invention.

33. I understand that the Board has accepted a definition of POSA as a person with an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. (Institution Decision, '504 Paper 15 at 20-21.) I agree with this definition, and I provide my opinions from the perspective of a POSA of March 15, 2007, with a focus on issues pertaining to antibody formulation.

34. I also understand that Dr. Balthasar proposed that "a POSA may have worked as part of a multidisciplinary team and drawn upon not only her or her own skills, but also taken advantage of certain specialized skills of others on the team," including "a clinician and a formulation chemist." (AMG1002 ¶ 20.) I agree that a POSA with respect to the '504 patent could have – and in the context of drug development, would have – consulted with others having specialized skill and experience concerning the formulation of pharmaceutical compositions of monoclonal antibodies, as well as others having specialized skill and experience in clinical therapy.

35. I understand from counsel that, for purposes of this proceeding, the '504 patent and other pertinent information is to be considered from the

perspective of a POSA **prior to March 15, 2007**, which counsel informs me is the earliest filing date for the ’504 patent.

VI. STATE OF THE ART REGARDING FORMULATION OF THERAPEUTIC ANTIBODIES AS OF MARCH 15, 2007

A. Monoclonal Antibodies for Human Therapeutic Use

36. As of March 15, 2007, a POSA would have known that antibodies[1] are large, roughly Y-shaped protein molecules. Figure 1 below, adapted from Dr. Balthasar’s declaration, is a simplified two-dimensional illustration of the general structure of an antibody. (AMG1002 ¶ 26.) As seen in the figure, antibody structure can be divided into two regions: the “variable” region at the top of the Y-shaped structure, and the “constant” regions that start below the variable regions

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[1] Unless otherwise noted, I use the term “antibodies” to refer to intact, full-length antibody structures. A POSA would have also known of various antibody-related molecules that are structurally different from full-length, intact antibodies. These would have included “Fab” fragments, each consisting of one antigen-binding “arm” of an IgG antibody – *i.e.*, the variable and constant regions from a light chain, and the variable and first part of the constant region from a heavy chain – and “single-chain variable fragments,” or “scFv,” each consisting of the variable region of a heavy chain linked by a synthetic peptide to the variable region of a light chain. (AMG1029 at 8; *see also* AMG1030 at 699-700.)

through the stem of the Y structure. The variable regions at the top of the "Y" were understood to include the sites that bind to certain target compounds, known as "antigens," and were also referred to as the "antigen binding region."

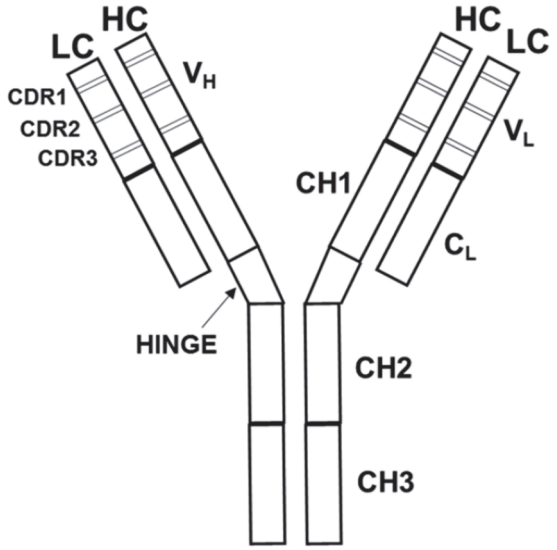

Figure 1: General structure of an IgG-class antibody

37. Following the creation of "monoclonal" antibody technology that (if successfully carried out) could potentially result in the development of highly selective antibodies directed only against a specific target antigen, monoclonal antibodies became an area of interest of pharmaceutical development. (AMG1030 at 686-87.) As Dr. Balthasar notes, and I do not dispute, there were at least 23 monoclonal antibody products (including partial antibody structures ("Fab") and conjugates) approved for commercial marketing in the United States as of March 15, 2007. (AMG1002 ¶¶ 28, 98 fn 7, Appendix I; AMG1029 at 2-4 (Table 1).)

38. The majority of commercial monoclonal antibody products were full-length antibodies of the IgG class. (AMG1029 at 2-4 (Table 1).) Of "humanized" antibodies – *i.e.*, antibodies made from the combination of human variable and constant regions with mouse CDRs – the IgG1 subclass was most common, followed by IgG4. (*Id.*; AMG1030 at 688.) All of the approved antibodies used naturally-occurring isotypes – there were no approved antibodies with a non-naturally occurring, engineered (*e.g.*, "hybrid") constant region isotype. (*Id.*)

39. These 23 commercial monoclonal antibody products were developed for a variety of therapeutic and diagnostic applications in humans, including treatment of cancer (*e.g.*, Avastin (bevacizumab)) and chronic inflammatory conditions (*e.g.*, Humira (adalimumab)). (AMG1029 at 2-4 (Table 1).) A POSA as of March 15, 2007 would have known that, to be marketed commercially in the United States, the makers of these 23 products had to demonstrate to the U.S. Food and Drug Administration ("FDA") that these products were safe and effective for their indicated use. (ALXN2032 at 46:20-48:2; ALXN 2079 at 19.)

40. A POSA would have further known that, to obtain the FDA's authorization to even study these monoclonal antibody products in human clinical trials prior to their approval for commercial marketing, the FDA would have required the submission of extensive information characterizing the product to be administered to humans – including information regarding the monoclonal

antibody in the form of the pharmaceutical composition to be used in clinical trials. (ALXN2029 at 12-13, 23, 31-33; ALXN2079 at 19.) As a POSA understood, the purpose of this FDA review was to ensure that human subjects would not be put at undue risk when receiving the antibody product in experimental clinical trials. (*See* ALXN2032 at 46:20-48:2.)

B. Challenges to Formulation of Therapeutic Monoclonal Antibody Products as of March 15, 2007

41. A POSA would have understood that, for a monoclonal antibody to be made available for therapeutic use in humans, a "formulation" or "pharmaceutical composition" would need to be developed, which would include the monoclonal antibody itself as the active ingredient, as well as additional, "inactive" ingredients. (AMG1029 at 14; AMG1030 at 701; ALXN2080 at 163-64, 175-76, 178.) But, as of March 15, 2007, developing suitable pharmaceutical compositions of new, previously-unformulated monoclonal antibodies was not a straightforward task. In particular, a POSA would have understood that a suitable formulation for one antibody might not be suitable for another antibody – even if the two were closely related in sequence and structure. In fact, a POSA would understand that the approach to formulating a given antibody was to develop a formulation from scratch, not plug the antibody into formulations that were developed for other antibodies. (*See, e.g.*, AMG1029 at 5 ("[T]he behavior of antibodies [in pharmaceutical compositions] seems to vary, even though they have similar

structures.”); AMG1030 at 690 (“Each antibody seems to have a unique personality related to its requirements for stability. . . . [T]he interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.”).)

42. In my 20-plus years of experience working in conjunction with pharmaceutical companies on the development of pharmaceutical formulations, I have personally seen on many occasions that an antibody that appeared to be promising from studies in the “discovery” phase of development could not move forward into clinical development because it was not capable of being made into a suitable pharmaceutical composition.

43. As discussed below, there were a variety of issues that a POSA would have needed to address in formulating a monoclonal antibody, with numerous options for addressing them. For example, a POSA would have needed to consider the intrinsic stability of the monoclonal antibody, and the effects of a formulation on its rates of chemical and physical degradation. (AMG1029 at 15-17; AMG1030 at 689-90; ALXN2080 at 163-64, 175-76, 178.) Formulation development – including the concentration of an antibody formulation – could be influenced by the desired route of administration (*e.g.*, intravenous or subcutaneous) and type of formulation (liquid vs. lyophilized), and, vice versa, the desired route of administration and chosen formulation type could be influenced by the outcome of

studies during formulation development. (ALXN2079 at 2, 4 (Table 2), 10-12; *see also* ALXN2080 at 178; AMG1029 at 14-15; AMG1030 at 694-95.) As of March 15, 2007, monoclonal antibody formulation development was not a linear process, but instead involved significant empirical testing, and rounds of decisions made based on the results of formulation development studies.

44. Overall, a POSA as of March 15, 2007 would have understood that a primary goal of developing an antibody formulation was to achieve sufficient **stability** so that the product could be **stored and transported**, and thereafter, **safely and effectively** administered to human patients. As one major 2007 review cited by Dr. Balthasar explained, "The **major purpose** of formulating antibodies as therapeutic agents [was] to **control the rate of antibody degradation** to provide an acceptable shelf life for worldwide shipping and storage."[2] (AMG1029 at 14 (emphases added); *see also* ALXN2079 at 19 ("[T]he formulation should maintain the safety and efficacy profile of the protein drug during all the handling and uses specified on the label."); ALXN2080 at 178 ("In the development of a protein formulation, the most challenging task is the stabilization of a protein to achieve an acceptable shelf life.").)

[2] Unless otherwise noted, all emphases are added.

45. In general, a POSA understood "stability" in the context of monoclonal antibody pharmaceutical compositions to refer to a variety of types of physical or chemical degradation, resulting in unwanted "degradants" or "degradation products." (*See* AMG1029 at 8-14; AMG1030 at 690-94; ALXN2080 at 137-45; *see also* ALXN2082 at 300-01.)

46. A POSA developing an antibody for therapeutic use would have been particularly concerned about the effects on patients resulting from administering an insufficiently stable formulation containing such degradation products. For example, a POSA understood that the degradation products may have reduced therapeutic activity relative to the therapeutic antibody itself. (AMG1029 at 14; AMG1030 at 690; ALXN2079 at 9; ALXN2080 at 137; *see also* ALXN2082 at 300-01.) A POSA would have also understood that administering an insufficiently stable formulation could result in safety risks, such as increased immunogenicity – which could lead to "neutralization" of the therapeutic antibody by the patient's immune system, as well as immune reactions against a patient's own endogenous proteins. (ALXN2083 at E503; ALXN2082 at 300-01; AMG1029 at 14; *see also* ALXN2081 at 897, 901; ALXN2080 at 137; ALXN2079 at 9.)

47. As of March 15, 2007, a POSA would have understood that multiple pathways could contribute to antibody physical and chemical degradation. For example, types of physical instability included denaturation (misfolding of the

protein) and partial denaturation, which could be caused by temperature change, shear-stress, certain processing steps, or time; and aggregation, which can be impacted by antibody concentration, temperature, storage, shaking, viscosity, ionic strength, pH, and lyophilization process parameters, amongst other factors. (AMG1029 at 8-9; AMG1030 at 689-90, 692-95; *see also* ALXN2080 at 137-40; ALXN2079 at 13 (Table 6).)

48. A POSA would have also been aware of various potential pathways for chemical instability of antibody formulations, including, for example, cross-linking (potentially resulting in chemical aggregation); deamidation, isomerization, and oxidation (resulting in changes to certain amino acids of the primary amino acid sequence); formation of acidic or basic species; C-terminal clipping (removal of certain lysine amino acids); fragmentation; and sugar adduct formation. (AMG1029 at 11-14; AMG1030 at 690-92; *see also* ALXN2080 at 140-145; ALXN2079 at 13 (Table 6).) Chemical instability was known to be influenced by factors such as storage, temperature, pH, and (for oxidation) light exposure. (AMG1029 at 11-14.) It was understood that, generally speaking, both physical and chemical instability tended to increase with increased temperature and storage time. (*See* AMG1029 at 8-14; ALXN2079 at 15-16.)

49. Aggregation in particular was a prevalent stability issue for antibody formulations. It was one of the more commonly experienced physical instability

issues and could potentially limit the concentration of an antibody formulation. (AMG1029 at 8, 14-15; *see also* AMG1030 at 692-93; ALXN2080 at 137-140.) Antibody aggregates were generally known to have reduced activity and greater potential to cause immune reactions due to the aggregates' altered conformation and interaction with epitopes. (AMG1029 at 9; ALXN2080 at 137; ALXN2079 at 9; *see also* ALXN2082 at E503; ALXN2081 at 901 (describing aggregation as a concern for immunogenicity of even fully human proteins).) Due to aggregates' potential to impact safety and efficacy, even low levels could be unacceptable for a pharmaceutical composition to be administered to human patients. (ALXN2079 at 9 ("[E]ven at levels of a few percent or less of the total protein population, non-native aggregates can cause adverse reactions in patients such as immune responses and even anaphylactic shock."); ALXN2080 at 137.)

50. A POSA would also have understood that development of liquid formulations was especially challenging. This was because liquid formulations were known to have more stability issues than lyophilized formulations, including concentration-dependent aggregation, physical instability due to shaking/shear-stress, and increased potential for chemical instability due to storage in water-based formulations, which could facilitate the chemical reactions known to cause antibody degradation. (AMG1029 at 14-17; AMG1030 at 694; ALXN2080 at 150, 152; ALXN2079 at 10.) Although liquid formulations were generally preferred

because they were easier to administer and less expensive to manufacture, as of 2007 many commercial antibody products could not be stabilized as a liquid formulation. (AMG1029 at 2-4 (Table 1), 14; *see also* AMG1030 at 694; ALXN2079 at 10-11 ("Because lyophilized products have less stability-related issues and have a much greater potential tolerance for room-temperature storage, many biopharmaceutical industries consider the lyophilized formulation as a default option.").) Lyophilized formulations were often used where stability issues prevented development of a liquid formulation. (ALXN2079 at 10.)

51. Although generally considered more stable than liquid formulations, a POSA would still have understood that lyophilized formulations were associated with their own set of potential instabilities and development challenges. (*See* ALXN2080 at 175 ("[F]reeze-dried solid protein formulation is generally more stable [than liquid formulation], although lyophilization often causes significant protein instability.").) For example, a POSA would have understood that design of a lyophilized formulation would require selection of an acceptable bulking agent and stabilizers to form a solid "cake," and that lyophilization came with a risk of aggregation and other degradation processes during lyophilization, reconstitution and storage. (AMG1029 at 18-20; AMG1030 at 694-95.) Such risk could be exacerbated depending on the moisture content. (AMG1029 at 18-20; AMG1030 at 694-95.)

52. A POSA would have been aware of antibody stability issues related to the concentration of antibody formulations. Sufficiently high antibody concentration was understood to be desirable for formulations to be administered by subcutaneous injection, to achieve low enough injection volume required for patient administration. (AMG1029 at 14; AMG1030 at 688, 692.) However, in liquid formulations higher antibody concentration was generally thought to increase the risk of antibody aggregation by increasing the frequency of protein-protein interactions. (AMG1029 at 14; AMG1030 at 692; ALXN2080 at 152.)

53. Accordingly, a POSA as of March 15, 2007 would have understood that antibody formulation development would encompass significant empirical work to develop a formulation with sufficient stability for therapeutic use, and still might not succeed. (ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.) A POSA would have generally understood that stability testing was to reflect the various "external conditions which can affect the [antibody] product's potency, purity and quality." (ALXN2084 at 2.) Stability testing typically would include, among other things, studies of the integrity of the antibody and its degradation under various conditions over time, to account for stability in storage and shipment. (ALXN2085 at 2; *see also* ALXN2079 at 5-7, 15-16.)

54. Typically, testing would be done early in the development process to assess an antibody's susceptibility for various forms of degradation, identify likely formulation challenges, and develop relevant analytical methods for assessing stability. (ALXN2079 at 5.) These tests would include accelerated stability studies, in which an antibody's stability was assessed under stress conditions to try to predict instability that could develop over its shelf-life. (ALXN2079 at 5; ALXN2080 at 177; ALXN2084 at 7; ALXN2085 at 17; ALXN2029 at 23; *see also* AMG1029 at 17-18, 20.) Stress conditions could include exposing an antibody formulation to high temperature, mechanical stress such as agitation (shaking / stirring), light, multiple freeze/thaw cycles, oxidation, or exposure to denaturants. (ALXN2079 at 5-6; ALXN2080 at 177.)

55. A POSA would have known to examine various product characteristics to assess stability. These included biologic activity, rate of antibody degradation and identity of degradants, formation of aggregates / precipitation (antibody coming out of solution – typically due to formation of aggregates), solution color, pH, viscosity, and sterility. (ALXN2080 at 177; ALXN2079 at 7; *see also* ALXN2084 at 5-6; ALXN2029 at 23.) Analytical methods used to assess these characteristics could have included various forms of chromatography (*e.g.*, HPLC), electrophoresis (*e.g.*, SDS-PAGE), spectroscopy, thermal analysis, and light scattering / turbidity. (ALXN2079 at 7.) It was understood that a variety of

analytical methods were necessary to accurately assess antibody stability, due to the complex nature and multiple pathways for antibody degradation. (ALXN2079 at 6; ALXN2080 at 178 ("[N]o single technique can satisfactorily provide sufficient information about a protein. Thus, a combination of analytical methods needs to be used to characterize a protein and to monitor protein instability.").)

56. As development progressed, additional studies would need to be performed to further progress development of candidate formulations, and to assess the impact of transportation and handling and process scale-up on antibody stability. (ALXN2079 at 13-16.) Further, a POSA would have understood that real-time storage studies, lasting months to years, would need to be performed to assess the actual stability of an antibody over the course of its shelf-life, as accelerated studies were known to be not entirely predictive. (ALXN2079 at 16; ALXN2080 at 178; ALXN2084 at 2; ALXN2085 at 4, 10; ALXN2029 at 23.)

VII. THE '504 PATENT

57. In forming my opinions in this case, I have reviewed and considered the '504 patent, including its specification and claims. I understand from counsel that the '504 patent was not available to a POSA prior to March 15, 2007, and that analysis of whether the claims of the '504 patent would have been obvious to a POSA prior to March 15, 2007 must be done from the perspective of a POSA without hindsight knowledge of the '504 patent or its claims.

58. Claims 1-10 of the ’504 patent read as follows:

> **1.** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 2. The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.
>
> 3. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.
>
> 4. The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.
>
> 5. The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.
>
> 6. The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg

single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. The method of claim 1, wherein the patient is anemic.

8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7+1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7+1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14+2 days.

9. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

59. The specification of the ’504 patent includes a description of a randomized, multi-center, double-blind, placebo controlled clinical trial (“TRIUMPH”) assessing the efficacy of eculizumab to treat paroxysmal nocturnal hemoglobinuria (“PNH”). (AMG1001 at 19:51-28:38.) Eculizumab, or placebo,

was administered by intravenous infusion, at 600 mg every 7 days for 4 doses, followed by 900 mg (or placebo) by IV infusion 7 days later, followed by a maintenance dose of 900 mg (or placebo) by IV infusion every 14 days, for a total of 26 weeks of treatment. (AMG1001 at 20:39-50.) The results of the study showed that eculizumab was a "safe and effective therapy for patients with the rare disorder PNH." (AMG1001 at 28:21-24.) Patients in the study experienced an improvement in PNH symptoms, including reduced intravascular hemolysis, stabilized hemoglobin levels, reduced fatigue, and a reduction in the need for blood transfusions such that most patients became transfusion independent, and an improved quality of life. (AMG1001 at 28:25-30.)

60. The '504 patent identifies "eculizumab" as an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (AMG1001 at 30:22-31, 30:38-44.)

61. The '504 patent describes the invention as including "a method of treating a patient suffering from [PNH] by administering a pharmaceutical composition comprising an antibody that binds C5," and, more specifically, eculizumab. (AMG1001 at 3:13-19.) The '504 patent further states that the antibody can be administered in a "300 mg single-use dosage form, comprising 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001 at 4:15-18, 4:22-24.)

62. I understand that there is a dispute between Amgen and Alexion as to, among other things, (1) whether an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4 was disclosed by, or obvious in view of, the prior art available prior to March 15, 2007, and (2) whether, prior to March 15, 2007, a POSA would have known that "eculizumab" was an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4. For purposes of this proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the claimed amino acid sequence, except to say that in my review of Bell (AMG1005) and Wang (AMG1028), I did not see **any** disclosure of the specific amino acid sequence recited in claims 1-10 of the '504 patent, or **any** disclosure that "eculizumab" had the specific amino acid sequence recited in claims 1-10 of the '504 patent.

63. I further understand that there is a dispute between Amgen and Alexion as to whether it was known prior to March 15, 2007 that "eculizumab" had a hybrid IgG2/IgG4 constant region structure. I understand that it is known **today** that, eculizumab, as used the commercial product SOLIRIS®, contains a non-naturally occurring, engineered heavy chain constant region including a specific combination of sequences from human "IgG2" and human "IgG4" constant regions. I further understand it is known **today** that the heavy chain consisting of SEQ ID NO: 2 in claims 1-10 of the '504 patent reflects the sequence of the non-

naturally occurring heavy chain constant region in SOLIRIS® (eculizumab). For purposes of this proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the identity of the constant region or isotype of "eculizumab." It is my opinion, however, that prior to March 15, 2007, there were no FDA-approved or commercially marketed products in the United States containing any non-naturally occurring, engineered "hybrid" isotypes, let alone the specific hybrid isotype of SOLIRIS® reflected in SEQ ID NO: 2 of the '504 patent. (*See* AMG1029 at 2-4 (Table 1).)

VIII. BELL (AMG1005), OR BELL AND WANG (AMG1028), DID NOT MOTIVATE A POSA TO MAKE THE CLAIMED COMPOSITIONS OF THE '504 PATENT, OR GIVE A POSA A REASONABLE EXPECTATION OF SUCCESS IN DOING SO

64. In my opinion, nothing in the Bell (AMG1005) and Wang (AMG1028) documents, alone or in any combination, would have motivated a POSA as of March 15, 2007 to make the pharmaceutical compositions recited in claims 1-10 of the '504 patent, or would have given a POSA a reasonable expectation of success in doing so.

65. I have reviewed and considered Dr. Balthasar's arguments regarding the teachings of Bell (AMG1005) and Wang (AMG1028) as they relate to the claims of the '504 patent, and I disagree. In my opinion, Dr. Balthasar uses his hindsight knowledge of the claimed invention of the '504 patent to make assumptions about Bell and Wang that are not supported by the text available to a

POSA prior to March 15, 2007, and misconstrues how a POSA without hindsight would have understood the teachings of those documents.

66. While both Bell (AMG1005) and Wang (AMG1028) refer to the antibody "eculizumab," I have seen nothing in either document that discloses the complete amino acid sequence for "eculizumab," or in any way associates "eculizumab" with an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, the sequence that is recited in the claims of the '504 patent. I also did not see anything in my review of Bell or Wang that identified "eculizumab" as having a hybrid IgG2/IgG4 isotype. I understand Dr. Balthasar agrees with me that Bell and Wang (AMG1028) did not disclose the specific amino acid sequence of the '504 patent claims. (*See, e.g.*, AMG1002 ¶ 139 ("Bell does not provide the amino acid sequence of eculizumab . . . ."); ALXN2032 at 146:15-25, 256:15-257:20.)

67. Despite his admissions regarding the limits of Bell and Wang, Dr. Balthasar contends a POSA would have connected the "eculizumab" antibody of Bell and Wang with the '504 patent's specific claimed amino acid sequence, based on information he combines from other documents outside of Bell and Wang. (*See, e.g.*, AMG1002 ¶¶ 120, 130 ("Bowdish and Evans together"); AMG1002 ¶ 172 (citing "Evans and Mueller").) I understand that Alexion disagrees that Dr. Balthasar's cited combinations of documents disclosed the claimed amino acid

sequence of the ’504 patent, or that a POSA as of March 15, 2007 would have known the “eculizumab” antibody of the Bell (AMG1005) or Wang (AMG1028) to have the claimed amino acid sequence of the ’504 patent.

68. Regardless of whether Alexion or Amgen is correct on what a POSA as of March 15, 2007 knew, if anything, about the specific amino acid sequence of the “eculizumab” antibody referenced in Bell (AMG1005) and Wang (AMG1028), it is my opinion that a POSA would **not** have been motivated by Bell and Wang to make the claimed pharmaceutical compositions of the ’504 patent, and would not have reasonably expected success in doing so. Specifically:

- **If Bell’s and Wang’s “eculizumab” was *not* known to be an antibody with the claimed sequence of the ’504 patent:** A POSA as of March 15, 2007 would not have been motivated by Bell (for claims 1-5 and claims 7-10) or Bell and Wang (for claim 6) to make the claimed pharmaceutical compositions of the ’504 patent, and would not have reasonably expected to succeed in doing so, because, among other things, a POSA would have had no evidence that an antibody with the sequence claimed in the ’504 patent had **ever** been successfully formulated for therapeutic use. In view of the challenges regarding therapeutic antibody formulation (*see* Section VI.B above), a POSA would not have reasonably assumed that any particular new, previously-unformulated

antibody could be made into a pharmaceutical composition suitable for human therapeutic use, let alone the specific composition recited in claim 6 of the ’504 patent. And even if, hypothetically, a POSA had understood generally that eculizumab had a hybrid IgG2/IgG4 isotype, but did not know that “eculizumab” corresponded to the specific claimed amino acid sequence, a POSA would not have been motivated by Bell and Wang to create the claimed compositions with a reasonable expectation of success. In particular, there were no commercial antibodies with a non-natural IgG2/IgG4 isotype available as of March 15, 2007, and Bell and Wang do not provide guidance as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. Even if there were, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

- **Even under Amgen’s theory that Bell’s and Wang’s “eculizumab” was known to be an antibody with the claimed sequence of the ’504 patent:** It is my opinion that, in this scenario, a POSA as of March 15, 2007 would not have been motivated by Bell and Wang to make the specific claimed pharmaceutical composition of at least claim 6 of the

’504 patent, (*i.e.*, “a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution”), and would not have reasonably expected success in doing so. Nothing in Bell (AMG1005) provided a POSA with any specific guidance towards the pharmaceutical composition of claim 6. And Wang (AMG1028) – which described various antibodies for inhalation administration with nebulizers – neither disclosed the specific pharmaceutical composition of claim 6, nor would it have motivated a POSA to make such a composition, or provided a POSA with a reasonable expectation of success in doing so. Further, as stated above, Bell and Wang would not have provided a POSA with motivation to create a formulation for an antibody with a non-natural, IgG2/IgG4 isotype, because there were no commercial antibodies at the time with this isotype, and Bell and Wang did not provide any guidance as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. . Even if they did, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4

69. If it were the case that a POSA as of March 15, 2007 did not know that the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028) was the claimed antibody comprising SEQ ID NOs: 2 and 4 recited in the '504 patent, then in my opinion, a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, the pharmaceutical compositions recited in claim 6 of the '504 patent. In this scenario, neither Bell nor Wang would have taught a POSA that **any** pharmaceutical composition of an antibody comprising SEQ ID NOs: 2 and 4 had ever been created or even attempted. With no evidence that an antibody comprising SEQ ID NOs: 2 and 4 even **could** be formulated into a pharmaceutical composition suitable for therapeutic use, and understanding the complexity of antibody formulation development as of March 15, 2007, a POSA would not have been motivated to make such a composition, or reasonably expected success in doing so.

70. With respect to motivation, Dr. Balthasar argues that a POSA would have combined the references cited in Amgen's Grounds 2 and 3 because these references, according to Dr. Balthasar, all relate to therapeutic treatment with eculizumab. (AMG1002 ¶¶ 98 (stating Hillmen (2004) and Bell both teach methods of treating PNH), 117 (describing Ground 3 references as related to

"therapeutic use of eculizumab").) Dr. Balthasar also argues that a POSA would have combined the references in Amgen's Grounds 5-7 based on a POSA's desire to create eculizumab compositions "to treat a patient suffering from PNH" and because the cited references "relate to therapeutic use of an anti-C5 antibody." (*Id.* at ¶¶ 139, 169, 189, 208.) Further, Dr. Balthasar argues Wang taught that, at concentrations of 1 to 30 mg/mL, eculizumab could be formulated so that it would be "sufficiently stable to be used as a therapeutic." (*Id.* at ¶ 113; *see also id.* at ¶ 113 ("Wang disclosed that eculizumab could be stably formulated at a concentration between 1 and 30 mg/mL"), ¶ 138 (same).) While I agree with Dr. Balthasar that developing a formulation that would be sufficiently stable for therapeutic use was an important aspect of antibody formulation development, I disagree that the disclosures of Bell and Wang would have motivated a POSA to prepare a stable formulation of an antibody with the amino acid sequence claimed in the '504 patent – which is not disclosed in Bell or Wang and which, under this first scenario, I assume would not have been understood by a POSA to correspond to "eculizumab." Moreover, I disagree with Dr. Balthasar that Bell and Wang, read alone or in combination, would have taught a POSA that "eculizumab" would be stable when formulated as in the claimed compositions.

71. As discussed above in Section VI.B, the pharmaceutical formulation development of a new, previously-unformulated monoclonal antibody required

many experiments the results of which were unpredictable as of March 15, 2007. A POSA as of March 15, 2007 knew that, even for closely-related antibody sequences, the formulation that is suitable for one antibody could not be assumed to be suitable for another.[3] (*See* Section VI.B; AMG1029 at 5; AMG1030 at 690.) For that reason, a POSA having no information about whether an antibody comprising SEQ ID NOs: 2 and 4 had ever been attempted to be formulated into a pharmaceutical composition, or whether that antibody had ever been administered to humans to test its clinical effects, would not have reasonably expected that the antibody was even capable of being used in a suitable pharmaceutical formulation. Without significant empirical testing, a POSA would not have known whether an antibody comprising SEQ ID NOs: 2 and 4 could be formulated into a sufficiently stable product using known antibody formulation approaches, including those in Wang (AMG1029) and Daugherty (AMG1030), as of March 15, 2007. (*See*

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[3] For this reason, even assuming hypothetically that a POSA would have known that an antibody comprising SEQ ID NOs: 2 and 4 was related in sequence to the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028), a POSA would not have reasonably expected any formulation used for Bell and Wang's "eculizumab" to also work for antibody comprising SEQ ID NOs: 2 and 4.

ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.)

72. If, as Dr. Balthasar argues, a POSA had known that an antibody comprising SEQ ID NOs: 2 and 4 had a hybrid IgG2/IgG4 constant region (*e.g.*, AMG1002 ¶ 56), that further supports my opinion that a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, any pharmaceutical compositions of that antibody suitable for therapeutic use. As of March 15, 2007, there were no commercially marketed antibodies demonstrating that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation.[4] (AMG1029 at 2-4 (Table 1); ALXN2032 at 251:3-7.) Furthermore, nothing in Bell (AMG1005) or Wang (AMG1028)

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[4] And hypothetically, even if a different IgG2/IgG4 isotype antibody had been previously formulated, it was still the case that a POSA could not assume from the formulation of one antibody construct to a particular concentration in liquid that a different antibody could be formulated to a given concentration, if at all, because even slightly different antibodies could have markedly different formulation properties. (*See* Section VI.B above.)

stated that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation or had been used in any human clinical studies.[5]

73. A POSA would have been particularly concerned about whether a new, previously-unformulated and untested antibody comprising SEQ ID NOs: 2 and 4 could be formulated as a single-use dosage form in **solution**, as claim 6 of the '504 patent requires. A POSA as of March 15, 2007 would have known that, even "[a]mong all the **commercial antibody products**," only "**about half** are stable enough to be formulated in a liquid form" (which a solution is). (AMG1029 at 14.) For a previously-unformulated and unstudied antibody, a POSA would have had an even lower expectation of success in making a solution formulation

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[5] Dr. Balthasar also asserts that Evans (AMG1007) "provided information regarding how to prepare pharmaceutical compositions comprising eculizumab." (AMG1002 ¶¶ 80, 91 (citing AMG1007, 18:30-43.) I have reviewed Evans (AMG1007), as well as Dr. Balthasar's deposition testimony regarding Evans, and it is my understanding that Evans does not disclose "eculizumab," an antibody with SEQ ID NOs: 2 and 4, or any other full-length humanized antibodies, and thus does not provide any information on pharmaceutical compositions of such antibodies. (ALXN2032 at 163:5-15, 163:25-164:19, 169:13-18, 199:15-17.)

than what was known for the products that had already been commercially marketed.

74. I note that Dr. Balthasar's "Appendix I" is misleading with respect to the number of FDA approved formulations in solution as opposed to lyophilized form. While all the products he lists were injectables, many of them were formulated as single-unit dosage forms of **lyophilized powders** – a **solid** form, not a solution.[6] (AMG1029 at 2-4 (Table 1); AMG1059 at 1; AMG1061 at 1;

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[6] While lyophilized (solid) formulations are eventually reconstituted into a solution just prior to administration by injection, a POSA as of March 15, 2007 would have understood that does not make the **pharmaceutical composition** itself (*i.e.*, the product of manufacture) a "solution." (*See* AMG1029 at 2-4 (Table 1) (containing entries for formulations described as "solution[s]" and, separately, entries for formulations with a specific concentration "on reconstitution"), 14; AMG1030 at 694; ALXN2079 at 10-11.) As a POSA would have known, there were potential advantages to making a liquid (solution) composition for injection versus a lyophilized composition – but obtaining the benefit of these potential advantages was dependent on the unpredictable question of whether a suitable solution formulation was even possible. (AMG1029 at 14; AMG1030 at 694; ALXN2079 at 10-11.)

AMG1066 at 1; AMG1067 at 1; 1070 at 1; 1071 at 1; AMG1074 at 1.) For example, while the product Remicade® (infliximab) was administered by intravenous infusion, its pharmaceutical composition was "a sterile, white, **lyophilized powder**." (AMG1067 at 1.) As discussed above, lyophilization was a formulation approach that generally leads to a more stable formulation than a solution formulation. (*See* Section VI.B above.)

75. Accordingly, if a POSA as of March 15, 2007 had no information regarding the pharmaceutical formulation or clinical use of an antibody comprising SEQ ID NOs: 2 and 4, it is my opinion that a POSA would not have been motivated to make the pharmaceutical compositions recited in claims 1-10 of the '504 patent, and would not have reasonably expected to succeed in doing so.

B. Bell (AMG1005) and Wang (AMG1028) Would Not Have Motivated a POSA Prior to March 15, 2007 to Make the Pharmaceutical Composition of '504 Patent Claim 6, or Given a POSA a Reasonable Expectation of Success in Doing So

76. Assuming, hypothetically, that a POSA prior to March 15, 2007 would have identified the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) as an antibody comprising SEQ ID NOs: 2 and 4 of the '504 patent,[7]

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[7] As noted throughout my Declaration, I have not seen any evidence in my review of Bell (AMG1005) or Wang (AMG1028) that a POSA prior to March 15,

it is my opinion that a POSA prior to that date would not have been motivated by Bell and Wang to make a "300 mg single-use formulation of 30 ml of a 10 mg/mL sterile, preservative free solution" of the antibody comprising SEQ ID NOs: 2 and 4, as recited in claim 6 of the '504 patent, or a "300 mg single unit dosage form" of such an antibody as recited in claim 5 of the '504 patent, and that a POSA prior to that date would not have reasonably expected to succeed in doing so. Nothing in Bell or Wang, alone or in any combination, disclosed a pharmaceutical composition of "eculizumab" featuring a 300 mg single-use dosage form a 10 mg/ml solution of "eculizumab," or would have motivated or given a POSA a reasonable expectation of success in making such a pharmaceutical composition of "eculizumab."

77. First, nothing in Bell (AMG1005), Wang (AMG1028) or Dr. Balthasar's other cited documents would have motivated a POSA prior to March 15, 2007 to specifically make a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single-use dosage form. Neither Bell nor Wang

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2007 would have known the specific, complete amino acid sequence of the "eculizumab" antibody they disclose, or that a POSA would have connected an antibody comprising SEQ ID NOs: 2 and 4 to the "eculizumab" antibody of Bell and Wang.

disclosed such a pharmaceutical composition, or would have given a POSA any confidence that a 10 mg/ml concentration of "eculizumab" in solution would have been suitable for a pharmaceutical composition as claimed in the '504 patent.

78. Bell (AMG1005) discloses nothing about a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" (or any other concentration of "eculizumab") in a single use dosage form. Bell described, among other things, the results of an 11-patient, 12 week clinical trial (and 52-week and 2-year extensions of that clinical trial), where "eculizumab" was administered to PNH patients by "intravenous infusion," in 600 mg weekly doses for four weeks, followed by 900 mg for all successive doses, and was shown to alleviate their symptoms. (AMG1005 ¶¶ [0081]-[0096].) A POSA reading Bell would have understood that "eculizumab" could in fact be formulated as some kind of pharmaceutical composition suitable for therapeutic use (including for use in treating patients with PNH). But a POSA would **not** have known from Bell any of the details regarding that pharmaceutical composition, including, for example, whether the composition was in solution or was a solid, lyophilized composition; and if the composition was in solution, what was the specific **concentration** of "eculizumab" in that solution.

79. Dr. Balthasar's suggestion that Bell provided information for "formulating eculizumab" or "prepar[ing] pharmaceutical compositions

comprising eculizumab" is thus misleading. (*E.g.*, AMG1002 ¶¶ 80, 91 (citing AMG1005 ¶ [0062]); AMG1002 ¶ 130 (citing AMG1005 ¶¶ [0060], [0062]).) A POSA prior to March 15, 2007 would have seen that paragraphs [0060] and [0062] of Bell were very general statements discussing, for example, all conceivable routes of administration (whether feasible or not), and reference to a general reference book for the concept of "[f]ormulations suitable for injection." Nothing in Bell suggested specifically making a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form, or would have given a POSA a reasonable expectation that such a composition would have been suitable as a pharmaceutical formulation, for the treatment of patients with PNH or otherwise.

80. Further, even if Bell were combined with the information in Wang (AMG1028), a POSA prior to March 15, 2007 would not have envisioned or been motivated to make a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form, and would not have reasonably expected success in making or using such a composition.

81. First, I disagree with Dr. Balthasar's premise that a POSA prior to March 15, 2007 would have had any motivation to combine Bell (AMG1005) with Wang (AMG1028). (AMG1002 ¶ 149.) While Bell described clinical studies showing that "eculizumab" safely and effectively treated **PNH** when administered

by **intravenous infusion** (AMG1005 ¶ [0082]),[8] Wang (AMG1028) had an entirely different focus – "treating **pulmonary diseases**" (*i.e.*, respiratory diseases such as asthma) by "**nebulization**" (dispersing into small particles for inhalation) of various different monoclonal antibodies (AMG1028 at, e.g., ¶¶ [0004]-[0009], [0058]-[0066]; ALXN2032 at 256:24-258:9.) A POSA would have had no reason to disregard the clinically proven intravenous route for "eculizumab" in treating PNH – a systemic blood condition – and instead use Wang's "nebulization" technology intended to deliver drugs locally to the respiratory tract. (*See* AMG1004 at 553-54; AMG1012 at 1234-35; AMG1047 at 2559-60; ALXN2032 at 258:10-16.)

82. As Dr. Balthasar concedes, nothing in Wang (AMG1028) disclosed a 10 mg/ml composition of "eculizumab" for intravenous infusion. (ALXN2032 at 260:5-13.) And even if a POSA were to have combined Bell with Wang, it is my opinion that nothing in that combination disclosed a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form.

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[8] I understand that the other reported clinical trials of "eculizumab" in treating PNH prior to March 15, 2007 likewise administered the drug by intravenous infusion. (AMG1004 at 554; AMG1012 at 1235; AMG1047 at 2560.)

83. While I agree with Dr. Balthasar that ensuring adequate stability is an important part of formulation development, contrary to Dr. Balthasar's assertions, nothing in Wang "disclose[d] that eculizumab is stable when formulated at a range of concentrations between 1 mg/ml and 30 mg/ml." (*E.g.*, AMG1002 ¶ 16.) First, the range of "1 to 30 mg/ml" that Dr. Balthasar cites from paragraph [0170] and Figure 10 of Wang (AMG1028) is **not a range for eculizumab**, but refers to a broad range that can include different possible antibodies, including at least the anti-mouse C5 antibody "BB5.1." (*See* AMG1028 ¶ [0170], Figure 10; *see also id.* at ¶ [0067] (describing "an antibody of the present application" as including antibodies specific to various targets, full-length antibodies and fragments, amongst others).) Neither paragraph [0170] nor Figure 10 use the term "eculizumab"; instead, paragraph [0170] refers to "examples for nebulization of **an antibody**," and Figure 10 provides two "Example" formulations with no specific antibody identified.[9] (*Id.* at ¶ [0170], Figure 10.) While Wang (AMG1028) contains some examples of a **30 mg/ml solution** of "eculizumab" (which, as

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[9] In Formulation 1 in Figure 10, only a generic "mAb" is listed with no names or indication of any specific mAb, and certainly not "eculizumab"; and in Formulation 2, there is no monoclonal antibody listed, not even a generic one. (AMG1028, Fig. 10.)

explained below, was **not** shown to be stable), there is simply nothing in Wang disclosing a 10 mg/ml solution composition of "eculizumab," for nebulization or any other use.

84. Nor does anything in Wang (AMG1028) state that "eculizumab could be stably formulated at a concentration between 1 and 30 mg/ml," as Dr. Balthasar further asserts. (*E.g.*, AMG1002 ¶ 113 (citing AMG1028 at Fig. 10 and ¶¶ [0170]-[0172]).) Rather, all that Wang showed with respect to "eculizumab" was that a 30 mg/ml solution of "eculizumab" could be "effectively and efficiently nebulized" by a nebulizer. (AMG1028 at Fig. 10 and ¶¶ [0170]-[0172].) Nothing in Wang provided any of the standard data that a POSA as March 15, 2007 would have expected to see in establishing the stability of an antibody formulation, including, for example, data **over time** and under various **storage conditions** to establish that the composition is sufficiently stable to be stored for a reasonable time prior to human administration. (ALXN2085 at 2; ALXN2084 at 2, 5-6; ALXN2029 at 23; ALXN2080 at 177-78; ALXN2079 at 6-7, 15-16.)

85. For example, paragraph [0170] and Figure 10 of Wang, which Dr. Balthasar cites for the range of "1-30 mg/ml," does not state anything about the stability of eculizumab formulations within that range. Paragraph [0170] merely says that "[e]xamples of formulations suitable for nebulization of an antibody are shown in FIG. 10." Furthermore, paragraph [0170] mentions "BB5.1," but not

"eculizumab." (AMG1028 ¶ [0170]; *see also* AMG1028 ¶ [0025] ("FIG. 10 shows exemplary formulations suitable for nebulization of an antibody.") Figure 10 of Wang, in turn, lists a "Formulation 1," with 1-30 mg/ml of an unspecified antibody, and a "Formulation 2," with 40-200 mg/ml of an unspecified antibody. (AMG1028, Fig. 10.) Nothing in these statements would have indicated to a POSA that **eculizumab** "could be stably formulated at a concentration between 1 and 30 mg/ml," let alone in a 10 mg/ml solution specifically.

86. The **only** statement in Wang (AMG1028) actually mentioning "stability" states: "The antibody may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (AMG1028 ¶ [0067].) First, in the context of this statement, a POSA would have understood that "[t]he antibody" refers to a wide variety of possible antibodies, fragments and other compounds "specific to C5" (including even different antibodies for different epitopes). (AMG1028 ¶ [0067].) Second, in light of the use of the term "may," a POSA would not have viewed this isolated statement as teaching that every possible anti-C5 antibody and fragment within its scope would necessarily be stable at all concentrations within the broad recited range. Accordingly, a POSA would have understood that this statement was, at best, hypothetical, with no specific consideration of "eculizumab" or any other antibody, and that it did not reflect the results of any actual stability testing performed on any specific antibody at any specific

concentration – including a 10 mg/ml solution of "eculizumab." With no understanding that Wang provided any specific guidance for a stable "eculizumab" formulation, a POSA would not have looked to Wang to make such a composition, as Dr. Balthasar contends.

87. Figures 11-15 referenced in paragraphs [0170]-[0172] of Wang (AMG1028) also provide no evidence that, as Dr. Balthasar contends, "eculizumab could be stably formulated" in a 10 mg/ml solution composition. (AMG1002 ¶ 113.) Figure 11, described further in Wang paragraph [0170], is a test of a **different** antibody ("BB5.1") in a mouse respiratory model.[10] (AMG1028 at Fig. 11, ¶ [0170].) Figure 12, using 30 mg/ml eculizumab in "Formulation 1," likewise did not test for stability pertinent to developing a single-use dosage form of a solution for intravenous infusion (*e.g.*, degradation over time and under potential storage conditions). Instead Figures 12 and 13 rather looked at whether the composition could be "effectively and efficiently delivered through a nebulizer" – using *in vitro* tests designed to measure the size of particles being delivered by the nebulizer and the efficiency of nebulizer delivery. (AMG1028 at Fig. 12-13, ¶¶ [0171]-[0172]; ALXN2032 at 259:6-9.) Figures 12 and 13, referenced in

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[10] I note that Wang (AMG1028) does not disclose the administration of any "eculizumab" composition even to animals, let alone to humans.

paragraphs [00171-0172], only disclose data related directly to the testing of the nebulization process, do not include any stability information, and neither in Figure 13 nor in the description of it in [0172] and [0028] is the specific tested concentration of "eculizumab" disclosed.

88. I also disagree with Dr. Balthasar that Figures 14 and 15 of Wang (AMG1028) "indicate[] that eculizumab is sufficiently stable to be used as a therapeutic when formulated at a concentration of 1 to 30 mg/ml." (AMG1002 ¶ 113.) Figures 14 and 15 of Wang only studied one type of stress very specific to formulations for use in nebulization: "the integrity of the nebulized antibody through various sizes of the spray mouth piece." (AMG1028 ¶ [0173].) Further, there is nothing in Wang indicating exactly what concentration of eculizumab was used in the experiments reported in Figs. 14 and 15, just identifying it as "[e]culizumab in a suitable formulation." (AMG1028 ¶ [0173].) Figures 14 and 15 do not report the stability of their undefined "suitable formulation" over time, or under any stresses or conditions that a POSA would have understood to be pertinent to assessing the stability of a single use dosage form containing a monoclonal antibody solution.

89. Without suitable information disclosed in Wang (AMG1028) or elsewhere regarding the stability of a single use dosage form containing 10 mg/ml eculizumab formulated in solution, a POSA would not have reasonably expected

success with the pharmaceutical compositions recited in claim 6 of the ’504 patent. As discussed above in Section VI.B, an insufficiently stable antibody formulation could lack efficacy and result in serious safety issues. A POSA prior to March 15, 2007 would not have had a reasonable expectation of success in making the claimed pharmaceutical composition of claim 6 of the ’504 patent without evidence that a 10 mg/ml eculizumab solution composition was suitably stable” – particularly given that the claims require use of the pharmaceutical composition in “[a] method of treating a patient suffering from [PNH].” (*See* Section [ ], *supra*.)

90. A POSA prior to March 15, 2007 also could not have reasonably predicted from any of the commercialized products as of that date that a single-use dosage form containing a 10 mg/ml solution of “eculizumab” could be used in a suitable pharmaceutical composition. (*See* AMG1029 at 5 (antibody formulation development not straightforward due to antibodies’ variable behavior, despite similar structures); AMG1030 at 690 (each antibody presents unique requirements for stability).) Dr. Balthasar is mistaken that 5 out of 23 commercially marketed antibodies as of March 15, 2007 were 10 mg/ml antibody solutions (AMG1002 ¶ 114), because one of the five products that he identifies was not even a solution composition (Remicade®). (AMG1002 ¶ 114, Appendix I; AMG1029 at 2-4 (Table 1); AMG1067 at 1.) And even counting Remicade®, only **one** of the 23 commercialized antibodies as of March 15, 2007 was a **full-length humanized**

antibody formulated as a 10 mg/ml solution (Campath®)[11] – and that product had an IgG1 isotype, not the "hybrid" isotype that Dr. Balthasar attributes to "eculizumab." (AMG1002 ¶ 114, Appendix I; AMG1029 at 2-4 (Table 1); AMG1058 at 13; AMG1063 at 4; AMG1067 at 1; AMG1069 at 1; AMG1073 at 1.) Further, a POSA would have seen that many commercialized full-length humanized antibodies appeared unsuitable for solution compositions, and instead were produced as solid, lyophilized compositions. (AMG1029 at 2-4 (Table 1), 14; AMG1056 at 1; AMG1071 at 1; AMG1074 at 1; AMG1061 at 1.) Having said all of that, even if were the case that 10 mg/ml were a common concentration for antibody formulations, that would have given a POSA no indication of whether or not a particular antibody (*e.g.,* eculizumab) could be formulated at 10 mg/ml without applying hindsight reasoning. (*See* VI.B above.)

91. I also disagree with Dr. Balthasar that it would have been obvious in view of Bell (AMG1005) to formulate "eculizumab" as a 300 mg single-use dosage form. (*E.g.*, AMG1002 at 102.) Dr. Balthasar asserts, with no support, that a POSA would have necessarily been motivated to make a 300 mg single-use dosage form to achieve the 600 and 900 mg doses described in Bell, rather than

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[11] The other products were a mouse Fab (Verluma®), mouse/human chimeric antibodies (Rituxan®, Remicade®), and a humanized IgG1 fragment (Lucentis®).

make 600 mg and 900 mg single use dosage forms, asserting that it would have been "the simplest, most efficient, and most convenient way." (AMG1002 ¶ 106.) I disagree. For example, it would be beneficial for ease and accuracy of administration for providers to use a single unit for each administration, rather than to use two or three. It is quite common for pharmaceutical products, including monoclonal antibody products, to be available in different dosage amounts, for the convenience of patients and health care providers. Dr. Balthasar's own references provide information on multiple antibody products that are available in difference doses. For example, bevacizumab was supplied in both 100 mg and 400 mg doses (AMG 1056, p. 2, 25); tositumomab was supplied in both 35 mg and 225 mg doses, and a given carton contains two 225 mg vials and one 35 mg vial (AMG 1057, p. 2,3); and rituximab was supplied in both 100 mg and 500 mg doses (AMG 1069, p. 1, 2).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that I made these statements with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: November 22, 2019

Bernhardt L. Trout, Ph.D.

Appendix A

Bernhardt L. Trout

Department of Chemical Engineering
Massachusetts Institute of Technology
77 Massachusetts Avenue, E19-502B
Cambridge, MA 02139

Tel: (617) 258-5021
Fax: (617) 253-2272
trout@mit.edu

Research Interests:

Pharmaceutical manufacturing and development research, Biopharmaceutical (protein and antibody) processes and stabilization, Pharmaceutical crystallization and separations, Multi-scale modeling, Electronic-structure calculations, Rare events simulations.

Positions:

Massachusetts Institute of Technology, Cambridge, MA

Raymond F. Baddour, ScD, (1949) Professor of Chemical Engineering, October 2014 – present
Director, SEE: Society, Engineering and Ethics, Jan., 2009 - present
Director, Novartis-MIT Center for Continuous Manufacturing, June 2007 – May 2019
Co-Chair, Chemical and Pharmaceutical Engineering Singapore-MIT Alliance Program, July 2006 – October 2014
Professor of Chemical Engineering, January 2008 – October 2014
Director, Concourse Freshman Educational Program, July 2009 – June 2012
Associate Professor of Chemical Engineering, July 2003 – December 2007
Assistant Professor of Chemical Engineering, January 1998 – July 2003

Max-Planck-Institut für Festköperforschung, Stuttgart, Germany

Post-Doctoral Researcher, 1996 – 1997
Director: Michele Parrinello

Teaching:

10.01 Ethics for Engineers, 10.02 Foundations of Principled Entrepreneurship for Engineers , 10.213: Undergraduate Thermodynamics, 10.40: Graduate Thermodynamics, 10.65: Chemical Reactor Engineering, 10.541: Kinetics of Biological and Chemical Systems, 10.37: Chemical Kinetics and Reactor Design, 10.27: Process Engineering Laboratory, 10.675: Molecular Computational Methods in Chemical Engineering, 10.491: Chemical Engineering Design Module, 10A16: Freshman Advising Seminar, 10.04J Philosophical History of Energy,

Education:

University of California, Berkeley
Ph.D. in Chemical Engineering, 1996
Thesis: Reaction Processes in ZSM-5 Zeolites Elucidated by Quantum Density Functional Theory and by Dynamic Monte Carlo
Advisors: Arup K. Chakraborty and Alexis T. Bell

Université de Paris IV
Certificat de Langue et de Civilisation Françaises, 1991

Massachusetts Institute of Technology
M.S. in Chemical Engineering Practice, 1990

Massachusetts Institute of Technology
B.S. in Chemical Engineering, 1990

Awards and Honors:

The Medicine Maker "Power List", 2019
ISCMP Co-Chair, 2018
The Medicine Maker "Power List", 2017
ISCMP Co-Chair, 2016
The Medicine Maker "Power List", 2016
AIChE Division 15 (FPBE) Plenary Speaking Award, 2015
Armenian Academy of Engineering, Foreign Member, elected 2015
The Medicine Maker "Power List", 2015
AIChE Excellence in Process Development Research Award, 2014
ISCMP Co-Chair, 2014
ISCMP Downstream Pharmaceutical Panel Chair, 2014
CCR Research Collaboration Award, 2014
Manufacturing Technology Runner-up for the Wall Street Journal Technology Innovation Award, 2012
Impact Award from the Computational Molecular Science and Engineering Forum of the AIChE (CoMSEF), 2011
ACS Plenary Lecture, 2011
AIChE Area 1A Program Chair, 2006
National Academy of Engineering participant in "Frontiers in Engineering," 2001
Henry L. and Grace Doherty Professorship, 2001 – 2003
Ford Motor Company Young Investigator Award, 2001
NSF CAREER Award, 2000 – 2004
Joseph R. Mares Junior Faculty Chair, 1998 – 2001
Max-Planck Institute Fellowship, 1996 – 1997
NSF Graduate Fellowship, 1991 – 1994

Committees/Memberships:

MIT Advisory Board for Social and Ethical Responsibilities of Computing (SERC), 2019-2020
MIT Schwarzman College of Computing Committee on Social Implications, 2019
MIT Task Force on Open Access, 2017 – 2019
Task Force on Open Access, Contracts subteam, 2017-2019
United States Pharmacopeia Expert Panel: Quality Standards for Pharmaceutical Continuous Manufacturing, 2016 – present
Molecular Systems Design & Engineering (MSDE), Royal Society of Chemistry Journal, Editorial Board Member, 2016 – present
FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, Consultant, 2015 – 2018
MIT Chemical Engineering Department Head Search Advisory Committee, 2015
FDA Coordination Group at MIT, 2014 – 2016
MIT Committee on Intellectual Property, 2011 – 2016
MIT Committee on the Undergraduate Program, 2006 – present
MIT Faculty Search Committee, 2006 – present
MIT Practice School Steering Committee, 2004 – 2015
ISPE Subcommittee on Pharmaceutical Manufacturing, 2010 – 2011
ISPE Subcommittee on Continuous Production, 2008
MIT Graduate Committee, 2006 – 2009
DuPont-MIT Advisory Committee, 2005 – 2007
Hottel Lecture Committee, 2004 – 2007
SMA Annual Report Committee, 2003 – 2012
Department Computer Committee, 2002 – 2007

Conferences Organization:

Co-Chair, International Symposium on Continuous Manufacturing, October 2018
Co-Chair, International Symposium on Continuous Manufacturing, September 2016
Chair, MIT Mastery of Nature Conference, May 2016
Organizing Committee, AIChE/FDA P2DM Workshop on Continuous Manufacturing, March 2016
Co-Chair, International Symposium on Continuous Manufacturing, May 2014

Scientific Publications:

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Philosophical Publications:

2. Trout, B.L., "Quantum Mechanics and Political Philosophy" Minkov, S. Y. and Trout, Bernhardt L. (Eds.), *Mastery of Nature: Promises and Prospects* (pp. 220-232) Philadelphia, PA: University of Pennsylvania Press (2018).

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Non-Peer Reviewed Publications:

3. Livingston, A., et al. "Challenges and Directions for Green Chemical Engineering-- Role of Nanoscale Materials" in *Sustainable Nanoscale Engineering*, Elsevier, Amsterdam 2020.

2. Trout, B.L., "Foreword." *Developability of Biotherapeutics: Computational Approaches,* CRC Press, 2015.

1. Mascia, S., Trout, B.L., "Integrated Continuous Manufacturing," *Pharmaceutical Manufacturing,* December 2014, pp. 26-29.

Conference Publications:

6. Buck, P.M., Kumar, S., Wang, X., Agrawal, N.J., Trout, B.L., and Singh, S.K., "Computational Methods to Predict Biotherapeutic Protein Aggregation", *Therapeutic Proteins: Methods and Protocols, Second Edition*, Springer, Humana Press. pp. 425-451 (2012).

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4. Radhakrishnan, R., Demurov, A., Herzog, H.J. and Trout, B.L., "Modeling the dissolution of liquid CO_2 in water under hydrate forming conditions," Proceedings of the Fourth International Conference on Gas Hydrates, Yokohama, Japan, May 2002, pp. 262- 266.

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Patents:

18. "Continuous Freeze-drying Methods and Related Products." US 62/500,466, Filing Date: May 2, 2017

17. "Continuous Crystallization on Excipient Surface and Tablet Making." US 62/477253, Filing Date: 27.03.2017

16. "Core-Shell Particles for Controlled Release of Organic Material." US 62/348371, Filing Date: 23.09.2016

15. "Biocompatible Polymeric Hydrogels for Controlling Nucleation from Solution and Loading of Hydrophobic and Hydrophilic Pharmaceuticals." U.S. Patent Application: 14/575069, Filing Date: 18.12.2014

14. "Computer-Implemented Methods of Determining Protein Viscosity," U.S. Patent Application: 61/824680, PCT/US2014/038368, International Filing Date: May 16, 2014.

13. "Plasticity Induced Bonding," U.S. Patent No.: 10,213,**960**, Date of Patent: Feb. 26, 2019, PCT/US2015/031666, International Filing Date: May 20, 2015.

12. "Methods and Systems for Manufacturing a Tablet." U.S. Patent No.: 10,053,798, Date of Patent: Aug. 21, 2018, Filed: Apr. 30, 2015.

11. "Layer Processing for Pharmaceuticals." U.S. Patent No.: 9,205,089, Date of Patent: Dec. 8, 2015, Filed Apr. 27, 2012.

10. "Compositions, Methods, and Systems Relating to Controlled Crystallization and/or Nucleation of Molecular Species." U.S. Patent No.: 9,138,659, Date of Patent: Sept. 22, 2015, Filed: Aug. 23, 2011.

9. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 9,676,841, Date of Patent: Jun. 13, 2017, PCT/US2009/047948, International Filing Date: June 19, 2009.

8. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 8,747,848, Date of Patent: Jun. 10, 2014, PCT/US2009/047948, International Filing Date: June 19, 2009.

7. "HER2 and VEGF-A-binding Proteins with Enhanced Stability." U.S. Patent No.: 9,777,067, Date of Patent: Oct. 3, 2017, PCT/US2013/062108, International Filing Date: Sept. 27, 2013

6. "Methods to Identify Amino Acid Residues Involved in Macromolecular Binding and Uses Therefor." U.S Patent No.: 10,431,325, Date of Patent: Oct. 1, 2019, PCT/US2013/053499, International Filing Date: Aug. 2, 2013.

5. "Methods and Systems Relating to the Selection of Substrates Comprising Crystalline Templates for the Controlled Crystallization of Molecular Species," U.S. Patent No.: 9,822,467, Date of Patent: Nov. 21, 2017, Filing Date: Nov. 15, 2012.

4. "Dendrimer-Based Excipients for the Attenuation of Protein Aggregation," U.S. Patent No.: 9,410,142, Date of Patent: Aug. 9, 2016, PCT/US2011/060400, International Filing Date: Nov. 11, 2011.

3. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 9,629,925, Date of Patent: Apr. 25, 2017, PCT/US2010/037517, International Filing Date: June 4, 2010.

2. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 8,834,885, Date of Patent: Sept. 16, 2014, PCT/US2010/037517, International Filing Date: June 4, 2010.

1. "Methods to Identify Macromolecule Binding and Aggregation Prone Regions in Proteins and Uses Therefor,", U.S. Patent No.: 9,922,164, Date of Patent: Mar. 20, 2018, PCT/US2009/047954, International Filing Date: June 19, 2009.

Invited Talks and Plenary Lectures:

160. November 20, 2019, "Machine Learning for Developability and Formulation Design," CDD for Biologics, Boston, MA.

159. October 30, 2019, "Ethical Issues in AI and Implications for the Law," Artificial Intelligence Driving Life Sciences, Cambridge, MA.

158. October 23, 2019, "Continuous Lyophilization of Unit Doses," Lyophilization USA, Boston, MA.

157. September 26, 2019, “Continuous Manufacturing: State of the Art, Challenges, and Future Prospect,” IMA conference “Can’t Stop the Future: Spotlight on Continuous Manufacturing,” Bologna, Italy.

156. June 11, 2019, “Formulation Starts in Discovery,” Gordon Research Conference on Preclinical Form and Formulation, Waterville Valley, NH.

155. May 14, 2019, “Developability and Machine Learning for Formulation Design,” Biovia Community Day, Dusseldorf, Germany (via webcast).

154. February 27, 2019, “Living a Life of Leisure While Teaching Science in a Classical Secondary School Education,” Great Heats Academies, Sandra Day O'Connor College of Law, Phoenix, Arizona.

153. December 1, 2018, “Truths About Quantum Mechanics,” St. John’s College, Santa Fe, NM.

152. November 7, 2018, “Product and Process Development Start in Discovery,” Takeda Pharmaceutical Company, Cambridge, MA.

151. October 25, 2018, “Product and Process Development Start in Discovery,” Biovia Community Day, Boston, MA.

150. September 10, 2018, “Developability for Biologics and Approaches to Formulation Design,” BioMan Process Intensification Conference, Cambridge, MA.

149. August 3, 2018, “Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities,” Acceleron Pharma, Cambridge, MA.

148. May 30, 2018, “Continuous Lyophilization of Pharmaceutical Products in Unit Doses,” Hudson Valley LyoMac Webinair.

147. December 7, 2017, “Enabling Developability via Molecular Modeling,” CDD for Biologics, Boston, MA.

146. December 1, 2017, “The Significance of Quantum Mechanics,” St. John’s College, Annapolis, MD.

145. October 17, 2017, “Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities”, Biovia Community Day, Cambridge, MA.

144. September 21, 2017, “Developability for Biologics and Approaches to Formulation Design,” Biologics, Modeling, and Informatics (BMI) Discussion Group, Cambridge, MA.

143. July 19, 2017, “Biopharmaceuticals and Continuous Manufacturing,” Senate Competitive Caucus, U.S. Senate, Washington D.C.

142. May 10, 2017, “New Continuous Crystallization Technologies for Small Molecule Pharmaceutical Manufacturing,” Vertex Pharmaceuticals, Boston, MA.

141. April 13, 2017, “Ethics and Engineering: How to Think About the Ethics of AI,” MIT Course 6 Super UROP, Cambridge, MA.

140. February 10, 2017, “New Technologies for Holistic Pharmaceutical Creation,” United States Pharmacopeia, Rockville, MD.

139. February 1, 2017, “New Technologies for Holistic Pharmaceutical Creation: Focus on 3D Printing,” Takeda, Zurich, Switzerland.

138. January 31, 2017, “Developability and Manufacturability in Pharmaceutical Creation,” Roche, Basel, Switzerland.

137. January 31, 2017, “Developability and Manufacturability in Pharmaceutical Creation,” Lonza, Basel, Switzerland.

136. December 15, 2016, “Enabling Developability Via Molecular Modeling,” IBC Antibody Engineering & Therapeutics, San Diego, CA.

135. October 26, 2016, “Integrating Discovery, Development and Manufacturing in Pharmaceutical Creation,” University of Pennsylvania Department of Chemical and Biomolecular Engineering, Philadelphia, PA.

134. May 13, 2016, “Quantum Mechanics and Political Philosophy,” MIT Conference on Mastery of Nature, Cambridge, MA.

133. March 17, 2016, “Ethics in Engineering,” MIT Course 6 Super-UROP, Cambridge, MA.

132. October 5, 2015, “New Technologies for Enabling Continuous Manufacturing,” PQRI Meeting, Bethesda, MD (plenary lecture)

131. September 16, 2015, “Rational Approaches for the Developability of Biotherapeutics” Boston University Department of Physical Chemistry, Boston, MA

130. September 7, 2015, “MIT’s Success at Teaching and Research,” National Polytechnic University, Yerevan, Armenia

129. June 4, 2015 “Continuous Processing in (Bio)Pharmaceutical Manufacturing,” Ipsen Corporation, Paris, FR

128. May 15, 2015 “Advanced Formulation, Stabilization, and Manufacturing of Therapeutic Antibodies” MassBiologics, Boston, MA

127. April 29, 2015 “Continuous Pharmaceutical Manufacture and Advances in Biopharmaceuticals Formulation” The Pall Corporation Technology Symposium, Cambridge, MA. (Keynote Address)

126. April 14, 2015 “Rational Approaches for the Development of Biotherapeutics,”4th International Symposium on Higher Order Structure of Protein Therapeutics, Boston, MA

125. March 27, 2015 “Molecular and Macroscopic Engineering of Small Molecular Crystallization,” Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

124. March 24, 2015 “Holistic Pharmaceutical Process Development,” Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

123. Sept. 16, 2014 “Enabling Technologies for the Continuous Manufacturing of APIs: Continuous Crystallization” at FDA/PQRI Conference, Silver Spring, MD

122. June 10, 2014 “How ‘Continuous’ Manufacturing will Transform Biotherapeutic Manufacturing” The Annual Bio Manufacturing & Process Innovation Leaders Summit USA 2014 (MANU-BIO), Boston, MA (Keynote Address)

121. June 6, 2014 “Strategic Approaches for Understanding and Hindering Aggregation” IBC’s Protein Aggregation, Stability & Solubility Conference, San Francisco, CA (Keynote Address)

120. March 26, 2014 “Rational Approaches to Developability and Manufacturability” Accelyrs, Cambridge, MA

119. March 21, 2014 “Rational Approaches to Developability and Manufacturability” Bayer, Wuppertal, Germany

118. January 21, 2014 “Rational Approaches for Biologics and Small Molecule Pharmaceutical Development and Manufacturing” Columbia University, New York, NY

117. January 8, 2014 “Rational Approaches to Developability and Manufacturability” Pfizer, Cambridge, MA

116. December 16, 2013 “Rational Approaches to Developability and Manufacturability”BMS, Devens, MA

115. November 7, 2013, “Recent Updates at the Novartis-MIT Center for Continuous Manufacturing”, FDA, Silver Spring, MD

114. November 5, 2013 "Transforming Manufacturing to "Continuous": Flexible API and Final Dosage Form" ISPE Meeting, Washington, DC

113. October 21, 2013 "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Integrated Continuous Biomanufacturing, an ECI Conference, Barcelona, Spain (Keynote Address)

112. September 11, 2013 "Rational Approaches to Developability and Manufacturability," Biogen Idec, Cambridge, MA

111. September 10, 2013 "Rational Approaches to Developability and Manufacturability," Pfizer, Andover, MA

110. July 10, 2013 "What Molecular Modeling in Pharmaceutical Development Can Do for You," BMS Symposium on Modeling, New Brunswick, NJ (Keynote Address)

109. June 27, 2013 "Capitalizing on Continuous Manufacturing," 8th Global Pharma Manufacturing Summit, Boston, MA (Plenary Lecture)

108. June 12, 2013, "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Biomanufacturing Leaders Summit, Boston, MA (Keynote Address)

107. April 24, 2013 "From Molecular Computations to Continuous Manufacturing and Their Role in Shaping a Sustainable Future," 9th European Congress of Chemical Engineering, The Hague, Netherlands (Plenary Lecture)

106. April 19, 2013 "Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing," Pharmintech, Bologna, Italy (Keynote Address)

105. March 26, 2013, "Rational Approaches to Developability for Stabilization Against Aggregation and Other Routes," 6th Annual Proteins Conference, London, UK.

104. November 15, 2012, "Rational Approaches to Developability, Formulation, and Design of Biobetters," MIT Center for Biomedical Innovation: Biomanufacturing Summit, Cambridge, MA

103. November 14, 2012, "Advanced manufacturing for pharmaceuticals and the Novartis-MIT center for continuous manufacturing," MIT ILP R&D Conference, Cambridge, MA

102. August 21, 2012, "Technical Update for the FDA on the Downstream Continuous Manufacturing Toolbox," FDA, Cambridge, MA

101. May 5, 2012, "Rational Approaches to the Stabilization of Biologics: Incorporating Developability and Manufacturability," Ispen, Milford, MA.

100. November 18, 2011, “Protein Aggregation Modeling and Novel Excipients for Downstream Processing: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics,” BioMan, Cambridge, MA.

99. November 9, 2011, “Predication of Aggregation Prone Regions in Proteins: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics,” CASSS Symposium on Immunogenicity, Gaithersburg, MD

98. October 20, 2011, “Heterogeneous Crystallization of API’s on Excipients for “Continuous” Process and Product Design,” Peck Symposium at Purdue University, West Lafayette, IN

97. October 19, 2011, “Transforming Pharmaceutical Development and Manufacturing with Molecular Computations ,” AIChE Annual Symposium, CoMSEF Award, Minneapolis, MN

96. September 15, 2011, “Transforming Pharmaceutical Manufacturing, Continuous: The Ultra Lean Way of Manufacturing,” President Obama’s Advanced Manufacturing Partnership, Cambridge, MA

95. August 4, 2011 “Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases,” GSK, King of Prussia, PA

94. July 28, 2011 “Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases,” Pfizer Research, Cambridge, MA

93. July 21, 2011, “Molecular Modeling Approaches for Predicting The Stability of Biotherapeutics, Antibodies in Particular,” Colorado Protein Stability Conference , Breckenridge, CO

92. May 19, 2011, “Computational Approaches for Identifying Degradation “Hotspots”: Spatial Aggregation Propensity and Implementation in Pipeline Pilot,”Accelrys North America-UGM Conference, Newark, NJ

91. March 29, 2011, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization,” ACS, Anaheim, CA (Plenary Lecture)

90. March 15, 2011, “Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing,” ISPE-NJ

89. November, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” AAPS Annual Meeting, New Orleans, LA

88. October, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” PEGS Biotechnology conference, Hannover, Germany

87. September, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” Ipsen Corporation, Milford, MA

86. September, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” IBC Protein Formulation Conference, Providence, RI

85. August, 2010, “Molecular Modeling for the Rational Control of Polymorphism and Morphology,” Sepracor Corporation, Marlborough, MA

84. July, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” MedImmune Corporation, Gaithersburg, MD

83. July, 2010, “Continuous Manufacturing: The Ultimate in Quality by Design,” Sepracor Corporation, Marlborough, MA

82. May, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” Accelrys Annual International Conference, Boston, MA

81. April, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” ISPE Biotech Meeting, Cambridge, MA

80. April, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” Merck, West Point, PA

79. March, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” Genzyme, MA

78. March, 2010, “Molecular Modeling for the Rational Control of Polymorphism and Morphology,” Gilead Corporation, Foster City, CA

77. March, 2010, “Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD,” Genentech, South San Francisco, CA

76. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Amgen, Thousand Oaks, CA

75. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Biogen-Idec, Cambridge, MA

74. December, 2009, "Continuous Manufacturing of Small Molecule Pharmaceuticals," Leaders for Global Manufacturing, MIT, Cambridge, MA

73. November, 2009, "Order parameter methods for reactions in complex systems," Princeton Center for Theoretical Sciences, Department of Physics, Princeton, NJ

72. October, 2009, "Rational approaches to protein and antibody stabilization," Schering-Plough, Elizabeth, NJ

71. September, 2009, "Rational approaches to protein and antibody stabilization," Merck & Co., West Point, PA.

70. September, 2009, "Modeling of crystallization processes," Merck Research Laboratories, Rahway, NJ.

69. September, 2009, "Rational approaches to pharmaceutical manufacturing," Merck Research Laboratories, Rahway, NJ.

68. July, 2009, "Continuous manufacturing: the ultra lean way of manufacturing," Biochemical Engineering XVI, Burlington, VT.

67. June, 2009, "Rational approaches to protein and antibody stabilization," Bristol-Meyers Squibb, New Brunswick, NJ.

66. April, 2009, "Reactivity in complex systems," University of Washington.

65. March, 2009, "Reactivity in complex systems," North Carolina Theory Seminar.

64. February, 2009, "Reactivity in complex systems," UCLA.

63. September, 2008, "Continuous manufacturing of pharmaceuticals: the ultra lean way of manufacturing," Global Pharmaceutical Manufacturing Summit, Chicago.

62. June, 2008, "Rational design of solvent formulations via molecular computations," American Association of Pharmaceutical Science National Biotechnology Conference, Toronto, Canada.

61. March, 2008, “Frontiers in chemical reactivity and pharmaceutical manufacturing,” Department of Chemical Engineering, University of Puerto-Rico.

60. March, 2008, “Frontiers in chemical reactivity and pharmaceutical manufacturing,” Department of Chemical and Biomolecular Engineering, University of Illinois, Urbana-Champaign.

59. Oct., 2007, “Formulation approaches for the future,” IBC Life Sciences on Formulation Strategies for Protein Therapeutics, Hynes Convention Center, Boston, Keynote Address.

58. July, 2007, “Understanding reaction processes in complex media such as liquids,” Gordon Conference on the Chemistry of Liquids, Holderness School, New Hampshire

57. June, 2007, “Molecular Design of New Excipients for Large Molecule Stabilization,” AAP National Biotechnology Conference, San Diego, CA.

56. March, 2007, “Finding reactions coordinates for complex processes via likelihood maximization,” ACS Spring Meeting, Chicago, IL.

55. November, 2006, “Understanding complex reaction processes,” Department of Chemical Engineering, University of Buffalo, Buffalo, New York.

54. July, 2006, "Molecular simulations of ice and gas hydrate nucleation," Physics and Chemistry of Ice Conference, Bremerhaven, Germany, Keynote Address.

53. June, 2006, “Reaction coordinates from likelihood maximization,” U.S.-Poland Workshop on Nanoscience and Nanostructured Materials, Poznan, Poland.

52. June, 2006, “Understanding complex reaction processes with applications to pharmaceuticals and heterogeneous catalysis,” Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

51. February, 2006, “Statistical physics applied to the development of biopharmaceuticals,” Department of Physics, University of Rome “La Sapienza,” Rome, Italy.

50. February, 2006, “Statistical physics applied to the development of biopharmaceuticals,” SISSA, International School for Advanced Studies, Trieste, Italy.

49. September, 2005, “Molecular engineering of chemical systems,” Department of Chemical Engineering, Drexel University, Philadelphia, Pennsylvania.

48. September, 2005, “Molecular engineering of chemical systems,” Department of Chemical Engineering, Texas A&M, College Station, Texas.

47. September, 2005, "Reactivity in complex systems," Meeting in honor of Michele Parrinello's 60th Birthday, Agno, Switzerland.

46. July, 2005, "Molecular computational engineering: mechanism of methionine oxidation and rational design of additives for hindering aggregation," Protein Stability Conference, Breckenridge, Colorado.

45. May, 2005, “Transition Path Sampling Calculations in Complex Systems or How Can We Find the Reaction Coordinate?” 2005 International Conference on Scientific Computation and Differential Equations (SciCADE), Nagoya, Japan.

44. March, 2005, "Molecular computations for predictions of clathrate-hydrate nucleation and phase-behavior of multi-component hydrates," Hydrate Symposium at the American Chemical Society Spring Meeting, San Diego, California.

43. March, 2005, "Water structuring in phase transitions and in chemical reactions at sulfur sites in proteins," Water: Structure, Dynamics and Reactions Across the Phase Diagram at the American Chemical Society Spring Meeting, San Diego, California.

42. July, 2004, "A unified approach for the nucleation of ice and ice-like systems in homogeneous and inhomogeneous environments," Telluride Workshop on Studies of ice, icy particles, ice surfaces, and ice-adsorbate interactions: a molecular view," Telluride, Colorado.

41. April, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tufts University, Medford, Massachusetts.

40. April 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemistry, Boston University, Boston, Massachusetts.

39. March, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Cornell University, Ithaca, New York.

38. March, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemical Engineering, University of Rochester, Rochester, New York.

37. February, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tsinghua University, Beijing, China.

36. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemistry, Fudan University, Shanghai, China.

35. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Center for Atomic-Scale Materials Physics (CAMP) and Department of Physics, Technical University of Copenhagen, Copenhagen, Denmark.

34. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Chemistry, Washington University, St. Louis, MO.

33. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Physics, University of Missouri, Columbus, MO.

32. October, 2003, "Nucleation and growth of clathrate-hydrates and ice and a new theoretical framework to address those," Dartmouth University, Thayer School of Engineering, Dartmouth, NH.

31. September, 2003, "Finding reaction pathways for industrial chemical problems," Statistical Mechanics of Rare Events, Paris, France.

30. September, 2003, "Analyses of reactions in acid zeolites and of proteins via nudged elastic band calculations and Car-Parrinello simulations," CECAM Workshop on Reactivity, Lyon, France.

29. May, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," Advances in the Understanding and Application of Catalysis, Moscow, Russia, *Plenary Lecture*.

28. April, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, Princeton University, Princeton, NJ.

27. April, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA.

26. March, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, University of Texas, Austin, TX.

25. March, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," invited talk in “Mechanistic Surface Chemistry,” Spring Meeting of the American Chemical Society, New Orleans, LA.

24. March, 2003, "Effects of solvation on biological processes," invited talk in “Symposium in Honor of Professor Clayton J. Radke, recipient of the American Chemical Society Award in Colloid Chemistry,” Spring Meeting of the American Chemical Society, New Orleans, LA.

23. March, 2003, February, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, Stanford University, Palo Alto, CA.

22. February, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, Tsinghua Univeristy, Beijing, China.

21. February, 2003, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, North Carolina State University, Raleigh, NC.

20. November, 2002, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, University of California, Berkeley, CA.

19. November, 2002, “Solvation effects in clathrate-hydrates and biological systems,” Department of Chemical Engineering, California Institute of Technology, Pasadena, CA.

18. July, 2002, “Nucleation of and transport in clathrate-hydrates and ice,” Physics and Chemistry of Ice Conference, New Foundland, Canada.

17. June 2002, “Quantum mechanical calculations applied to engineering problems,” Steacie Institute of Molecular Sciences, National Research Council, Ottawa, Ontario, Canada.

16. April, 2002, “Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates,” Rensselaer Polytechnic Institute, Troy, NY.

15. April, 2002, “Quantification of reactive sites in zeolitic and transition metal catalysts via first-principles,” ACS Meeting, Orlando, Fl.

14. February, 2002, “The identification and study of sites of varying activity in zeolites and transition metal catalysts,” First-Principles Catalysis, Vienna, Austria.

13. February, 2002, “Order-disorder transitions on the surface of ice and in bulk ice and clathrate-hydrates,” Swiss Center for Computational Sciences, Manno, Switzerland.

12. February, 2002, “Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates,” Colorado School of Mines, Golden, CO.

11. August, 2001, “Car-Parrinello simulations of the disordering of ice and dissociation of HCl, relevant to stratospheric chemistry,” ACS Meeting, Chicago, IL.

10. July, 2001, “Insight into the stabilization of therapeutic proteins via molecular simulations,” National University of Singapore, Singapore.

8. June, 2001, “Insight into the stabilization of therapeutic proteins via molecular simulations,” Hong Kong University of Science and Technology, Hong Kong.

8. April, 2001, “Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics,” University of Connecticut, Storrs, CT.

6. February, 2001, “Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics,” Georgia Institute of Technology, Atlanta, GA.

6. January, 2001, “Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics,” National University of Singapore, Singapore.

5. November 1999, “Sustainable development,” ΤΒΠ Leonardo Lecture, MIT.

4. June, 1999, “Application of molecular modeling to automotive catalysis,” Workshop held at Ford Motor Company, Dearborn.

3. March, 1999, “Defect structure and its relation to methanol activation”, ACS Annual Conference, Annaheim, CA.

2. April, 1998, “Quantum mechanical methods in catalysis: a primer”, New England Catalysis Society, Worchester, MA.

1. September, 1996, “Dynamic Monte Carlo study of reaction and diffusion sites in ZSM-5 Zeolites”, Technical University of Athens, Athens, Greece.

Professional Affiliations:

AIChE, ACS, ASEE, AAPS

Languages:

French, German, Ancient Greek

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent 9,725,504 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., “Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria,” N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., “Method of Treating Hemolytic Disease,” U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., “Rationally Designed Antibodies,” U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., “C5-Specific Antibodies for The Treatment of Inflammatory Diseases,” U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1012	Hillmen, P., et al., “The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria,” N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., “Antibody Structure, Instability, and Formulation,” Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1030	Daugherty, A. and Mrsny, R., "Formulation and delivery issues for monoclonal antibody therapeutics," Advanced Drug Delivery Reviews 58: 686-706 (2006)
AMG1031	Mueller, P., et al., “Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells,” Molecular Immunology 34: 441 -452 (1997)

Exh. No.	Description
AMG1047	Hill, A., et al., “Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria,” Blood 106: 2559-2565 (2005) ("Hill '05")
AMG1056	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
AMG1058	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm
AMG1059	Immunomedics, Inc., CEA-Scan 1999 Package Insert, available at https://pharmacyce.unm.edu/nuclear_program/neolibrary/libraryfiles/package_inserts/CEA-scan.pdf
AMG1061	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf
AMG1063	Genentech, Inc., Lucentis 2006 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf
AMG1066	Genentech, Inc., Raptiva 2009 Package Insert, available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143346.pdf
AMG1067	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
AMG1069	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
AMG1070	Novartis Pharm. Corp., Simulect 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/basnov051298lb.pdf
AMG1071	MedImmune, Inc., Synagis 1999 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/palimed102302LB.pdf
AMG1073	Boehringer Ingelheim Int'l GmbH, Verluma 1996 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1996/nofedrk082096lb.pdf

Exh. No.	Description
AMG1074	Genentech, Inc., Xolair 2007 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf
ALXN2005	SOLIRIS® Label (2007)
ALXN2025	*Curriculum Vitae* of Bernhardt L. Trout, Ph.D.
ALXN2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
ALXN2032	Deposition Transcript of Joseph P. Balthasar, Ph.D., *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.,* IPR No. 2019-00740 (Oct. 23, 2019)
ALXN2079	Chang, Byeong S. and Hershenson, Susan, "Practical Approaches to Protein Formulation Development," Pharmaceutical Biotechnology Vol. 13, 1-25 (2002)
ALXN2080	Wang, Wei, "Instability, stabilization, and formulation of liquid protein pharmaceuticals," International Journal of Pharmaceutics, 185:129-188 (April 28, 1999)
ALXN2081	Hermeling, S. et al., "Structure-Immunogenicity Relationships of Therapeutic Proteins, " Pharmaceutical Research, 12:6, 897-903 (June 2004)
ALXN2082	Frokjaer, Sven and Otzen, Daniel E., "Protein Drug Stability: A Formulation Challenge," Nature Reviews, Drug Discovery, 4:298-306 (April 2005)
ALXN2083	Rosenberg, Amy S., "Effects of Protein Aggregates: An Immunologic Perspective," AAPS Journal 8, Article 59, pp. E501-E507 (Aug. 4, 2006)
ALXN2084	ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," European Medicines Agency (July 1996)
ALXN2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)