UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner

U.S. Patent No.: 8,802,100
Issue Date: Aug. 12, 2014
Title: Formulation of Human Antibodies for Treating TNF-Alpha Associated Disorders

---

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,802,100 PURSUANT TO 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42

TABLE OF CONTENTS

Page

I. INTRODUCTION 1

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1) 4

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1)) 4

B. Related Matters (37 C.F.R. § 42.8(b)(2)) 4

1. Related Litigations 4

2. Related Board Proceedings 5

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)) 6

D. Service Information (37 C.F.R. § 42.8(b)(4)) 6

E. Fee Payment Authorization (37 C.F.R. § 42.103(a)) 6

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a)) 7

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.104(b)) 7

A. Effective Filing Date of the '100 Patent 7

B. The Prior Art and Statutory Grounds of the Challenge (37 CFR § 42.104(b)(2)) 7

V. SUMMARY OF THE '100 PATENT 8

A. Background of the '100 Patent 8

B. Person of Ordinary Skill in the Art 11

C. Challenged Claims and Claim Construction (37 C.F.R. § 42.104(b)(1) and (b)(3)) 11

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED (37 C.F.R. § 42.104(b)(4) and (b)(5)) 12

A. Patents and Printed Publications Relied on in this Petition 12

Page

1. Salfeld (ex. 1003) Discloses a Stable Aqueous Solution of D2E7 with a Polyol, a Surfactant and a Buffer System 12

2. van de Putte (ex. 1004) Disclosed the Claimed Concentrations by Disclosing Effective Doses of 20, 40 and 80 mg D2E7 16

3. Remington (ex. 1008) Taught the Use of Tonicity Agents To Achieve Isotonicity in Injectable Solutions.....16

4. Barrera (ex. 1011) Disclosed a Parenteral D2E7 Formulation with the Claimed 12 $^{mg}/_{ml}$ Mannitol and Components of the Exemplified Buffer.....17

5. Lam (ex. 1005) Discloses a Stable Aqueous Solution of an Antibody with a Polyol, a Surfactant and an Acetate Buffer with a pH of 4.8 to 5.5.....17

6. Remington (ex. 1008) Disclosed Polysorbate as a Surfactant in Pharmaceutical Formulations.....19

B. Summary of the Argument.....20

C. Salfeld Combined with van de Putte, Barrera, Remington and Lam Render Obvious Claims 1-29.....24

1. The Prior Art Provided a POSA with a Motivation To Combine Salfeld with van de Putte, Remington, Barrera and Lam To Obtain the Stable, High Concentration D2E7 Aqueous Solution for Subcutaneous Injection Comprising a Polyol, Polysorbate and a Buffer with a pH of 4-8 Required by All Claims.....24

a. D2E7 Concentration 24

b. Polyol and Polyol Concentration.....25

c. Polysorbate and Polysorbate Concentration.....27

d. Buffer System and Requisite pH 28

2. 20, 40 and 80 mg D2E7 Correspond to a Concentration of 6 to 160 $^{mg}/_{ml}$ or at most 2.5 to 400 $^{mg}/_{ml}$ (ex. 1002).....29

Page

a. In Prior Proceedings, Amgen and AbbVie Neither Comprehensively Reviewed the Prior Art nor Properly Accounted for Injection Volumes and Number of Injections 29

b. Remmele Properly Accounted for Injection Volume and Number of Injections 31

3. A POSA Would Have a Reasonable Expectation of Success in Making a Stable, High Concentration, Aqueous, Subcutaneously Injectable Solution According to Salfeld 33

4. AbbVie Cannot Rebut Prima Facie Obviousness over Salfeld in Combination with van de Putte, Barrera, Remington and Lam 38

a. The Prior Art Did Not Teach Away from the Claimed Invention 39

(1) The literature reviews relied upon by AbbVie ignored the art that taught stable high concentration formulations 39

(2) Lam does not teach away 42

(3) The fact that commercially available liquid antibody formulations have low concentrations does not teach away 42

b. The ’100 Patent Provides No Evidence of Any Unexpected Results 49

c. Commercial Success Does Not Demonstrate Nonobviousness 49

5. Summary of Grounds for Invalidity 52

VII. CONCLUSION 63

TABLE OF AUTHORITIES

Page(s)

Cases

Amgen Inc. v. AbbVie Biotech. Ltd.,
Case No. IPR2015-01514, Decision Denying Institution
of *Inter Partes* Review (P.T.A.B. Jan. 14 2016) 41

Amgen Inc. v. AbbVie Biotech. Ltd.,
Case No. IPR2015-01517, Decision Denying Institution
of *Inter Partes* Review (P.T.A.B. Jan. 14, 2016) 20, 28, 31, 41

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
314 F.3d 1313 (Fed. Cir. 2003) 34

Apotex Inc. v. OSI Pharm., Inc.,
IPR2016-01284, 2017 WL 379496 (P.T.A.B. Jan. 9, 2017) 38

Coalition for Affordable Drugs II LLC v. NPS Pharm., Inc.,
No. IPR2015-01093, Final Written Decision, Paper 67
(P.T.A.B. Oct. 21, 2016).....50

Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.,
No. IPR2016-00172, Final Written Decision, Paper 60
(P.T.A.B. May 16, 2017) 51

Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.,
Case No. IPR2016-01018, Decision Denying Institution
of *Inter Partes* Review (P.T.A.B. Nov. 7, 2016).....12, 41

Eli Lilly & Co. v. Trs. of Univ. of Pa, IPR2016-00458, 2016 WL
5103461 (P.T.A.B. July 14, 2016)..... 38-39

Galderma Labs., L.P. v. Tolmar, Inc.,
737 F.3d 731 (Fed. Cir. 2013) 25, 38

In re Antor Media Corp.,
689 F.3d 1282 (Fed. Cir. 2012) 34

In re Cuozzo Speed Techs., LLC,
793 F.3d 1268 (Fed. Cir. 2015) 11

In re Dill,
604 F.2d 1356 (C.C.P.A. 1979) 49

In re Grasselli,
713 F.2d 731 (Fed. Cir. 1983) 52

In re Payne,
606 F.2d 303 (C.C.P.A. 1979) 49

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007).....52

Luye Pharma Grp. Ltd. v. Alkermes Pharma Ireland Ltd.,
IPR2016-01096, 2016 WL 7985470 (P.T.A.B. Nov. 30, 2016).....39

Merck & Co. v. Teva Pharm. USA, Inc.,
395 F.3d 1364 (Fed. Cir. 2005) 50

Par Pharm., Inc. v. Twi Pharm., Inc.,
773 F.3d 1186 (Fed. Cir. 2014) 37-38, 40

W. Union Co. v. MoneyGram Payment Sys., Inc.,
626 F.3d 1361 (Fed. Cir. 2010) 52

Statutes

35 U.S.C. § 102(b) 8

35 U.S.C. § 103.....7

35 U.S.C. § 103(a) 8

35 U.S.C. §§ 311-319.....1

35 U.S.C. § 314(a) 12

Other Authorities

37 C.F.R. § 42 1

37 C.F.R. § 42.6(c).....7

37 C.F.R. § 42.8(A)(1)..... 4-6

37 C.F.R. § 42.8(b)(1).....4
37 C.F.R. § 42.8(b)(2)..... 4-6
37 C.F.R. § 42.8(b)(3).....6
37 C.F.R. § 42.8(b)(4).....6
37 C.F.R. § 42.15(a).....6
37 C.F.R. § 42.100(b) 11
37 C.F.R. § 42.103(a).....6
37 C.F.R. § 42.104(a).....7
37 C.F.R. § 42.104(b) 7
37 C.F.R. § 42.104(b)(1).....11
37 C.F.R. § 42.104(b)(2).....7
37 C.F.R. § 42.104(b)(3).....11
37 C.F.R. § 42.104(b)(4).....12
37 C.F.R. §42.104(b)(5).....12
MPEP § 2144.05(I) 25, 29
MPEP § 2144.05(II).....27, 28

EXHIBIT LIST

Exhibit No.	Description	Referenced As	Reference Type[1]
1001	United States Patent No. 8,802,100, filed Nov. 27, 2013, issued Aug. 12, 2014	"'100 patent"	n/a
1002	Declaration of Richard Remmele, Ph.D.	"Remmele Decl."	n/a
1003	United States Patent No. 6,090,382, filed Feb. 9, 1996, issued July 18, 2000	"Salfeld"	102(b)
1004	B. A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM (1999) (ACR Abstract Concurrent Session, RA: TNF-Blockade, Wednesday, Nov. 17, 1999 S400)	"van de Putte"	102(b)
1005	United States Patent No. 6,171,586, filed June 12, 1998, issued Jan. 9, 2001	"Lam"	102(b)
1006	M. Schattenkirchner et al. *Long-Term Use of the Fully Human Anti-TNF Antibody D2E7 in Combination with Methotrexate in Active Rheumatoid Arthritis*, 43 ARTHRITIS & RHEUMATISM. S228 [968] (2000)	"Schatten-kirchner"	102(b)
1007	Joachim Kempeni, *Update on D2E7: A Fully Human Anti-Tumour Necrosis Factor α Monoclonal Antibody*, 59 ANNALS RHEUMATIC DISEASES i44 (2000)	"Kempeni"	102(b)
1008	REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)	"Remington"	102(b)
1009	Assignment of U.S. Patent No. 6,090,382 from BASF	"Assignment of Salfeld"	n/a

[1] This column indicates whether an exhibit is prior art under 35 U.S.C. §§ 102(a), (b) or (e). "n/a" indicates the exhibit is not being relied upon as prior art.

Exhibit No.	Description	Referenced As	Reference Type[1]
	Aktiengesellschaft to Abbott Biotechnology Ltd. (Feb. 5, 2003)		
1010	Change of Name from Abbott Biotechnology Ltd. to AbbVie Biotechnology Ltd. (June 25, 2012)	"Abbott Name Change"	n/a
1011	P. Barrera et al., *Effects of Treatment with a Fully Human Anti-Tumour Necrosis Factor α Monoclonal Antibody on the Local and Systemic Homeostasis of Interleukin 1 and TNFα in Patients with Rheumatoid Arthritis*, 60 ANNALS RHEUMATIC DISEASE 660 (July 2001)	"Barrera"	102(b)
1012	United States Patent No. 7,250,165, filed Aug. 1, 2001, issued July 31, 2007	"Heavner"	102(e)
1013	Eric L. Matteson et al., *Treatment of Active Refractory Rheumatoid Arthritis with Humanized Monoclonal Antibody Campath-1H Administered by Daily Subcutaneous Injection*, 38 ARTHRITIS & RHEUMATISM 1187 (1995)	"Matteson"	102(b)
1014	WO 00/56772, filed Mar. 24, 2000, published Sept. 28, 2000	"WO 00/56772"	102(b)
1015	United States Patent No. 5,981,485, filed July 14, 1997, issued Nov. 9, 1999	"'485 patent"	102(b)
1016	Patent Term Extension Certificate for U.S. Patent No. 6,090,382 (dated Apr. 3, 2007)	"PTE Certificate"	n/a
1017	WO 02/12502, filed Aug. 7, 2001, published Feb. 14, 2002	"WO '502"	102(e)
1018	WO 02/30463, filed Oct. 4, 2001, published Apr. 18, 2002	"WO '463"	102(e)
1019	Gayle A. Brazeau et al., *Current Perspectives on Pain Upon Injection of Drugs*, 87 J. PHARMACEUTICAL SCI. 667 (1998)	"Brazeau"	102(b)
1020	United States Patent No. 6,267,958, filed Mar. 14, 1996, issued July 31,	"Andya"	102(b)

Exhibit No.	Description	Referenced As	Reference Type[1]
	2001		
1021	Wei Wang, *Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*, 185 INT'L J. PHARMACEUTICS 129 (1999)	"Wang"	102(b)
1022	RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE vol. 13 (John F. Carpenter & Mark C. Manning, eds. 2002)[2]	"Manning & Carpenter"	102(a)
1023	HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Ainley Wade & Paul J. Weller, eds. 2nd ed. 1994)	"Handbook of Pharmaceutical Excipients"	102(b)
1024	ReoPro® (Abciximab) Package Insert (Centocor B.V. revised Feb. 12, 1998), 2001 Physician's Desk Reference (55th ed. published Nov. 2000[3])	"ReoPro® Package Insert"	102(b)
1025	Simulect® (Basiliximab) Package Insert (Novartis Pharma AG revised July 2000), 2001 Physician's Desk Reference (55th ed. published Nov. 2000[4])	"Simulect® Package Insert"	102(b)

[2] Databases indicate that the publication date for ex. 1022 is April 2002. *See, e.g.*, https://isbnsearch.org/isbn/0306467410; https://www.amazon.com/gp/search/ref=sr_adv_b/?search-alias=stripbooks&unfiltered=1&field-keywords=&field-author=&field-title=&field-isbn=0-306-46741-0&field-publisher=&node=&field-p_n_condition-type=&p_n_feature_browse-bin=&field-age_range=&field-language=&field-dateop=During&field-datemod=&field-dateyear=&sort=relevanceexprank&Adv-Srch-Books-Submit.x=16&Adv-Srch-Books-Submit.y=7.

[3] According to Amazon the 2001 PDR was published in November 2000. *See* https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752.

[4] *Id*.

Exhibit No.	Description	Referenced As	Reference Type[1]
1026	2001 Physician's Desk Reference (55th ed. published Nov. 2000[5]) excerpts for Orthoclone (revised Reb. 1999), Rituxan (Revised July 1999) and Zenapax (Labeling in effect June 2000)	"2001 PDR"	102(b)
1027	Campath® (alemtuzumab) Package Insert (Millennium and ILEX Partners, LP issued May 2001), 2002 Physician's Desk Reference (56th ed. published Jan. 2002[6])	"Campath® Package Insert"	102(b)
1028	Herceptin® (Trastuzumab) Package Insert (Genentech, Inc. revised Jan. 2000), 2001 Physician's Desk Reference (55th ed. published Nov. 2000[7])	"Herceptin® Package Insert"	102(b)
1029	Zevalin™ (Ibritumomab Tiuxetan) Package Insert (IDEC Pharmaceuticals Corp. Dec. 21, 2001)	"Zevalin™ Package Insert"	102(a)
1030	Synagis® (Palivizumab) Package Insert (MedImmune, Inc. revised Dec. 2, 1999)	"Synagis® Package Insert"	102(b)
1031	ProstaScint™ (Capromab Pendetide) Package Insert (Cytogen Corp. revised Oct. 28, 1996)	"ProstaScint™ Package Insert"	102(b)
1032	Jan T. Jørgensen et al., *Pain Assessment of Subcutaneous Injections*, *30 ANNALS PHARMACOTHERAPY* 729 (1996)	"Jørgensen"	102(b)

[5] *Id*.

[6] According to Amazon, the 2002 PDR was published in January 2002. *See* https://www.amazon.com/Physicians-Desk-Reference-Medical-Economics/dp/1563634112. The package insert for alemtuzumab included in the 2002 PDR however was issued May 2001. Ex. 1027 at 995.

[7] According to Amazon the 2001 PDR was published in November 2000. *See* https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752.

Exhibit No.	Description	Referenced As	Reference Type[1]
1033	Humira® (adalimumab) Package Insert (AbbVie Inc. revised Apr. 2017), 2017 Physician's Desk Reference	"2017 Humira® Package Insert"	n/a
1034	Larry A. Gatlin & Carol A. Brister Gatlin, *Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated With Parenteral Products*, *in* INJECTABLE DRUG DEVELOPMENT: TECHNIQUES TO REDUCE PAIN AND IRRITATION 401-425 (Pramod K. Gupta & Gayle A. Brazeau, eds. 1999)	"Gatlin"	102(b)
1035	WO 02/100330, filed June 5, 2002, published Dec. 19, 2002	"WO '330"	102(e)
1036	E. C. Keystone et al., *Golimumab, a Human Antibody to Tumour Necrosis Factor α Given by Monthly Subcutaneous Injections, in Active Rheumatoid Arthritis Despite Methotrexate Therapy: The GO-FORWARD Study*, 68 ANNALS RHEUMATIC DISEASES 789 (2009)	"Keystone"	n/a
1037	United States Patent No. 7,648,702, filed Apr. 6, 2007, issued Jan. 19, 2010	"'702 patent"	n/a
1038	R. Ritzel et al., *Pharmacokinetic, Insulinotropic, and Glucagonostatic Properties of GLP-1 [7-36 Amide] After Subcutaneous Injection in Healthy Volunteers. Dose-Response-Relationships*, 38 DIABETOLOGIA 720 (1995)	"Ritzel"	n/a
1039	Humira™ (adalimumab) Package Insert (Abbott Laboratories issued Dec. 20, 2002)	"Humira™ 2002 Package Insert"	n/a
1040	PROTEIN FORMULATION AND DELIVERY (Eugene J. McNally, ed. 2000)	"McNally"	102(b)
1041	U.S. Environmental Protection Agency,	"EPA	102(b)

Exhibit No.	Description	Referenced As	Reference Type[1]
	Office of Research and Development, EXPOSURE FACTORS HANDBOOK (Aug. 1997)	Handbook"	
1042	Remicade® (infliximab) Package Insert (Centocor, Inc. revised June 2002)	"Remicade® 2002 Package Insert"	102(a)
1043	Hai Won Chang & Ernest Bock, *Pitfalls in the Use of Commercial Nonionic Detergents for the Solubilization of Integral Membrane Proteins: Sulfhydryl Oxidizing Contaminants and Their Elimination*, 104 ANALYTICAL BIOCHEMISTRY 112 (1980)	"Chang"	102(b)
1044	Serial No. 11/784,358, Richard L. Remmele Declaration (dated July 24, 2009)	"'702 Decl."	n/a
1045	*Amgen Inc. v. AbbVie Biotech. Ltd.*, No. IPR2015-01517 (Declaration of Dr. Theodore W. Randolph, June 25, 2015)	"Randolph Decl. in '158 IPR"	n/a
1046	*Amgen v. AbbVie Biotech. Ltd.*, No. IPR2015-01514 (Petition for *Inter Partes* Review, June 26, 2015)	"Petition in '157 IPR"	n/a
1047	*Amgen Inc. v. AbbVie Biotech. Ltd.*, No. IPR2015-01517 (Petition for *Inter Partes* Review, June 26, 2015)	"Petition in '158 IPR"	n/a
1048	*Amgen Inc. v. AbbVie Biotech. Ltd.*, No. IPR2015-01517 (Patent Owner's Preliminary Response, Oct. 19, 2015)	"Prelim. Response in '158 IPR"	n/a
1049	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-01018 (Patent Owner's Preliminary Response, Aug. 9, 2016)	"Prelim. Response in '166 IPR"	n/a
1050	*Amgen v. AbbVie Biotech. Ltd.*, No. IPR2015-01514 (Patent Owner's Preliminary Response, Oct. 19, 2015)	"Prelim. Response in '157 IPR"	n/a
1051	*Amgen v. AbbVie Biotech. Ltd.*, No. IPR2015-01514 (Declaration of Dr.	"Randolph Decl. in '157	n/a

Exhibit No.	Description	Referenced As	Reference Type[1]
	Theodore W. Randolph, June 25, 2015)	IPR"	
1052	WinRho SDF™ (Rh_o (D) Immune Globulin Intravenous (Human)) Package Insert (Cangene Corp. revised Jan. 2000), 2002 Physician's Desk Reference (56th ed. published Jan. 2002[8])	"WinRho SDF™ 2002 Package Insert"	102(b)
1053	Ovidrel® (choriogonadotropin alfa) Package Insert (Serono, Inc. draft Sept. 20, 2000)[9]	"Ovidrel® 2000 label"	102(b)
1054	Rebif® (interferon beta-1a) Package Insert (Serono, Inc. issued Mar. 8, 2002)	"Rebif® 2002 Package Insert"	102(a)
1055	2002 Physician's Desk Reference (56th ed. published Jan. 2002[10]) excerpts	"2002 PDR"	102(a)
1056	2002 Physician's Desk Reference (56th ed. published Jan. 2002[11]) excerpts	"2002 PDR"	102(a)
1057	U.S. Application No. 13/471,820, Non-Final Rejection (Sept. 9, 2013)	"'591 Non-final Rejection"	n/a
1058	Center for Drug Evaluation and Research List of Licensed Biological Products (updated May 1, 2017), *available at* https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDru	"CDER list"	n/a

[8] *Id.*

[9] Ovidrel was launched February 5, 2001 in the United States. *See* https://www.icis.com/resources/news/2001/02/05/131842/serono-launches-ovidrel-cetrotide-fertility-drugs-in-us/

[10]https://www.amazon.com/Physicians-Desk-Reference-Medical-Economics/dp/1563634112/ref=sr_1_1?ie=UTF8&qid=1499215858&sr=8-1&keywords=2002+Physician%E2%80%99s+Desk+Reference

[11] *Id.*

Exhibit No.	Description	Referenced As	Reference Type[1]
	gsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf		
1059	WinRho® SDF (Rh_o(D) Immune Globulin Intravenous (Human)) Package Insert (Cangene BioPharma, LLC revised June 2016)	"WinRho® SDF 2016 Package Insert"	n/a
1060	Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug That Toppled Lipitor as No. 1*, XCONOMY (Apr. 16, 2012), *available at* http://www.xconomy.com/national/2012/04/16/abbotts-humira-the-3rd-in-class-drug-that-toppled-lipitor-as-no-1/#	"Timmerman"	n/a
1061	Vincent S. Stoll & John S. Blanchard, *Buffers: Principles and Practice*, 463 METHODS IN ENZYMOLOGY (1990)	"Stoll"	102(b)
1062	M. Donbrow et al., *Autoxidation of Polysorbates*, 67 J. PHARM. SCI. 1676 (1978)	"Donbrow"	102(b)
1063	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172 (Patent Owner's Preliminary Response, Paper No. 8, Feb. 18, 2016)	"Prelim. Response in '135 IPR"	n/a
1064	Jared S. Bee et al., *Formulation Strategy and Tactics for mAbs: Not All mAbs Are the Same*, *in* MONOCLONAL ANTIBODIES: DEVELOPMENT, DELIVERY AND APPLICATIONS (2015)	"Remmele Chapter"	n/a
1065	U.S. Application No. 14/091,661, Notice of Allowance and Fee(s) Due (mailed June 26, 2014)	"'100 Examiner Interview"	n/a
1066	John F. Carpenter et al., *Inhibition of Stress-Induced Aggregation of Protein Therapeutics*, 309 METHODS IN ENZYMOLOGY 236 (1999)	"Carpenter"	102(b)

Exhibit No.	Description	Referenced As	Reference Type[1]
1067	United States Patent No. 8,216,583, filed August 15, 2003, issued July 10, 2012	"'583 patent"	n/a
1068	United States Patent No. 8,932,591, filed May 15, 2012, issued Jan. 13, 2015	"'591 patent"	n/a
1069	U.S. Application No. 10/525,292, Notice of Allowance and Fee(s) Due (mailed Apr. 5, 2012)	"'583 Notice of Allowance"	n/a
1070	https://isbnsearch.org/isbn/0306467410		n/a
1071	https://www.amazon.com/gp/search/ref=sr_adv_b/?search-alias=stripbooks&unfiltered=1&field-keywords=&field-author=&field-title=&field-isbn=0-306-46741-0&field-publisher=&node=&field-p_n_condition-type=&p_n_feature_browse-bin=&field-age_range=&field-language=&field-dateop=During&field-datemod=&field-dateyear=&sort=relevanceexprank&Adv-Srch-Books-Submit.x=16&Adv-Srch-Books-Submit.y=7		n/a
1072	https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752		n/a
1073	https://www.amazon.com/Physicians-Desk-Reference-Medical-Economics/dp/1563634112		n/a
1074	Images from: https://www.amazon.com/Injectable-Drug-Development-Techniques-Irritation/dp/1574910957/ref=sr_1_1?ie=UTF8&qid=1499288758&sr=8-1&keywords=INJECTABLE+DRUG+DEVELOPMENT%3A+TECHNIQUES+TO+REDUCE+PAIN+AND+IRRIT		n/a

Exhibit No.	Description	Referenced As	Reference Type[1]
	ATION		
1075	Declaration of Daniel L. Reisner	"Reisner Declaration"	n/a

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Sandoz Inc. ("Sandoz" or "Petitioner") respectfully requests *Inter Partes* Review ("IPR") of claims 1-29 of U.S. Patent No. 8,802,100 to Krause et al., titled "Formulation of Human Antibodies for Treating TNF-Alpha Associated Disorders" ("'100 patent," Ex. 1001), which is currently assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner").

Exemplary claim 1 of the '100 patent covers "stable liquid aqueous" formulations of (a) the anti-TNF-α antibody D2E7 in concentrations of 45 to 150 mg/ml, (b) a polyol, (c) a polysorbate at a concentration of 0.1 to 10 mg/ml, and (d) a buffer system having a pH of 4.5 to 7.0. D2E7 is the antibody in AbbVie's Humira® product.

The prior art includes U.S. Patent No. 6,090,382 ("Salfeld"), also owned by AbbVie,[12] which provided it with over 14 years of exclusivity on Humira®. Salfeld provides a complete guideline for the claimed subject matter of the '100 patent because it described stable, subcutaneously injectable liquid aqueous formulations of D2E7, including formulations containing polyalcohols (polyols, including

[12] BASF Aktiengesellschaft assigned Salfeld to Abbott Biotechnology Ltd. on February 5, 2003. Ex. 1009 at 1. On June 25, 2012 Abbott Biotechnology Ltd. was renamed AbbVie Biotechnology Ltd. Ex. 1010 at 1-2. (Footnote numbering begins with the footnotes in the Exhibit List.)

mannitol), surfactants and buffers (which adjust pH). Salfeld further described a dosage range for D2E7 of 0.1-20 $^{mg}/_{kg}$, with a more preferred range of 1-10 $^{mg}/_{kg}$, which allows a Person of Ordinary Skill in the Art ("POSA") to calculate appropriate D2E7 concentrations for an injectable formulation. Claim 29 of Salfeld claimed this genus of formulations. The claims of the '100 patent merely follow Salfeld's guideline by varying the D2E7 concentration, the amount of polyol, the type and amount of surfactant and the pH range of the formulations described in Salfeld.

All of this, however, is obvious over the prior art. A POSA seeking to formulate D2E7 would (1) determine the concentration of D2E7 to use based upon AbbVie's own van de Putte disclosure of clinical data demonstrating the safety and efficacy of 20, 40 and 80 mg doses, which are readily converted to concentrations; (2) use Salfeld's teaching that D2E7 should be combined with a tonicity agent like mannitol, a surfactant and a buffer; (3) determine the amount of mannitol based upon Remington's teaching of how to use tonicity agents and AbbVie's own Barrera disclosure of a D2E7 formulation having 12 $^{mg}/_{ml}$ mannitol; and (4) identify the type and amount of surfactant based on Remington's teaching that polysorbate is the most widely used surfactant and Lam's teaching of a 0.01% to about 0.1% concentration of polysorbate, which is readily converted into $^{mg}/_{ml}$.

Each of the elements of the claims of the ’100 patent is clearly embraced within AbbVie’s own Salfeld, van de Putte and Barrera prior art references, in view of either Remington, a principal reference for pharmaceutical formulations or Lam, a U.S. patent issued to Genentech, a leading antibody formulator. The clear motivation to combine these references and reasonable expectation of success are described herein.

Despite this prior art, the ’100 patent attempts to extend the coverage AbbVie enjoyed from the now-expired Salfeld patent with similar generic claims to stable liquid aqueous formulations of D2E7 comprising any buffer. The ’100 claims are squarely encompassed within the genus of formulations disclosed and claimed by Salfeld, but have a significantly longer patent term.

The ’100 patent necessarily relies upon the teachings of the prior art to support its broad claims. The specification discloses only a single example of a formulation. AbbVie’s first patent in the chain of 21 applications and patents sharing the same specification that led to the ’100 patent had claims limited to formulations having the specific buffer of that single example (Example 1). In subsequent patents, however, AbbVie obtained broader claims to formulations, such as those of the ’100 patent, where the buffer is not limited. The only possible way these broad claims could be supported by this single example is if a POSA would understand from the prior art that all (or nearly all) D2E7 formulations

within the scope of the claims (and thus having the excipients disclosed by Salfeld and other prior art references) would yield a stable "high concentration" D2E7 formulation. Accordingly, AbbVie cannot simultaneously argue that its '100 patent satisfies the disclosure requirements based on this prior art and that the claims of the '100 patent are also not obvious over the same prior art.

Petitioner recognizes that the Board declined to institute trial on prior petitions filed against three related AbbVie D2E7 formulation patents. Petitioner addresses the Board's reasons for not instituting trial on these prior petitions, including arguments raised by AbbVie in its preliminary responses, and respectfully submits that it has met its burden of establishing a likelihood that at least one claim of the '100 patent is invalid.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Sandoz is the real party-in-interest.

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

1. Related Litigations

The '100 patent is related to three of the patents at issue[13] in the following judicial matter in which Petitioner was not and is not a party, which may affect, or be affected by, a decision in this proceeding: *AbbVie Inc. et al. v. Amgen Inc. et.*

[13] U.S. Patent Nos. 8,916,157; 9,220,781; 9,272,041, and the '100 patent claim priority to the same application, SN 10/222,140 filed August 16, 2002.

al., No. 1:16-cv-00666-SLR-SRF (D. Del. filed Aug. 4, 2016). Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '100 patent.

2. Related Board Proceedings

The '100 patent is related to patents at issue in the following administrative matters, which may affect, or be affected by, a decision in this proceeding: (1) *Amgen Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2015-01514 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 8,916,157 ("'157 Patent"), dated June 26, 2015 ("the '157 IPR"); (2) *Amgen Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2015-01517 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,916,158 ("'158 Patent"), dated June 26, 2015 ("the '158 IPR"); and (3) *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2016-01018, Petition for *Inter Partes* Review of U.S. Patent No. 9,114,166 ("'166 Patent"), dated May 9, 2016 ("the '166 IPR"). The '157, '158,'166 and '100 patents claim priority to the same initial application, SN 10/222,140, filed August 16, 2002. On January 14, 2016,[14] the Board issued decisions denying institution for Case Nos. IPR2015-01514 and IPR2015-01517. On November 7, 2016, the Board issued a decision denying institution for Case No. IPR2016-01018.

[14] The January 14, 2015 date on the IPR2015-01514 decision appears to be incorrect.

The following list includes U.S. applications and patents that claim the benefit of the priority date of the '100 patent or from which the '100 patent claims priority: U.S. Patent Nos. 9,220,781; 9,114,166; 8,911,741; 8,795,670; 8,932,591; 8,216,583; 8,802,101; 8,802,102; 8,940,305; 8,916,157; 8,916,158; 9,302,011; 9,327,032; 9,272,041; 9,295,725; 9,272,042; 9,289,497; and U.S. Application Nos. 10/222,140; 15/095,393; 15/418,460; 15/418,465; and 15/418,469.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	**Back-up Counsel**
David K. Barr (Reg. No. 31,940) David.Barr@apks.com Arnold & Porter Kaye Scholer LLP 250 W. 55th Street New York, NY 10019 T: 212-836-7560 F: 212-836-6560	Daniel L. Reisner (*pro hac vice* motion to be filed) Daniel.Reisner@apks.com Arnold & Porter Kaye Scholer LLP 250 West 55th Street New York, NY 10019 T: 212-836-8132 F: 212-836-6432

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

Please address all correspondence to the lead and backup counsel shown above. Petitioner consents to service by email (above).

E. Fee Payment Authorization (37 C.F.R. § 42.103(a))

The Petitioner authorizes the Patent and Trademark Office (the "PTO") to charge Deposit Account No. 502387 for the fees in 37 C.F.R. § 42.15(a) for this Petition, and further authorizes payment of any additional fees to be charged to this account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '100 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR on the grounds identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.104(b))

A. Effective Filing Date of the '100 Patent

The '100 patent issued from U.S. patent application No. 14/091,661 filed on November 27, 2013 and claims priority to several continuation applications with the earliest, SN 10/222,140, having a filing date of August 16, 2002. For purposes of this petition only, the effective filing date of the challenged claims is August 16, 2002.

B. The Prior Art and Statutory Grounds of the Challenge (37 CFR § 42.104(b)(2))

Petitioner requests *inter partes* review and cancellation of claims 1-29 of the '100 patent on one ground pursuant to 35 U.S.C. § 103 set forth below. In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. In addition, the Petition is accompanied by the declaration of Richard Remmele, Ph.D. Ex. 1002.

The challenged claims are unpatentable in view of Salfeld, van de Putte, Barrera, Remington and Lam—all of which are prior art to the '100 patent under

pre-AIA 35 U.S.C. § 102(b) because each issued or published more than one year before the effective filing date (August 16, 2002) of the '100 patent.

The challenged claims are unpatentable based upon the following ground:

Table 1. Ground for Inter Partes Review

Ground	Claims	Statutory Basis and Prior Art
1	1-29	Obvious under 35 U.S.C. § 103(a) over Salfeld in combination with van de Putte, Barrera, Remington and Lam

Section VI and the Declaration of Richard Remmele, Ph.D. (ex. 1002) further describe the ground for invalidation of the '100 patent. Remmele spent 23 years working as a formulation scientist in the pharmaceutical industry where he specialized in the formulation of protein and antibody drugs including aqueous liquid antibody formulations. *Id.* at ¶¶ 3-14.

Remmele is qualified to provide an opinion as to what a POSA would have understood, known, or concluded as of August 16, 2002 (*id.* at ¶¶ 31-34), and is therefore competent to testify in this proceeding.

V. SUMMARY OF THE '100 PATENT[15]

A. Background of the '100 Patent

The '100 patent states "[t]here is a need for a stable aqueous pharmaceutical formulation with an extended shelf life" that has a high antibody concentration for

[15] Some references have been stamped with page numbers. Pincites for references that have such stamped-on page numbers refer to those page numbers, otherwise they refer to the document's original page numbering.

treating detrimental TNF-α activity. Ex. 1001 at 3:7-14. "A 'stable' formulation," according to the patent, "is one in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage." Ex. 1001 at 7:16-18. The patent does not provide any limitation on the time a formulation must retain stability to qualify as "stable." Ex. 1001 at 7:24-26.

The '100 patent provides only a single example of a formulation (example 1) that the patentee tested for stability (example 2), which it did using a freeze/thaw cycle. *Id*. at 7:27-30, 21:42 – 23:24; Ex. 1002 at ¶ 29. The claims, however, are not limited to this exemplified formulation and instead, much like AbbVie's prior Salfeld patent, cover a generic formulation that can be used with a broad range of D2E7 concentrations, buffers and other excipients. Specifically, the '100 patent exemplifies only a single buffer combination with specific concentrations, but even the narrowest dependent claims are directed to only the term "buffer system," essentially claiming the full scope of possible buffers. The '100 patent, however, does not teach what imparts stability to the claimed genus of formulations, but instead presumes this knowledge was known to a POSA. Ex. 1002 at ¶ 29.[16]

[16] Patents in the chain preceding the '100 patent claimed formulations having the specific buffer of the single example (example 1) or other specific buffers as required by the examiner. *See, e.g.*, exs. 1067, 1068; *see also* ex. 1069 at 7-8 (explaining in the "Reasons for Allowance" that the rejections were withdrawn because the prior art does not teach "a liquid formulation comprising a high concentration of the TNFα antibody of the instant claims, in conjunction with a polyol, surfactant and a citrate and phosphate buffer[,]" as claimed here (emphasis

The ’100 patent discloses using its formulation with D2E7 or any other antibody directed to TNF-α. Ex. 1001 at 3:7-55, 4:18-21, 6:8-13, 6:54-60, 12:1-4.

D2E7 is a human antibody to TNF-α containing CDR regions having the amino acid sequences specified in Salfeld. A version of D2E7, adalimumab, is contained in AbbVie’s Humira® product. Ex. 1039 at 1.

The specification discloses a wide range of antibody concentrations from “about 1-150 $^{mg}/_{ml}$” (*id.* at 3:54, 13:37), and a number of sub-ranges (*id.* at 13:36-45). The patent also discloses the generic formulation including a pH range “from about 4 to about 8” (*id.* at 13:59-64), various buffers to “control the pH” (*id.* at 13:67, 14:4-26), a number of different polyols (including “mannitol” and “sorbitol”) at various concentrations (*id.* at 14:1-46) and detergents (surfactants) at various concentrations (*id.* at 14:47-50).

Nothing in the ’100 patent teaches the skilled artisan how to select particular polyols, polysorbates, buffers or amounts of those excipients to make stable formulations. Ex. 1002 at ¶ 29.

---

in original); ex. 1057 at 7 (concluding that the prior art does not teach “a liquid formulation comprising a high concentration of the TNFα antibody of the instant claims, in conjunction with a polyol, surfactant and a citrate and phosphate buffer.”). However, AbbVie subsequently pursued claims while prosecuting the application leading to the ’100 patent that were not limited to a particular buffer and the examiner without explanation neglected to renew the prior rejections. *See, e.g.*, ex. 1065 at 5 (noting that the examiner withdrew her previous rejections for the ’100 patent after considering the Applicant’s arguments without further explanation).

B. Person of Ordinary Skill in the Art

As explained by Remmele, a POSA, would have had a Pharm. D. or Ph.D. in biology, biochemistry, or chemistry. The POSA would also have had at least two years of experience preparing stable formulations of therapeutic protein drugs. *Id.* at ¶ 33.

C. Challenged Claims and Claim Construction (37 C.F.R. § 42.104(b)(1) and (b)(3))

The claim terms are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278-79 (Fed. Cir. 2015).

Claim 1 recites a "stable" liquid pharmaceutical formulation. AbbVie has three related formulation patents, the '157, '158 and '166, sharing the same specification as the '100 patent, which have been the subject of prior proceedings before the Board.[17] The Board previously construed "stable," as it is used in the claims of the '157, '158 and '166 patents, as "a formulation in which the antibody therein essentially retains its physical stability and/or chemical stability and/or

[17] The '100 patent issued from application no. 14/091,661, which is a continuation of application no. 13/471,820, which is a continuation of the application that issued as patent no. 8,216,583, which is a continuation of application no. 10/222,140. The '157, '158, '166 and '100 patents all claim priority to application 10/222,140, filed on August 16, 2002.

biological activity upon storage and use as a pharmaceutical formulation."[18] For purposes of this Petition only, Sandoz asserts this construction for "stable" and does not assert that any special meanings apply to other claim terms in the '100 patent.

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED (37 C.F.R. § 42.104(b)(4) and (b)(5))

This petition meets the threshold requirement for *inter partes* review because it establishes "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). As explained below, for the ground of unpatentability proposed, there is a reasonable likelihood that Petitioner will prevail on at least one of the challenged claims.

A. Patents and Printed Publications Relied on in this Petition

1. Salfeld (ex. 1003) Discloses a Stable Aqueous Solution of D2E7 with a Polyol, a Surfactant and a Buffer System

The '100 patent is not AbbVie's first patent on D2E7, nor its first patent claiming a pharmaceutical formulation of D2E7. The PTO granted Salfeld, assigned to AbbVie, a 20-year term followed by a 326-day PTE based upon the regulatory review of Humira®, so that Salfeld expired on December 31, 2016, over

[18] *See, e.g., Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2016-01018, Decision Denying Institution of *Inter Partes* Review, Paper No. 10, at 6 (Nov. 7, 2016) (internal quotation marks omitted).

14 years after its December 2002 grant. Ex. 1003; Ex. 1016 at 2. Claim 28 of Salfeld claimed "[a]n isolated human antibody that binds human TNFα and is the antibody D2E7" and claim 29 claimed "[a] pharmaceutical composition comprising" D2E7. Ex. 1003 at 58:26-31. As shown below, Salfeld describes a genus of stable D2E7 formulations that include the formulations claimed by the '100 patent.

Table 2. Salfeld Disclosed a Genus of Formulations That Include the Genus Covered by Claim 1 of the '100 Patent

Claim 1 of the '100 Patent	Salfeld
A ***stable liquid aqueous*** pharmaceutical formulation comprising	"Therapeutic compositions typically must be sterile and ***stable*** under the conditions of manufacture and storage." Ex. 1003 at 21:28-29, claim 29.[19] "[P]harmaceutically acceptable carriers include one or more of ***water, saline, phosphate buffered saline*** . . . ." *Id.* at 21:1-2.
(a) a human IgG1 anti-human Tumor Necrosis Factor alpha ***(TNFα)*** antibody, or an antigen-binding portion thereof, at a concentration of ***45-150 $^{mg}/_{ml}$***	"[A] therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is ***0.1–20 $^{mg}/_{kg}$***, more preferably ***1–10 $^{mg}/_{kg}$***." Ex. 1003 at 23:13-16; claim 29 (***D2E7***). Salfeld described the "pharmaceutical composition" of the invention as one that "typically must be sterile and stable under the conditions of manufacture and storage" and "can be formulated as a solution . . . to ***high drug concentration***." *Id.* at 20:61-62, 21:28-32. Salfeld's use of the term "***high drug concentration***" includes concentrations within ***45-150 $^{mg}/_{ml}$***.[20]

[19] Unless otherwise indicated, bold and italics reflect emphasis added to the original.

[20] A POSA would understand that Salfeld's reference to "high drug concentration" includes, at a minimum, a concentration of 70 $^{mg}/_{ml}$ based on Salfeld's disclosure of a 1-10 $^{mg}/_{kg}$ preferable dose range. Ex. 1003 at 23:16. Based on the average weight of an adult, about 70 kg, the lowest dose in this "prefer[red]" range would be 70 mg. Using a 1 ml injection volume, which is squarely within the range of reasonable volumes that Remmele used for his calculations, *infra* VI.C.2, this would be 70 $^{mg}/_{ml}$. Ex. 1002 at ¶ 47.

Claim 1 of the '100 Patent	Salfeld
(b) a ***polyol***;	"In many cases, it will be preferable to include isotonic agents, for example, sugars, ***polyalcohols*** such as ***mannitol***, ***sorbitol***, or ***sodium chloride*** in the composition." Ex. 1003 at 21:4-6.
(c) a ***polysorbate*** at a concentration of 0.1 to 10 $^{mg}/_{ml}$,	"The proper fluidity of a solution can be maintained, for example, . . . by the use of ***surfactants***." Ex. 1003 at 21:45-49.
and (d) a buffer system having a pH of ***4.5 to 7.0***,	"'[P]harmaceutically acceptable carrier' includes any and all solvents, . . ., and the like that are ***physiologically compatible***." Ex. 1003 at 20:63-67. "Examples of pharmaceutically acceptable carriers include one or more of water, saline, ***phosphate buffered saline*** . . . ." *Id*. at 21:1-2 (emphasis added). The use of "***buffers***" will "enhance the shelf life or effectiveness of the antibody." *Id.* at 21:7-11.
wherein the antibody comprises the light chain variable region and the heavy chain variable region of ***D2E7***.	"[A] pharmaceutical composition comprising [***D2E7***] and a pharmaceutically acceptable carrier." Ex. 1003 at claim 29.

Thus, Salfeld provided the roadmap to the '100 claims by disclosing stable, buffered, subcutaneously-injectable aqueous D2E7 formulations containing a polyol, and a surfactant. Ex. 1003 at 21:4-11, 21:21-23, claim 29.[21] Specifically, Salfeld also provided mannitol as the specific polyol and phosphate buffered saline as the buffer system that would have the claimed pH. *Id.* at 21:2-7.

[21] Although claim 29 of Salfeld does not require the formulation to be stable, it necessarily covered the stable formulations it disclosed.

Any details missing from Salfeld are provided by van de Putte (the concentration of D2E7), Remington and Barrera (the concentration of 12 $^{mg}/_{ml}$ mannitol), Remington (polysorbate 80 as a surfactant), and Lam (the concentration of polysorbate 80).

2. van de Putte (ex. 1004) Disclosed the Claimed Concentrations by Disclosing Effective Doses of 20, 40 and 80 mg D2E7

van de Putte described clinical trials for D2E7 and taught that subcutaneous injection of 20, 40 and 80 mg D2E7 per week resulted in a "statistically significant[]" benefit in treating rheumatoid arthritis. Ex. 1004 at 3. A POSA would understand that those doses correspond to concentrations that overlap with the claimed concentrations. *See infra* VI.C.2.

3. Remington (ex. 1008) Taught the Use of Tonicity Agents To Achieve Isotonicity in Injectable Solutions

Remington taught that "[o]smoticity is of great importance in parenteral injections . . . ." Ex. 1008 at 250. "A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell, when it is in contact with that solution." *Id.* at 246. Non-isotonic solutions "cause tissue irritation, pain on injection, and electrolyte shifts, the effect depending on the degree of deviation from tonicity." *Id*. at 250. Remington taught that when formulating solutions for injection, tonicity can be adjusted using a tonicity agent. Ex. 1008 at 250; Ex. 1002 at ¶ 64.

Remington taught how to formulate parenterals "to avoid the side effects" caused by "abnormal osmoticity," including the use of well-known equations to compute the tonicity of a dilute solution (such as 45-150 $^{mg}/_{ml}$ of D2E7) that would enable a POSA to adjust a formulation's tonicity by modifying the concentration of tonicity agents (like mannitol). Ex. 1008 at 247, 255; Ex. 1002 at ¶ 65.

4. Barrera (ex. 1011) Disclosed a Parenteral D2E7 Formulation with the Claimed 12 $^{mg}/_{ml}$ Mannitol and Components of the Exemplified Buffer

Barrera disclosed a parenteral D2E7 formulation used for RA clinical trials: an intravenous infusion of "25 $^{mg}/_{ml}$ D2E7 mAb in 1.2% mannitol [(12 $^{mg}/_{ml}$)], 0.12% citric acid, 0.02% sodium citrate." Ex. 1011 at 661. The results of the administration of this formulation to over 100 patients demonstrated that it was effective. *Id*. at 661, 667. Although Barrera did not explicitly disclose the pH of its formulation, a POSA would be able to determine based on the buffers used that the pH was between 4.5 and 6.5. Ex. 1061 at 50-51; Ex. 1002 at ¶¶ 94-98.

5. Lam (ex. 1005) Discloses a Stable Aqueous Solution of an Antibody with a Polyol, a Surfactant and an Acetate Buffer with a pH of 4.8 to 5.5

Like Salfeld, Lam disclosed stable, buffered aqueous subcutaneously-injectable high concentration antibody formulations, including for anti-TNF-α. Ex. 1005 at 2:25-29, Abstract, 23:32-38, 9:59-19:46. Lam disclosed an antibody

concentration range "[f]rom about 0.1 $^{mg}/_{mL}$ to about 50 $^{mg}/_{mL}$" and included various preferable subranges. *Id.* at 22:10-17.

Lam taught that the polyol can be "[m]annitol" (*id.* at 6:38-40, 6:50-52) "in the range from 1% to about 15% w/v, preferably in the range from about 2% to about 10% w[/]v" (*id.* at 22:42-43), which corresponds to 10 to 150 $^{mg}/_{ml}$ and 20 to 100 $^{mg}/_{ml}$ (ex. 1002 at ¶ 101) and disclosed various buffers. Ex. 1005 at 22:22-25.

Lam further taught adding a "surfactant . . . . such as polysorbates (e.g. polysorbates 20, 80 etc) . . . in an amount from about 0.001% to about 0.5% . . . and most preferably from about 0.01% to about 0.1%" *Id.* at 22:49-59. Based on a nominal density of water of 1 $^{g}/_{ml}$, a polysorbate concentration range of 0.001% to .5% is 0.01 $^{mg}/_{ml}$ to 5 $^{mg}/_{ml}$ and a range of 0.01% to 0.1% is 0.1 $^{mg}/_{ml}$ to 1 $^{mg}/_{ml}$. Ex. 1002 at ¶ 101. Lam, like Salfeld, explained that "the formulation contains the above-identified agents (i.e. antibody, buffer, polyol and surfactant) . . . ." Ex. 1005 at 22:60-61.

Based on this disclosure, Lam claimed:

> 1. A stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, an acetate buffer from about pH 4.8 to about 5.5, a surfactant and a polyol, wherein the formulation lacks a tonicifying amount of sodium chloride.

Id. at 57:1-6 (claim 1). Lam also claimed "[t]he formulation of claim 1 wherein the antibody concentration in the formulation is from about 0.1 to about 50 $^{mg}/_{mL}$. Ex. 1005 at 57:29-31 (claim 13).

6. Remington (ex. 1008) Disclosed Polysorbate as a Surfactant in Pharmaceutical Formulations

Remington is a principal reference for pharmaceutical formulators. Ex. 1002 at ¶ 58. The '100 patent, Lam and Heavner (ex. 1012) all cited to Remington. Ex. 1012 at 31:6-12; Ex. 1005 at 23:1-4; Ex. 1001 at 15:36-41. Remington's section on "surface-active agents" (surfactants) explained that "[t]he major class of compounds used in pharmaceutical systems are the nonionic surfactants . . . ." Ex. 1008 at 285-86. "The most widely used compounds [among the possible surfactants] are the polyoxyethylene sorbitan fatty acid esters," also known as polysorbates. *Id.* at 287, 1037; Ex. 1002 at ¶ 59. Remington disclosed polysorbate 20 and polysorbate 80 as two common polysorbates.[22] Ex. 1008 at 1037. Lam and Heavner confirm that polysorbate is a leading example of a commonly used surfactant in pharmaceutical formulations. Ex. 1005 at 22:50-52 ("Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbates 20, 80 etc.) . . . ."); Ex. 1012 at 31:1-2.

[22] While polysorbates can autoxidize, which can result in protein aggregation, a POSA would have known that purified polysorbate would not cause oxidation. Ex. 1022 at 14-15; Ex. 1043 at Abstract; Ex. 1002 at ¶ 61.

B. Summary of the Argument

Claim 1 recites [1] "[a] stable [2] liquid aqueous pharmaceutical formulation" of [3] D2E7 at a concentration of "45 to 150 $^{mg}/_{ml}$", [4] a polyol, [5] a polysorbate (surfactant) "at a concentration of 0.1 to 10 $^{mg}/_{ml}$", and [6] a buffer system having a pH of 4.5 to 7.0. *Id*. at 39:2-11. Claim 19, the only other independent claim, is similar except that the D2E7 concentration range is "45-105 $^{mg}/_{ml}$." *Id*. at 40:9-18. Salfeld provided the guideline for these two claims, disclosing every element except the D2E7 concentration and the surfactant type and concentration. *See supra* VI.A.1. The Board agreed that Salfeld disclosed all of these ingredients. *See Amgen, Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2015-01517, Decision Denying Institution of *Inter Partes* Review, Paper No. 9, at 21 (Jan. 14, 2016) ("Salfeld discloses the D2E7 antibody," and "teaches incorporating the antibody or antibody-portions into pharmaceutical compositions, including, *inter alia*, liquid dosage forms" and that they "may comprise buffers and/or surfactants."); Ex. 1003 at 20:60, 21:4-6 (the "pharmaceutical compositions," according to Salfeld, would also preferably "include isotonic agents, for example, . . . mannitol."). There can be no dispute that Salfeld also taught that its formulations could be "subcutaneous[ly-injectable]", contain a "high drug concentration," and should be "stable." Ex. 1003 at 21:26-29, 21:32.

A POSA developing a D2E7 formulation would have started with Salfeld because it is the foundational patent for Humira® and provided a general description of how to formulate D2E7. Ex. 1060 at 5; *see supra* VI.A.1. The only elements of claims 1 and 19 not expressly disclosed by Salfeld are [3] the D2E7 concentration and [5] the type and amount of surfactant. Both of these would be easily ascertained by a POSA based on van de Putte, Remington and Lam. These references provided any information a POSA could need to formulate D2E7 beyond the template provided by Salfeld.

A POSA would be motivated to combine van de Putte's disclosure of effective doses of D2E7 with Salfeld's guidance for formulating D2E7 to choose a D2E7 concentration that would conveniently deliver an amount proven to be effective, resulting in a range of concentrations that encompass the [3] claimed ranges. *See infra* VI.C.1.a.

Next, the POSA must choose the excipients. Salfeld taught using [5] a "surfactant[]." Ex. 1003 at 21:48-49. A POSA would be motivated to consult (a) Lam because it, like Salfeld, disclosed a stable, high concentration antibody formulation with ranges of surfactant (polysorbate) concentrations and (b) Remington because it was an authoritative source for information on surfactants. *See* ex. 1002 at ¶ 130; *infra* VI.C.1.c.

The ’100 patent, in addition to generically claiming D2E7 formulations with various excipients, also requires the formulations to be stable. Ex. 1001 at 39:2. A POSA having formulated D2E7 based on Salfeld, van de Putte, Barrera, Remington and Lam, and having consulted the patent literature for stable high concentration antibody formulations, would have reasonably expected these D2E7 formulations to be stable under the Board’s previous construction of “stable” as a formulation that retains stability “upon storage and use” without imposing any specific time period. *See supra* V.C; *infra* VI.C.3. Furthermore, according to the ’100 patent itself, a buffered D2E7 formulation with standard excipients (e.g. mannitol and polysorbate) would be expected to exhibit 18-month stability as required by claims 4 and 22. Ex. 1001 at 3:15-19.

The dependent claims of the ’100 patent further specify [3] narrower concentration ranges of D2E7, [4] particular polyols or polyol concentrations, [5] particular polysorbates or polysorbate concentrations, [6] narrower pH ranges and an 18-month shelf life and suitability for subcutaneous injection. *Id.* at 39:12-40:43.

A POSA would choose a D2E7 concentration based on the effective dosages disclosed in van de Putte and arrive at a range that encompasses the claimed [3] D2E7 subranges. *See infra* VI.C.1.a. A POSA would also know that subcutaneously-injected formulations should be isotonic and that isotonicity can be

achieved by using the appropriate amounts of various tonicity agents including, sodium chloride and mannitol. *See supra* VI.A.3. Salfeld itself taught using an "isotonic agent[] . . . such as mannitol" and a saline solution. Ex. 1003 at 21:4-7. A POSA would understand this could result in a range of mannitol concentrations including the claimed [4] mannitol range. A POSA would further be motivated to consult Barrera as the only published D2E7 formulation used in clinical trials. Its disclosure of 12 $^{mg}/_{ml}$ mannitol would confirm to a POSA that such an amount is both compatible with D2E7. A POSA would also be motivated to use the claimed [5] polysorbate and polysorbate concentrations because their use and amounts were taught by the leading text on formulation (Remington) and a patent (Lam) issued to a leading antibody formulator (Genentech). As for the claimed [6] pH ranges in the dependent claims, these are encompassed by the physiological range taught by Salfeld and the narrower range a POSA would infer from AbbVie's own D2E7 formulation disclosed in Barrera.

Accordingly, the combination of Salfeld, van de Putte, Barrera, Remington and Lam provide all elements of all of the claims, the motivation to combine them, and a reasonable expectation of success in making a stable aqueous D2E7 formulation based upon the template of Salfeld, as further described *infra* VI.C.1. and, on an element-by-element basis, *infra* VI.C.5.

C. Salfeld Combined with van de Putte, Barrera, Remington and Lam Render Obvious Claims 1-29

1. The Prior Art Provided a POSA with a Motivation To Combine Salfeld with van de Putte, Remington, Barrera and Lam To Obtain the Stable, High Concentration D2E7 Aqueous Solution for Subcutaneous Injection Comprising a Polyol, Polysorbate and a Buffer with a pH of 4-8 Required by All Claims

a. D2E7 Concentration

A POSA looking to choose a D2E7 concentration would know exactly what to do based on AbbVie's own prior art. Salfeld disclosed formulations with a "high [D2E7] concentration," preferably containing "1–10 $^{mg}/_{kg}$", a range which the prior art showed to be safe for humans. Ex. 1003 at 21:32, 23:13-16; Ex. 1011 at 661. A POSA would turn to van de Putte as the definitive source for determining an efficacious amount of D2E7 because it reported AbbVie's own D2E7 clinical trial data. Ex. 1002 at ¶¶ 153-54. van de Putte taught that 20, 40 and 80 mg of D2E7 were effective doses to treat RA in a subcutaneously-injectable formulation.[23] *See supra* VI.A.2; ex. 1004 at 3. These doses correspond to a concentration of 6 to160 $^{mg}/_{ml}$ based on reasonable assumptions of injection volume and number of injections, and at most correspond to a range of 2.5 to 400 $^{mg}/_{ml}$

[23] A POSA would be well-motivated to choose subcutaneous injection based on (a) van de Putte's reported success with "subcutaneous (s.c.) self injection" of D2E7; (b) Salfeld's statement that D2E7 could be formulated subcutaneously; and (c) the patient convenience provided by self-injection when treating long-term diseases like RA.

making less reasonable assumptions. Ex. 1002 at ¶ 111; *see infra* VI.C.2. Both of these ranges encompass the 45-150 $^{mg}/_{ml}$ required by claim 1 and the various subranges or amounts required by the remaining claims, thereby rendering them obvious.[24] Accordingly, a POSA would be motivated to combine Salfeld and van de Putte to arrive at a concentration that satisfies all claimed D2E7 concentrations and concentration ranges.

b. Polyol and Polyol Concentration

A POSA would need to look no further than Salfeld to know that a tonicity agent like mannitol (a polyol) should be included in the formulation. Salfeld explained that various polyols should be used as tonicity agents: "[i]n many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition." Ex. 1003 at 21:4-7; Ex. 1002 at ¶ 51. A POSA would be motivated to look to Remington's teaching of tonicity agents to understand their purpose and how much to use. Ex.

[24] As explained below, the prior art taught towards, not away from, the claimed invention. The '100 patent does not provide any evidence that 50 $^{mg}/_{ml}$ D2E7 yields an unexpected result and there are no secondary considerations that could rebut this prima facie showing of obviousness. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) ("[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations."); MPEP § 2144.05(I).

1002 at ¶¶ 64-65. A POSA would understand that the amount of any particular tonicity agent can be varied by varying the amount of other tonicity agents.

For example, lowering the amount of one tonicity agent (e.g., mannitol) could be balanced by increasing the amount of another (e.g., sodium chloride). *Id.* at ¶ 65; Ex. 1008 at 250 (referring to the use of sodium chloride); Ex. 1003 at 21:4-7 (referring to mannitol and other tonicity agents). Salfeld disclosed using "saline" (i.e. sodium chloride and water) as a "pharmaceutically acceptable carrier[]" and mannitol. Ex. 1003 at 21:1-2, 21:4-7. A POSA would understand that the contribution of sodium chloride and any excipients to overall tonicity would have to be taken into account when determining the amount of mannitol that should be used. Ex. 1002 at ¶ 65.

Based on this information, a POSA would know that 7.5-15 $^{mg}/_{ml}$ mannitol, such as required by claim 6, was a common amount to use as a tonicity agent in a formulation and was within the range of amounts that could be used in making routine adjustments to excipients contributing to formulation tonicity. *See, e.g.*, ex. 1015 at 2:21-25, 3:56-61; tbl. 3 (disclosing that "aqueous formulation [of the invention could include] . . . human growth hormone, a buffer, a non-ionic surfactant, and optionally, a neutral salt, mannitol, and a preservative" with the

"preferred amount of mannitol [being] about 5 $^{mg}/_{ml}$ to about 50 $^{mg}/_{ml}$");[25] Ex. 1002 at ¶ 66. In addition, a POSA would also consider Barrera's use of "1.2% mannitol" in its D2E7 formulation and be encouraged that this amount was compatible with D2E7. *See* ex. 1011 at 661; Ex. 1002 at ¶ 115; *supra* VI.A.1, VI.A.4; *see also* MPEP § 2144.05(II).

Accordingly, a POSA would be motivated to combine Salfeld with Remington and Barrera to arrive at a range of mannitol concentrations that encompasses all claimed polyols or mannitol concentration ranges.

c. Polysorbate and Polysorbate Concentration

Salfeld taught the use of surfactants in formulating D2E7. In choosing a particular surfactant, a POSA would be motivated to look to Remington as an undisputed leading formulation reference. *See supra* VI.A.6. The POSA would immediately recognize that there are a limited number of commonly used surfactants, and that polysorbate 20 and 80 are two of the most common. *See id*. A POSA would also be motivated to look to similar antibody formulations by industry leaders, such as Genentech's Lam formulation, to identify typical amounts of polysorbate that have been used. Ex. 1002 at ¶ 101; *see supra* VI.A.5 (Lam disclosed using 0.1 to 1 $^{mg}/_{ml}$). The fact that Lam also taught that the use of

[25] All of the examples that contain mannitol use 50 mM mannitol which corresponds to 9.1 $^{mg}/_{ml}$ based on the molecular weight of mannitol of 182.17 $^{g}/_{mol}$. Ex. 1023 at 294; Ex. 1002 at ¶ 66 n.3.

polysorbate improves stability by "reduc[ing] aggregation of the formulated antibody" would further motivate a POSA to follow Lam's teaching to use polysorbate. Ex. 1005 at 22:52-55; Ex. 1002 at ¶ 107 (reducing aggregation promotes formulation stability); *see also* MPEP § 2144.05(II).

Accordingly, a POSA would be motivated to combine Salfeld, Remington and Lam to arrive at a surfactant (polysorbate 80) and a polysorbate concentration that satisfies all claimed D2E7 concentrations and concentration ranges.

d. Buffer System and Requisite pH

Salfeld's disclosure of a D2E7 formulations taught both the importance of buffers and the need to use them to achieve an appropriate pH range. The '100 patent claims' requirement of a "buffer system having a pH of 4.5 to 7.0" (ex. 1001 at 39:9) fails to distinguish it over Salfeld because Salfeld stated that the excipients (including the buffer) must be "physiologically compatible" (ex. 1003 at 20:63-67), therefore the buffer should yield a pH of 4 to 9. Ex. 1002 at ¶ 90. The Board previously reached a similar conclusion. *Amgen, Inc.*, Case No. IPR2015-01517 at 23-24 (finding Amgen's argument that "Salfeld's 'physiologically compatible' carrier likewise would have indicated a pH between 4 and 8 to one of ordinary skill in the art . . . persuasive."). Therefore Salfeld disclosed using a buffer and a pH range that fully embraces the ranges claimed in the '100 patent. Moreover, a POSA formulating D2E7 would be motivated to consult other published clinical

formulations of D2E7 when choosing buffers, such as Barrera, which (a) disclosed a formulation using a buffer of "0.12% citric acid [and] 0.02% sodium citrate" that a POSA would know yields a pH of 4.5 to 6.5 and (b) confirmed that this formulation contains excipients that are compatible with D2E7. Ex. 1011 at 661, 667; Ex. 1002 at ¶¶ 94-98; *supra* VI.A.4. Because the claimed ranges fall within or overlap with the known pH ranges provided by the buffers used in AbbVie's own D2E7 disclosures, the prior art renders the claimed ranges obvious. *See* MPEP § 2144.05(I).

2. 20, 40 and 80 mg D2E7 Correspond to a Concentration of 6 to 160 $^{mg}/_{ml}$ or at most 2.5 to 400 $^{mg}/_{ml}$ (ex. 1002)

a. In Prior Proceedings, Amgen and AbbVie Neither Comprehensively Reviewed the Prior Art nor Properly Accounted for Injection Volumes and Number of Injections

Amgen Inc. ("Amgen") filed the '157 IPR and the '158 IPR (exs. 1046, 1047) and supporting declarations (*see, e.g.*, exs. 1045, 1051) by Dr. Theodore W. Randolph. Randolph calculated 50-90 $^{mg}/_{ml}$ as the range of D2E7 concentrations that could be derived by a POSA with a 1 $^{mg}/_{kg}$ dose based on an assumed average adult body mass of 70 kg and a volume range for subcutaneous injection of 0.8 ml to 1.5 ml.[26] Exs. 1045 at ¶ 52(a)-(d), 1051 at ¶ 52(a)-(d); Ex. 1002 at ¶ 148.

[26] The 1 $^{mg}/_{kg}$ is presumably based on Salfeld's disclosed preferred dosage range of 1-10 $^{mg}/_{kg}$. Ex. 1003 at 23:13-16.

AbbVie argued that Randolph failed to account for the possibility of a "multi-dose therapy" and that the correct calculation yields a range "from 4.6 to 4,666 $^{mg}/_{ml.}$" Ex. 1048 at 48-49. Remmele's analysis demonstrates that AbbVie's calculation is based on both faulty assumptions and a failure to consider prior art D2E7 clinical data. Ex. 1002 at ¶ 153.

Remmele inferred from AbbVie's response (which lacked explanation) that AbbVie performed the following calculations using the following assumptions:

- 0.1 $^{mg}/_{kg}$ (dose) x 70 kg (patient) x $^{1}/_{1.5ml}$ (injection volume) = 4.6 $^{mg}/_{ml}$
- 20 $^{mg}/_{kg}$ (dose) x 70 kg (patient) x $^{1}/_{0.3ml}$ (injection volume) = 4,666.6 $^{mg}/_{ml}$

Id. at ¶¶ 150-52.

AbbVie based the dosing range of 0.1 to 20 $^{mg}/_{kg}$ solely on Salfeld. Ex. 1003 at 23:13-16. A POSA, however, would have known about and relied upon the D2E7 clinical data described in van de Putte regarding the effectiveness of 20, 40 and 80 mg total body doses. Ex. 1002 at ¶ 154. Instead AbbVie used the 20 $^{mg}/_{kg}$ dose disclosed in Salfeld to yield a 1400 mg dose for an average 70 kg patient. *Id.* at ¶ 151 n.15. This is nearly 20 times the upper 80 mg total body dose described by AbbVie in its own published prior art clinical trials. Ex. 1004 at 3 (20, 40 and 80 mg); *see also* Ex. 1006 at 4 ("1 $^{mg}/_{kg}$ D2E7 sc"); *see also* ex. 1011 at 661 ("The clinical effect [of D2E7 administration] is maximal at a dose of 1 $^{mg}/_{kg}$ and shows a plateau in the dose-response curve thereafter."). Furthermore, it makes little sense,

as AbbVie did, to put the largest dose (20 $^{mg}/_{kg}$) in the smallest injection volume (0.3 ml) and the smallest dose (0.1 $^{mg}/_{kg}$) in the largest injection volume (1.5 ml). Nevertheless, Remmele used the same methodology to demonstrate that even doing so, the '100 patent's claimed D2E7 concentration ranges fall squarely within the prior art teaching. Ex. 1002 at Section VI.E.

The Board rejected Amgen's calculations because of their underlying assumptions, the lack of explanation, and the potential for "multi-dose therapy."[27] *Amgen, Inc.*, Case No. IPR2015-01517 at 23. Remmele, as explained *infra* VI.C.2.b, has made reasonable assumptions, has accounted for the possibility of multi-dose therapies and has explained his calculations in detail.

As demonstrated below, using the available D2E7 data and accounting for the possibility of multi-dose therapy results in a range of concentrations that is an order of magnitude less than the range AbbVie posited in the prior proceedings, and includes the claimed concentrations.

b. Remmele Properly Accounted for Injection Volume and Number of Injections

Remmele calculated the range of concentrations that would result from van de Putte's 20, 40 and 80 mg D2E7 doses assuming a range of subcutaneous

[27] The term "multi-dose," as used in the prior proceedings, referred to the use of multiple injections to deliver a desired dose because of an inability to develop a formulation that would permit administration of therapeutic antibody with a single injection.

injection volumes and number of injections. Ex. 1002 at Section VI.E. He conducted a survey of prior art subcutaneous drugs and determined that the range of injection volumes was 0.2 to 1.6 ml. *Id.* at ¶ 69, tbl. 1. Most injection regimens require only a single injection to deliver the desired therapeutic dose, although there are examples in which up to 2 injections have been used to deliver a therapeutic dose.[28] *Id.* at ¶ 70.

To obtain the lowest concentration based on these parameters, Remmele used the lowest dose disclosed by van de Putte (20 mg) (ex. 1004 at 3), the largest reasonable injection volume (1.6 ml) and the highest reasonable number of injections (2), resulting in a concentration of approximately 6 $^{mg}/_{ml}$.[29] *Id.* at ¶ 82. To obtain the highest concentration Remmele used the highest dose disclosed by van de Putte (80 mg) (ex. 1004 at 3), the smallest reasonable injection volume (0.5

[28] In the '166 IPR AbbVie argued that Matteson (ex. 1013 hereto and Exhibit 2047 in the '166 IPR) disclosed that "patients administered ten daily s.c. injections per dose of campath-1." Ex. 1049 at 47. This is clearly incorrect. Matteson explained that the "10 daily injections of C1H" were spread "over a 12-day period." Ex. 1013 at Abstract. Matteson further explained: "C1H was administered by subcutaneous injection into either the thigh or the abdomen on days 1–5 and 8–12, for a total of 10 injections. The 30.0 mg/day dose was administered as 2 separate subcutaneous injections because of volume considerations." *Id.* at 1188.

[29] Remmele rounded 6.25 to 6.0 in his declaration. Ex. 1002 at ¶ 84 n.10.

ml) and the smallest number of injections (1), resulting in a concentration of 160 $^{mg}/_{ml}$ and an overall concentration range of 6 to 160 $^{mg}/_{ml}$.[30] *Id.* at ¶¶ 83-84.

In addition to calculating what he concludes is the most reasonable range of concentrations that can be derived from van de Putte, Remmele calculated the concentration range of D2E7 that could be derived by using a more extreme range of injection volumes (0.2 to 2 ml) and a more extreme number of injections (up to 4) to deliver a desired therapeutic dose resulting in a concentration range of 2.5 to 400 $^{mg}/_{ml}$.[31] Ex. 1002 at ¶¶ 85-87. The claimed D2E7 concentrations are thus squarely within the ranges that a POSA would reasonably assume based on van de Putte.

3. A POSA Would Have a Reasonable Expectation of Success in Making a Stable, High Concentration, Aqueous, Subcutaneously Injectable Solution According to Salfeld

Every claim in the '100 patent, except 4 and 22, merely requires some degree of stability upon storage. *See supra* V.C. Salfeld gave a POSA a

[30] The range would be narrower if Remmele made the more reasonable assumption that the higher dose would be put in the larger volume instead of the smaller volume.

[31] The upper limit of this range exceeds the expected practical limit of 150 $^{mg}/_{ml}$ for antibody concentrations in 2002 (ex. 1002 at ¶ 87 n.11) and was only achieved by using an atypical injection volume of 0.2 ml. A POSA, knowing the 150 $^{mg}/_{ml}$ upper limit for antibody concentrations would not have used an injection volume below 0.5 ml for this very reason. This confirms that Remmele's use of a 0.5 ml as the smallest injection volume was reasonable.

reasonable expectation of success that such a stable high concentration subcutaneously-injectable formulation could be made using the combination of a D2E7, a polyol (such as mannitol), a surfactant (such as polysorbate) and a buffer yielding the required pH range. Salfeld provided the reasonable expectation of success by disclosing this combination of ingredients (*see supra* VI.A.1), and explaining that "[t]herapeutic compositions typically must be sterile and stable," so that they "can be formulated as a solution" and that such "[s]terile injectable solutions can be prepared by incorporating the active compound (i.e., antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above . . . ." Ex. 1003 at 21:28-36.

Furthermore, Salfeld's teaching of stability is entitled to a legal presumption that it is correct. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (a patent is presumed to be "enabled" for "both the claimed and unclaimed" pharmaceutical compositions it discloses); *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012) (same). AbbVie itself benefited from the presumption of validity for the life of the Salfeld patent. The '100 patent rests on nothing more than Salfeld's teaching of stability because the '100 patent fails to provide stability data for any formulations beyond the single example tested using a single freeze/thaw testing protocol. *See supra* V.A.

A POSA's reasonable expectation that a "high drug concentration" subcutaneously-injectable formulation made in accordance with Salfeld's disclosure (ex. 1003 at 21:28-32) would be stable is bolstered by numerous prior art examples of stable, injectable, high concentration antibody and other protein formulations:

- Heavner taught "stable formulations" comprising 0.1 to 100 $^{mg}/_{ml}$ of an anti-TNF antibody in "[a]queous or oily suspensions for injection." Ex. 1012 at 31:18-19, 44:42-51, 42:59-64; Ex. 1002 at ¶ 37.

- Lam taught "[a] stable aqueous pharmaceutical formulation," with an antibody concentration "[f]rom about 0.1 $^{mg}/_{mL}$ to about 50 $^{mg}/_{mL}$." Ex. 1005 at Abstract, 22:13-14; Ex. 1002 at ¶ 38.

- WO 00/56772 taught "stable" liquid compositions containing "0.1-250 $^{mg}/_{ml}$ [IL-12] antibody." Ex. 1014 at 5:23, 107:9-10, 107:18-20, 108:13-15, 108:18-21; Ex. 1002 at ¶ 39.

- U.S. Patent No. 6,267,958 ("Andya"): disclosed a liquid antibody formulation comprising 25 $^{mg}/_{ml}$ rhuMAb reconstituted to 100 $^{mg}/_{ml}$ that was stable after reconstitution "for up to 90 days at 5° C. and 30 days at 25° C." Ex. 1020 at 25:15-17, tbl. 4; Ex. 1002 at ¶ 40.[32]

- WO 02/12502 taught "stable formulations" with an anti-TNF antibody concentration of "0.1 to 100 $^{mg}/_{ml}$." Ex. 1017 at 40:13, 56:30-35. "Preserved formulations contain at least one known

[32] In the '158 IPR, AbbVie argued that lyophilization was necessary to achieve stable high protein concentration formulations. Ex. 1048 at 19-20. This is not the case because Lam and WO 00/56772 disclosed stable non-lyophilized protein formulations. *See* exs. 1005, 1014. Additionally, the '100 patent covers reconstituted formulations, such as the formulation disclosed by Andya, which can be reconstituted and stored for up to 90 days. Ex. 1020 at 25:15-17, tbl. 4.

preservative . . . in an aqueous diluent. *Id*. at 40:17-22; Ex. 1002 at ¶ 41.

- WO/30463: disclosed "stable formulation[s] . . . comprising a protein in an amount of at least about 80 $^{mg}/_{ml}$." Ex. 1018 at 5: 17-19. The formulations can be "lyophilized and then reconstituted to produce the reduced-viscosity stable liquid formulations of the invention." *Id.* at 35:17-19; Ex. 1002 at ¶ 42.

These patents were issued to Centocor, Genentech, and BASF Aktiengesellschaft—companies that pioneered the development of liquid antibody formulations. Ex. 1002 at ¶¶ 37-44. Collectively, they disclosed stable high concentration liquid formulations for a variety of antibodies including anti-TNF antibodies, IL-12 and, in the case of Lam, for any antibody that was not previously lyophilized. A POSA would consider their success in general, and their teachings in particular, in forming an expectation of success that, as Salfeld explicitly taught, a "stable," "high concentration" D2E7 formulation could be made. Ex. 1002 at ¶¶ 43-44.

A POSA would have reasonably expected a D2E7 formulation based on Salfeld, van de Putte, Barrera, Remington and Lam to possess at least the minimum stability required by all claims except claims 4 and 22 based on Salfeld and these other patented stable high concentration antibody formulations.

Claims 4 and 22 in the '100 patent require an "18 month" "shelf life." Ex. 1001 at claims 4 and 22. The '100 patent, however, does not disclose which

excipients or what amounts lead to an 18-month shelf life, and does not provide any data beyond "freeze/thaw" testing of a single formulation, which did not measure stability for any period of time, let alone 18 months as claimed. The '100 patent's only disclosure of (and basis for) 18-month stability is for antibody formulations in buffered solutions having a pH between 4 and 8. *Id*. at 3:15-23. As shown above, the pH ranges recited in '100 patent claims are obvious, rendering claims 4 and 22 obvious.

Thus, the '100 patent presumes that any D2E7 formulation within its broad claims will have the stability required by all of the claims, including claims 4 and 22. A POSA, having formulated D2E7 based on Salfeld, van de Putte, Barrera, Remington and Lam would have a formulation within the scope of claims l and 19, from which 4 and 22 depend, including within the pH range that provides the only basis for 18-month stability in the '100 patent. Even if the POSA would not have known in advance that these formulations would necessarily possess an 18-month shelf life, the fact that these obvious formulations necessarily have, according to the '100 patent, such stability, renders all of the claims obvious.[33] *See Par Pharm., Inc. v. Twi Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) ("We have

[33] In an IPR proceeding the Petitioner cannot challenge validity based on noncompliance with §112 and the Board must presume the patent satisfies this statutory requirement. Sandoz reserves its right to raise such challenges in other proceedings.

recognized that inherency may supply a missing claim limitation in an obviousness analysis.")

4. AbbVie Cannot Rebut Prima Facie Obviousness over Salfeld in Combination with van de Putte, Barrera, Remington and Lam

As explained *supra* VI.C.2, the prior art disclosed stable, subcutaneously-injectable formulations having a range of D2E7 concentrations (2.5 to 400 $^{mg}/_{ml}$) that embrace the recited concentration ranges of claims 1 (45-150 $^{mg}/_{ml}$) and 19 (45-105 $^{mg}/_{ml}$) and therefore renders the claims prima facie obvious. AbbVie cannot meet its "burden of production . . . to come forward with evidence" rebutting Sandoz's strong showing of prima facie obviousness. *See Galderma Labs., L.P.*, 737 F.3d at 738.

To the extent that AbbVie attempts to present new secondary considerations evidence which Sandoz will have no opportunity to address prior to the Board's decision on institution of trial, it would be premature to deny institution of Sandoz's petition on such an incomplete record. *See, e.g., Apotex Inc. v. OSI Pharm., Inc.*, IPR2016-01284, 2017 WL 379496, at *12 (P.T.A.B. Jan. 9, 2017) (We "determine that it would be premature at this stage of the proceeding to deny institution based on the secondary considerations evidence."); *Eli Lilly & Co. v. Trs. of Univ. of Pa*, IPR2016-00458, 2016 WL 5103461 (P.T.A.B. July 14, 2016)

(same); *see also Luye Pharma Grp. Ltd. v. Alkermes Pharma Ireland Ltd.*, IPR2016-01096, 2016 WL 7985470, at *15 (P.T.A.B. Nov. 30, 2016).

a. The Prior Art Did Not Teach Away from the Claimed Invention

In prior IPR proceedings, AbbVie argued that the prior art "*taught away* from the preparation of stable liquid antibody formulations." Ex. 1050 at 2 (emphasis in original). AbbVie's arguments are based on a misreading of the prior art.

(1) The literature reviews relied upon by AbbVie ignored the art that taught stable high concentration formulations

AbbVie relied on various references, principally Wang and Carpenter & Manning, to argue that formulating antibodies in stable solutions was inherently unpredictable. *See generally* ex. 1050; *see also* ex. 1021; ex. 1022. AbbVie however, ignored the standard for stability in the '100 patent, which only requires the formulation to retain some biological activity after storage for an indeterminate amount of time.

Those literature reviews, moreover, did not address this minimal level of stability, or the teachings of stable high antibody concentration formulations in Salfeld, Lam, Heavner, WO 00/56772, WO 02/12502, WO 02/30463 and Andya, despite the fact that these patents and published patent applications came from leading antibody formulators. Ex. 1002 at ¶¶ 37-44. AbbVie also ignored that its

own patent publication, WO 00/56772, taught "stable" liquid compositions containing "0.1-250 $^{mg}/_{ml}$ [IL-12] antibody." Ex. 1014 at 5:23, 107:9-10, 107:18-20, 108:13-15, 108:18-21; Ex. 1002 at ¶ 39.

A POSA would not disregard the teachings of the body of patent literature from industry leaders who were creating new antibody formulations in favor of literature reviews, and would reasonably expect to achieve at least the minimal degree of stability required by the '100 patent when applying those teachings to new formulations. The body of patent literature provides a reasonable expectation of stability of at least the minimum level required by every claim in the '100 patent except claims 4 and 22, and for those claims, the '100 patent associates 18-month stability with an obvious formulation pH range of 4-8. Ex. 1002 at ¶¶ 43-44.[34]

Even if some references suggested that developing a formulation with sufficient stability for a commercial product would be challenging, that is not a teaching away, as that is not the standard required by the claims of the '100 patent. The stability required by the '100 patent is only a "formulation . . . in which the antibody therein essentially retains its physical stability and/or chemical stability

[34] Even if the prior art does not provide the POSA with a reasonable expectation that a D2E7 formulation as taught by Salfeld combined with van de Putte, Barrera, Remington and Lam would exhibit the 18-month stability required by claims 4 and 18, those claims are still obvious because according to the '100 patent itself, such D2E7 formulations will necessarily have the required stability. *See Par Pharm.*, 773 F.3d at 1194–95.

and/or biological activity upon storage." Ex. 1001 at 7:16-18; *see also Amgen, Inc.*, Case No. IPR2015-01517 at 8 ("[O]ne of skill in the art 'would have understood that a formulation would need to be stable for storage and use.'"); *Amgen, Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2015-01514, Decision Denying Institution of *Inter Partes* Review, at 7, Paper No. 9 (Jan. 14, 2015) (same); *Coherus BioSciences Inc.*, Case No. IPR2016-01018, at 6 ("[W]e construe 'stable' to mean 'a formulation in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage and use as a pharmaceutical formulation."). With the exception of claims 4 and 22, no specific length of time is required. A POSA would not disregard the teachings of prior art patents, and AbbVie's own prior art D2E7 patents and publications, from which a POSA would expect to achieve ***some*** level of stability by applying those teachings to the D2E7 formulations encompassed within AbbVie's own disclosures.[35]

[35] In its Patent Owner's Responses in the '157 and '158 IPRs, AbbVie cited to the prosecution history of U.S. Patent No. 7,648,702, on which Remmele is a co-inventor, as apparent support for its position that the behavior of antibodies in solution is unpredictable. Ex. 1048 at 25-26; Ex. 1050 at 25-26. As Remmele explains, however, the '702 patent is directed to the discovery that a particular excipient is capable of stabilizing a particular protein in solution and refers to long-term storage. Ex. 1002 at ¶¶ 176-87. Remmele explains that, while it may be unpredictable that any particular excipient can stabilize any particular protein, Salfeld discloses a genus of stable aqueous antibody formulations which encompass the claimed formulations of the '100 patent, providing the skilled

Accordingly, AbbVie's prior art literature reviews do not teach away from the claimed invention.

(2) Lam does not teach away

AbbVie argued that Lam "expressly advised that a lower concentration might be needed to reduce protein aggregation." Ex. 1050 at 4, 36 (citing ex. 1005 at 22:13-17, 42:64-65). Lam never stated that lower concentrations must be used to achieve ***some*** level of stability. It merely explained that decreasing pH reduces aggregation, but that "[f]urther reduction in aggregation rate may require a decrease in the protein concentration." Ex. 1005 at 42:59-67. In addition, Lam demonstrated that its 40 $^{mg}/_{ml}$ "high concentration" formulation was "stable." Ex. 1005 at 46:23-32.

(3) The fact that commercially available liquid antibody formulations have low concentrations does not teach away

AbbVie argued in the '157 IPR that "all commercially available liquid antibody formulations in 2002 were exclusively *low concentration* formulations." Ex. 1050 at 18. AbbVie, however, failed to identify any references stating that these antibody formulations were formulated at low concentrations because high concentration formulations were challenging to make, or that one could not obtain a minimum level of stability. Without such evidence, there can be no teaching

---

person with a reasonable expectation of success with respect to making the claimed D2E7 formulations of the '100 patent. Ex. 1002 at ¶¶ 183, 187.

away. Furthermore, commercially acceptable stability is not the standard required by the '100 patent.

Even if commercial stability was the standard, Remmele explains that there is little reason for a drug manufacturer to develop a high concentration subcutaneously injectable formulation for patients who will undergo a short course of treatment under the direct supervision of medical professionals at the time of drug administration. The primary benefit for subcutaneously injectable formulations is that the patient can self-administer at home. Ex. 1002 at ¶ 160. As shown in Table 3 below, except Remicade®, nearly every commercial antibody formulation AbbVie identified was intended for a short course of treatment and required contemporaneous monitoring or blood tests. *Id.* at ¶¶ 161-71. Subcutaneous injection of these drugs would not obviate the need for travel to a medical care facility.

Table 3. Antibody Formulation Drugs from 1985-August 16, 2002

Drug	**Route of Admin.**	**Indication**	**Course of Treatment**	**Administration requires monitoring or blood tests?**
Orthoclone OKT3 (muromonab-CD3)	Intravenous (< 1 min. bolus)	Acute allograft rejection after renal, heart, and liver transplants	10-14 days	✓
ReoPro® (Abciximab	Intravenous	Adjunct to percutaneous	Bolus administered	✓

Drug	Route of Admin.	Indication	Course of Treatment	Administration requires monitoring or blood tests?
)		coronary intervention for prevention of cardiac ischemic complications	IO-60 minutes before procedure, followed by infusion for 12 hours	
WinRho SDF® (Rh_o(D) Immune Globulin)	Intravenous	Chronic or acute immune thrombocytopenia purpura (ITP)	Individualized dosing	✓
ProstaScint® (Capromab Pendetide)	Intravenous (5 mins.)	Diagnostic imaging agent	1	✓
Rituxan® (Rituximab)	Intravenous	B-cell Non-Hodgkin's Lymphoma	4 doses	✓
Zenapax® (Daclizumab)	Intravenous (15 min. infusion)	Prophylaxis of acute organ rejection after renal transplant	5 doses	✓
Simulect® (Basiliximab)	Intravenous (20-30 min infusion)	Prophylaxis of acute organ rejection for renal transplantation	2 doses	✓

Drug	Route of Admin.	Indication	Course of Treatment	Administration requires monitoring or blood tests?
Synagis®[36] (Palivizumab)	Intramuscular	For use in pediatric patients - prevention of serious lower respiratory tract disease by respiratory syncytial virus (RSV)	Administer prior to RSV season, repeated monthly throughout season	
Remicade® (Infliximab)	Intravenous (2 hr infusion)	Rheumatoid arthritis ("RA") and Crohn's Disease	RA: 3-dose administration within the first 6 weeks, followed by dosing every 8 weeks Crohn's: 3-dose induction treatment, followed by maintenance doses every 8 weeks	
Herceptin® (Trastuzumab)	Intravenous (30 – 90 min. infusion)	Breast Cancer where tumors overexpress HER2	not specified	✓

[36] As noted in Table 3, Synagis is indicated for pediatric patients, which results in different dosing and administration requirements from drugs used to treat adults. Ex. 1030 at 2.

Drug	Route of Admin.	Indication	Course of Treatment	Administration requires monitoring or blood tests?
Campath® (Alemtuzumab)	Intravenous (2 hr infusion)	B-cell chronic lymphocytic leukemia	Dose escalation for 3-7 days followed by maintenance dosing three times a week for 12 weeks	✓
Zevalin™ (Ibritumomab Tiuxetan)	Intravenous (10 min. push)	B-cell non-Hodgkin's lymphoma	2 doses administered within 7-9 days	✓

Nearly every drug listed above, or the diseases and medical situations for which they are indicated, raise safety concerns that make self-administration by the patient through subcutaneous injection unacceptable. Orthoclone OKT® patients must be "closely monitored" in a facility capable of "cardiopulmonary resuscitation." Ex. 1026 at 2303; Ex. 1002 at ¶ 162. "Campath can result in serious infusion reactions" therefore "[p]atients should be carefully monitored during infusions." Ex. 1027 at 992; Ex. 1002 at ¶ 163. Simulect® patients undergo kidney transplant and "should be managed in [appropriate medical] facilities." Ex. 1025 at 2218; Ex. 1002 at ¶ 164. Zenapax® patients also receive a kidney transplant and must be administered Zenapax® by specially trained personnel in an appropriate facility. Ex. 1026 at 2813; Ex. 1002 at ¶ 165. Zevalin® is a combination immunotherapy and radiotherapy for non-Hodgkin's lymphoma

requiring administration by medical professionals specifically trained "in the safe use and handling of radionuclides." Ex. 1029 at 2, 11; Ex. 1002 at ¶ 166. Administration of Herceptin® to treat breast cancer, requires observing patients "for fever and chills or other infusion-associated symptoms." Ex. 1028 at 1302-03; Ex. 1002 at ¶ 167. Administration of Rituxan® to treat non-Hodgkin's lymphoma, requires monitoring certain classes of patients – "during and after subsequent infusions of RITUXAN." Ex. 1026 at 1314; Ex. 1002 at ¶ 168. Administration of ReoPro® requires performing blood tests prior to the infusion. Ex. 1024 at 1773; Ex. 1002 at ¶ 169. Administration of WinRho® requires "monitor[ing] to determine clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels." Ex. 1052 at 2297-99; Ex. 1002 at ¶ 170.

Furthermore, because, as Table 3 shows, nearly every commercial antibody drug is only administered over a relatively short period of time and with a limited number of doses, patient convenience is much less likely to be a driver for developing a formulation.

The fact that the intravenous antibody formulations in Table 3 were low concentration does not indicate that (a) they could not have been formulated at higher concentrations, (b) it would be challenging to do so, or (c) a POSA would not be able to achieve the low level of stability required by every claim of the '100 patent except claims 4 and 22.

Once a determination is made that a drug should be administered intravenously, there is no need to develop a high concentration formulation because intravenous routes of administration, unlike routes of subcutaneous administration, do not impose significant volume constraints upon formulators. Ex. 1002 at ¶ 158.

Finally, as for Remicade®, there is no evidence that Centocor chose not to formulate infliximab for subcutaneous injection because developing a stable high concentration antibody formulation was too challenging. And even if that was the reason, it does not teach away from the '100 patent claims because the doses needed for infliximab (210-700 mg) are much greater than those for D2E7 (20-80 mg). *Id.* at ¶ 175. As Remmele explains, infliximab doses of 210-700 mg would require up to 14 injections if they were formulated at 50 $^{mg}/_{ml}$ for subcutaneous administration. *Id.* at ¶¶ 174-75. Therefore, a decision by Centocor not to formulate infliximab for subcutaneous injection has no bearing on whether a POSA would be motivated to do so for D2E7 when the required D2E7 dose is only $^{1}/_{10}$ the dose required for infliximab. *Id.*

For all of these reasons, a POSA would not have viewed the fact that Centocor developed Remicade® as an intravenous formulation as a reason for not developing D2E7 as a stable 50 $^{mg}/_{ml}$ subcutaneous formulation. Ex. 1002 at ¶ 175.

b. The ’100 Patent Provides No Evidence of Any Unexpected Results

AbbVie cannot overcome Sandoz’s showing of prima facie obviousness with unexpected results because the ’100 patent provides none. The only stability data in the ’100 patent is for a single formulation with specified excipients in specific amounts. Ex. 1001 at 21:45-23:25. The ’100 patent provides no basis for asserting these data are unexpected because there is no comparison to the closest prior art, nor, even if the data were unexpected, is there a basis to argue this one example with a single buffer is commensurate with the scope of the claims which cover any buffer or buffer combinations providing the desired pH ranges. *See In re Payne*, 606 F.2d 303, 316 (C.C.P.A. 1979) (“Payne may not, however, rely on his mere assertion that the [prior art] compound is ‘representative and superior in pesticidal properties to the compounds described in the prior art references].’ None of the latter, allegedly inferior, compounds was tested.”); *In re Dill*, 604 F.2d 1356, 1361 (C.C.P.A. 1979) (unexpected results “must be commensurate in scope with the claims to which it pertains.”).

c. Commercial Success Does Not Demonstrate Nonobviousness

AbbVie has made contradictory arguments on commercial success attempting to support the patentability of its varied portfolio of secondary D2E7-related patents. There can be no nexus between Humira®’s commercial success

and the claims of the '100 patent because at different times AbbVie has attributed the commercial success of Humira® to entirely different patents. The Federal Circuit has held that where one patent blocks market entry, any commercial success enjoyed by the product cannot be convincingly attributed to other patents. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak."); *Coal. for Affordable Drugs II LLC v. NPS Pharm., Inc.*, No. IPR2015-01093, Final Written Decision, Paper 67, at 30-32 (Oct. 21, 2016) (same).

Because AbbVie's own evidence and inconsistent assertions point to different patents as the driver of Humira®'s commercial success, it has no basis for now arguing, as it did previously, that the commercial success of Humira® was "driven in large part by" its formulation. Ex. 1048 at 28. However, the very evidence that AbbVie submitted, supposedly in support of its response to the '158 formulation patent petition, acknowledged that the commercial success of Humira® was due to its initial patent on D2E7 antibody itself: "Abbott loses its key patent on the composition of matter for Humira in 2016, meaning it could face

competition from cheaper 'biosimilar' knock-offs." Ex. 1060 at 5.[37] Furthermore, in defending the alleged patentability of U.S. Patent No. 8,889,135, which claims treatment of RA using adalimumab, AbbVie said nothing about its formulation driving Humira®'s commercial success; instead AbbVie attributed its commercial success to its RA dosing regimen. Ex. 1063 at 44-46.

The Board's Final Written Decision for the '135 IPR recognized that AbbVie has inconsistently argued in different proceedings that different attributes of Humira® have led to its commercial success: "[t]hus, Patent Owner has relied on features other than the dosing regimen recited in the '135 patent claims as driving the commercial success of HUMIRA®." *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172, Final Written Decision, Paper No. 60, at 40 (May 16, 2017). The Board stated: "it is not clear whether the sales of HUMIRA® are due to the dosing regimen recited in the '135 patent, or the formulation that Patent Owner argued was the driver of commercial success in another *inter partes* review, or the known and patented fully human D2E7 antibody." *Id.* at 41.

Accordingly, AbbVie cannot save the claims of the '100 patent from invalidity by asserting that the commercial success of Humira® is due to the

[37] This reference was cited as ex. 2003 in the '158 IPR. Without Salfeld, which blocked others from commercializing any adalimumab formulation until December 2016, there is no reason to conclude that an intravenously-administered form of Humira® similar to Remicade® would not also have been a commercial success.

formulations claimed in the ’100 patent, particularly when the teachings of the prior art so clearly render those formulations obvious. *See, e.g., W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) (“[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007)).

Moreover, even if AbbVie makes a showing that the ’100 patent claims cover Humira®, it must show that a representative number of formulations covered by those claims are supported by similar evidence of commercial success because “objective evidence or [sic] non-obviousness must be commensurate in scope with the [challenged] claims.” *In re Grasselli,* 713 F.2d 731, 743 (Fed. Cir. 1983) (internal quotation marks omitted). It plainly cannot make this showing.

* * *

Finally, even if the Board credits some or all of AbbVie’s rebuttal evidence, because Sandoz’s prima facie showing of obviousness so plainly discloses each element of AbbVie’s claimed invention, the Board should institute review and permit Sandoz an opportunity to respond.

5. Summary of Grounds for Invalidity

The claim charts below provide a summary of the prior art disclosures that render obvious each claim in the ’100 patent. The charts for the dependent claims

hereby incorporate all of the grounds in the independent and any other dependent claims from which they depend.

Independent Claims 1 and 19

Claim Language of the '100 Patent	Prior Art Disclosures
A stable liquid aqueous pharmaceutical formulation comprising	"A pharmaceutical composition comprising the isolated human antibody of any one of claims **26**, **27** or **28**, and a pharmaceutically acceptable carrier." Ex. 1003 at claim 29. "Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage." Ex. 1003 at 21:28-29. "[P]harmaceutically acceptable carriers include one or more of water . . . ." Ex. 1003 at 21:1-2. "A ***stable aqueous pharmaceutical formulation*** comprising a therapeutically effective amount of an antibody not subjected to prior lyophiliza[tion]." Ex. 1005 at Abstract (emphasis added).
Claim 1: (a) a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, at a concentration of 45 to 150 $^{mg}/_{ml}$	"Patients . . . receive[d] weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." Ex. 1004 at 3; Ex. 1002 at ¶¶ 79-87.
Claim 19: (a) 45-105 $^{mg}/_{ml}$ of a human IgG1 anti-human Tumor Necrosis Factor alpha (hTNFα) antibody,	"An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1–20 $^{mg}/_{kg}$, more preferably 1–10 $^{mg}/_{kg}$."

Claim Language of the '100 Patent	Prior Art Disclosures
	Ex. 1003 at 23:13-16.
(b) a polyol;	"In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition." Ex. 1003 at 21:4-7. "A 'polyol' is a substance with multiple hydroxyl groups, and includes sugars (reducing and nonreducing sugars), sugar alcohols and sugar acids." Ex. 1005 at 6:38-40.
Claim 1: (c) a polysorbate at a concentration of 0.1 to 10 $^{mg}/_{ml}$,	"The proper fluidity of a solution can be maintained, for example, . . . by the use of surfactants." Ex. 1003 at 21:45-49. "The major class of compounds used in pharmaceutical systems are the nonionic surfactants . . . ." and lists "polysorbate 20" and "polysorbate 80." Ex. 1008 at 286, 1037. "A surfactant is also added to the antibody formulation. Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbates 20, 80 etc) . . . ." Ex. 1005 at 22:49-51. "[T]he surfactant may be present in the formulation in an amount from about 0.001% to about 0.5%, preferably from about 0.005% to about 0.2% and most preferably from about 0.01% to about 0.1%." Ex. 1005 at 22:55-59.

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 19: (c) 0.1-10 $^{mg}/_{ml}$ of polysorbate 80,	"The most widely used compounds [among the possible surfactants] are the polyoxyethylene sorbitan fatty acid esters . . . ." Ex. 1008 at 287, 1037 (disclosing polysorbate 20 polysorbate 80) "A surfactant is also added to the antibody formulation. Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbates 20, 80 etc) . . . ." Ex. 1005 at 22:49-51 "The major class of compounds used in pharmaceutical systems are the nonionic surfactants . . . ." and lists "polysorbate 20" and "polysorbate 80." Ex. 1008 at 286, 1037.
and (d) a buffer system having a pH of 4.5 to 7.0,	"The antibodies and antibody-portions of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody or antibody portion of the invention and a pharmaceutically acceptable carrier. . . . As used herein, 'pharmaceutically acceptable carrier' includes any and all solvents, . . . and the like that are physiologically compatible." Ex. 1003 at 20:59-67; Ex. 1002 at ¶¶ 88-93; *supra* VI.C.1.d., VI.A.1. "Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline . . . ." Ex. 1003 at 21:2; Ex. 1002 at ¶¶ 88-93; *supra* VI.C.1.d; VI.A.1. "[T]he invention provides a stable

Claim Language of the '100 Patent	Prior Art Disclosures
	aqueous pharmaceutical formulation comprising . . . a buffer maintaining the pH in the range from about 4.5 to about 6.0 . . . ." Ex. 1005 at 2:26-30. "[A] non-pyrogenic solution of 25 $^{mg}/_{ml}$ D2E7 mAb in 1.2% mannitol, 0.12% citric acid, 0.02% sodium citrate." Ex. 1011 at 661; Ex. 1002 at ¶¶ 88-93; *supra* VI.A.4.
wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.	"A pharmaceutical composition comprising [D2E7] . . . and a pharmaceutically acceptable carrier." Ex. 1003 at claim 29. "Patients . . . receive[d] weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." Ex. 1004 at 3.

Claims 2, 3, 20 and 21

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 2: The formulation of claim **1**, wherein the concentration of the antibody or antigen-binding portion is 50 to 100 $^{mg}/_{ml}$.	The claimed 50-100 $^{mg}/_{ml}$ and 50 $^{mg}/_{ml}$ concentrations fall within the ranges described as obvious for claim 1 and thus for the same reasons are also obvious.
Claim 3: The formulation of claim **2**, wherein the concentration of the antibody or antigen-binding portion is 50 $^{mg}/_{ml}$.	
Claim 20: The formulation of claim **19**, wherein the concentration of the antibody is from 50 to 100 $^{mg}/_{ml}$.	
Claim 21: The formulation of claim **19**, wherein the concentration of the antibody is 50 $^{mg}/_{ml}$.	

Claims 4 and 22

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 4: The formulation of claim **1**, wherein the formation [sic] has a shelf life of at least 18 months.	*See supra* VI.B
Claim 22: The formulation of claim **19**, wherein the formulation has a shelf life of at least 18 months.	

Claims 5 and 23

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 5: The formulation of claim **1**, wherein the antibody is D2E7.	"A pharmaceutical composition comprising [D2E7] and a pharmaceutically acceptable carrier." Ex. 1003 at claim 29. "Patients . . . receive[d] weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." Ex. 1004 at 3.
Claim 23: The formulation of claim **19**, wherein the antibody is D2E7.	

Claims 7 – 10 and 28

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 7: The formulation of claim **1**, wherein the polyol is a sugar alcohol.	Mannitol is a sugar alcohol, as evidenced by claim 8. Salfeld taught the use of both sugars and mannitol, and therefore renders claims 7-10 obvious. Ex. 1003 at 21:5-6. Trehalose is a commonly used polyol in pharmaceutical formulations, therefore claim 28 is also obvious. Ex. 1005 at 22:36-37. "A 'polyol' is a substance with multiple hydroxyl groups, and includes sugars (reducing and nonreducing sugars),
Claim 8: The formulation of claim **7**, wherein the sugar alcohol is mannitol.	
Claim 9: The formulation of claim **1**, wherein the polyol is a sugar.	
Claim 10: The formulation of claim **9**, wherein the sugar is trehalose.	
Claim 28: The formulation of claim **19**, wherein the polyol is mannitol or trehalose.	

Claim Language of the ’100 Patent	Prior Art Disclosures
	sugar alcohols and sugar acids.” Ex. 1005 at 6:38-40. Nonreducing sugars include sucrose, trehalose . . . . Mannitol . . . [is an] example[] of [a] sugar alcohol[].” Ex. 1005 at 6:49-52.

Claims 11 – 12

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 11: The formulation of claim **1**, wherein the polysorbate is polysorbate 20.	Salfeld disclosed the use of surfactants. Ex. 1003 at 21:45-49. Lam, like Salfeld, taught stable antibody formulations and further noted that polysorbate 80 and polysorbate 20 could be used as the surfactant. Ex. 1005 at 22:49-51. Remington generally taught the use of polysorbates such as polysorbate 80 and polysorbate 20 as a surfactant. Ex. 1008 at 286-87, 1037.
Claim 12: The formulation of claim **1**, wherein the polysorbate is polysorbate 80.	

Claims 13 – 14

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 13: The formulation of claim **12**, wherein the polysorbate 80 concentration is from 0.5 to 5 $^{mg}/_{ml}$.	"[T]he surfactant may be present in the formulation in an amount from about 0.001% to about 0.5%, preferably from about 0.005% to about 0.2% and most preferably from about 0.01% to about 0.1%." Ex. 1005 at 22:55-59; 22:49-51 (polysorbate 80) "The major class of compounds used in pharmaceutical systems are the nonionic surfactants . . . ." and lists "polysorbate 20" and "polysorbate 80." Ex. 1008 at 286, 1037. "The most widely used compounds [among the possible surfactants] are the polyoxyethylene sorbitan fatty acid esters . . . ." Ex. 1008 at 287, 1037.
Claim 14: The formulation of claim **12**, wherein the polysorbate 80 concentration is 1 $^{mg}/_{ml}$.	

Claims 17 and 27

Claim Language of the '100 Patent	Prior Art Disclosures
Claim 17: The formulation of claim **1**, which is suitable for single use subcutaneous injection.	"The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). . . . In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection." Ex. 1003 at 21:21-26. Single-use formulations were well known. Ex. 1008 at 785. Furthermore, any formulation that is suitable for use is suitable for single use therefore this limitation has no practical effect. Ex. 1002 at ¶ 140.
Claim 27: The formulation of claim **19**, which is suitable for single use subcutaneous injection.	

Claims 6, 18, 24 and 29

Claim Language of the '100 Patent	Prior Art Disclosures
The formulation of claim [5, 1, 19], comprising: (a) 50-100 [or 50] $^{mg}/_{ml}$ of the antibody [or antigen-binding portion,] or [D2E7]	*See* disclosures for claims 2, 3, 20 and 21 above.
(b) 7.5-15 $^{mg}/_{ml}$ of mannitol, and	*See* disclosures for claims 7 – 10 and 28 above "[A] non-pyrogenic solution of 25 $^{mg}/_{ml}$ D2E7 mAb in 1.2% mannitol, 0.12% citric acid, 0.02% sodium citrate." Ex. 1011 at 661; Ex. 1002 at ¶ 115. *See supra* VI.A.1, VI.A.3 discussing Salfeld and Remington. "Preferably the aqueous formulation is isotonic, in which case suitable concentrations of the polyol in the formulation are in the range from about 1% to about 15 % w/v, preferably in the range from about 2% to about 10% w[/]v . . . ." Ex. 1005 at 22:39-43.
(c) 0.5-5 $^{mg}/_{ml}$ of polysorbate 80,	*See* disclosures for claim 13 above
(d) wherein said buffer system has a pH of 5.0 to 6.5 [4.5 to 6.0].	*See* disclosures for claims 1 and 19 (d) above.

Claims 15 – 16 and 25 – 26

Claim Language of the ’100 Patent	Prior Art Disclosures
Claim 15: The formulation of claim **1**, wherein the pH is from 4.5 to 6.0.	*See* disclosures for claims 1 and 19 (d) above.
Claim 16: The formulation of claim **15**, wherein the pH is from 4.8 to 5.5.	
Claim 25: The formulation of claim **19**, wherein the pH is from 4.5 to 6.0.	
Claim 26: The formulation of claim **19**, wherein the pH is from 4.8 to 5.5.	

VII. CONCLUSION

Petitioner demonstrated a reasonable likelihood that all claims of the '100 patent are obvious in view of the prior art identified herein and therefore requests that the Board institute *inter partes* review for all claims.

Dated: July 20, 2017

Respectfully submitted,
/s/ David K. Barr
David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer LLP
250 West 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 CFR 42.24(a), this Petition contains 13,254 words as counted by the word processing program used for its preparation (Microsoft Word 2010).

The undersigned further certifies that this brief complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Dated: July 20, 2017

/s/ David K. Barr

David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Sandoz Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 8,802,100 and Exhibits 1001 – 1075 were served on July 20, 2017 via Federal Express to the correspondence address for the attorney of record for AbbVie Biotechnology Ltd., the assignee of the '100 patent.

Ropes & Gray, LLP
IPRM Docketing 39/361
1211 Avenue of the Americas
New York, NY 10036

Dated: July 20, 2017

/s/ David K. Barr

David K. Barr (Reg. No. 31,940)
David.Barr@apks.com
Arnold & Porter Kaye Scholer LLP
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560