IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Junming Le, Jan T. Vilcek, Peter E. Daddona, John Ghrayeb, David M. Knight and Scott A. Siegel		
Control No.:	90/012,851	Group:	3991
Filing Date:	April 29, 2013	Examiner:	Ponnaluri, Padmashri
Patent No.:	6,284,471	Issued:	September 4, 2001
Confirmation No:	4111		
For:	Anti-TNFα Antibodies And Assays Employing Anti-TNFα Antibodies		

CERTIFICATE OF MAILING OR TRANSMISSION

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Commissioner:

Transmitted herewith is an Appeal Brief for filing in the subject application. The Appeal Brief is filed pursuant to the Notice of Appeal received by the U.S. Patent and Trademark Office on May 27, 2015.

1. ☐ Appellant hereby petitions to extend the time for filing an Appeal Brief for [ ] month(s) from [ ] to [ ].

2. ☐ A [ ] month extension of time to extend the time for filing an Appeal Brief from to was filed on [ ] with payment of a $[ ] fee.

   ☐ Appellant hereby petitions for an additional [ ] month extension of time for filing an Appeal Brief from to .

3. ☐ A Request for Oral Hearing before the Patent Trial and Appeal Board is being filed concurrently herewith.

4. Fees are submitted for the following:

☐	Extension of Time for [ ] month(s)		$_____
☐	Additional Extension of Time:		
	Fee for Extension ([ ] mo.)	$_____	
	Less fee paid ([ ] mo.)	$_____	
	Balance of fee due		$_____
☐	Other_____		$_____
		TOTAL	$_____

5. The method of payment for the total fees is as follows:

☐ A check in the amount of $[ ] is enclosed.

☐ Please charge Deposit Account No. 08-0380.

Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Dated: July 23, 2015

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: *Ex Parte* Reexamination of U.S. Patent No. 6,284,471	)	Reexamination Control No. 90/012,851
Originally Filed: Feb. 4, 1994 Originally Issued: Sept. 4, 2001	)	Filing Date of Reexamination: April 29, 2013
Inventors: Le et al.	)	Examiner: Padmashri Ponnaluri
For: ANTI-TNFα ANTIBODIES AND ASSAYS EMPLOYING ANTI-TNFα ANTIBODIES	)	Group Art Unit: 3991 Confirmation No.: 4111

DECLARATION OF JOHN GHRAYEB, PH.D. UNDER 37 C.F.R. § 1.132

I. INTRODUCTION

A. Background and Expertise

1. I have been retained by counsel for Janssen Biotech, Inc. ("Janssen") to provide my opinions on topics raised in the above-captioned *ex parte* reexamination proceeding. In connection with this engagement, I am being compensated for my time at a rate of $250 per hour. My *curriculum vitae* is attached as Exhibit C.

2. I am a named inventor on U.S. Patent No. 6,284,471 (the "'471 patent").

3. I am currently a consultant for Morphotek Inc.

4. I received my Bachelor of Science degree from Oxford University in 1974, and earned my Ph.D. in biochemistry at Kent State University in 1982. Afterward, I spent two years at State University of New York at Stony Brook completing my postdoctoral training before joining Centocor (a predecessor to Janssen) in July 1984.

5. I worked on the development of several products at Centocor, four of which were ultimately approved for use in humans. In particular, I was in charge of the team that developed

and characterized a chimeric version of the mouse antibody A2, called cA2, which is now known as infliximab, the active ingredient in Remicade®. I retired from Centocor in 2006.

6. I have been asked to provide background information on the development of certain biologic products at Centocor around the time of the invention of the '471 patent (March 1991) and the unpredictability of the field in March 1991.

B. Materials Considered

7. I reviewed the '471 patent, which I understand is being reexamined in *ex parte* reexamination Control No. 90/012,851. I also reviewed the "First Office Action" in that reexamination proceeding.

8. I also reviewed a number of publications, all of which are listed in Exhibit D to this declaration. Copies of these publications are attached to my declaration as Exhibits E26-E28, E33, E36, E43-E45, E54, E62-E65, E73, E76, and E78-E106.

II. DEVELOPMENT OF ANTI-TNFα MONOCLONAL ANTIBODY CA2

9. I worked with David Knight, who directed molecular biology efforts at Centocor, to develop a chimeric version of Centocor's murine anti-TNFα monoclonal antibody, A2, to create cA2 in the early 1990s. *See* D. Knight *et al.*, "Construction and initial characterization of a mouse-human chimeric anti-TNF antibody," *Molecular Immunology* 30:1443-53 (1993) [Exhibit E78]. The amino acid sequences of the heavy and light chain variable regions of cA2 (the active ingredient in Remicade®), appear in the '471 patent specification. *See* '471 patent at SEQ ID NO:3 & SEQ ID NO:5.

10. At the time cA2 was created, the field of antibody-based treatments for disease was unpredictable. As discussed below in Section III, many antibody-based treatments developed at Centocor in the early 1990s failed to develop into viable human therapeutics despite favorable initial results in preclinical and early clinical trials, including trials of cA2 in patients

with sepsis or multiple sclerosis, and trials of anti-CD4 antibodies in patients with rheumatoid arthritis or multiple sclerosis.

11. Thus, the results of early clinical trials that explored cA2 as a treatment option for patients suffering from rheumatoid arthritis or Crohn's disease were met with a fair degree of skepticism from the larger community.

12. In contrast to the clinical-trial failures discussed below in Section III, clinical trials in which rheumatoid arthritis patients received cA2 reported significant reductions in symptoms. *See* M.J. Elliott *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis & Rheumatism*, 36:1681-1690, at 1681 (Dec. 1993) [Exhibit E73]. I personally visited one of the patients during these clinical trials, who told me that she had regained the ability to go to work after her first treatment. She thanked me for my work, and encouraged me to continue working to develop the product.

13. Based on the success observed in rheumatoid arthritis patients, a single patient with Crohn's disease—the 16-year-old girl identified in Example XXI of the '471 patent specification—received treatment with cA2 under a compassionate use exception, which allows a seriously ill patient to receive an unapproved treatment when no other treatment options are available or where existing treatment options have failed. *See* H.H.F. Derkx *et al.*, "Tumour necrosis factor antibody treatment in Crohn's disease," *Lancet* 342:173-74 (1993) [Exhibit E76]. The marked reduction in symptoms she experienced allowed Centocor to pursue a larger clinical trial, whose results were reported in a subsequent review article as equally successful. *See* S.J.H. van Deventer, "Tumour necrosis factor and Crohn's disease," *Gut* 40:443-448, at 445 (1997) [Exhibit E79].

14. The FDA approved Remicade®, which contains cA2 (infliximab) as its active ingredient, for use in the treatment of Crohn's disease in 1998. *See* FDA Approval Letter for Infliximab (Aug. 24, 1998) [Exhibit 62]. The FDA first approved Remicade® for use in the treatment of rheumatoid arthritis in 1999. *See* FDA Approval Letter for Infliximab (Nov. 10, 1999) [Exhibit E100]. Those were the only two approved uses for Remicade® until 2004. In September 2004, Remicade® was approved for use in the treatment of patients with earlier stage rheumatoid arthritis with moderate to severe disease activity who had not previously been treated with methotrexate. *See* FDA Approval Letter for Infliximab (Sept. 29, 2004) [Exhibit E104]. Until this approval, Remicade® had only been approved for use in RA patients who had been treated or were being treated with methotrexate. *See* FDA Approval Letter for Infliximab (December 29, 2000) [Exhibit E105]; FDA Approval Letter for Infliximab (February 27, 2002) [Exhibit E106]. But the September 2004 approval indicated that Remicade® could be used as a first-line therapy, indicating that the FDA had acknowledged that clinical studies showed that Remicade® was better than previously approved therapies. In December 2004, Remicade® received its first FDA approval for an indication other than rheumatoid arthritis or Crohn's disease. *See* FDA Approval Letter for Infliximab (Dec. 17, 2004) [Exhibit E103].

15. From 2001 to 2003, Remicade® generated $3.5 billion in sales. *See, e.g.*, Johnson & Johnson Annual Report (2003) at 30 [Exhibit E101]. These sales, plus sales between 1998 and 2000, were all associated with uses of Remicade® to treat either rheumatoid arthritis patients or Crohn's disease patients. Today, Remicade® remains an incredibly successful treatment for both rheumatoid arthritis and Crohn's disease. Remicade has been approved for treating six different diseases, two of which are rheumatoid arthritis and Crohn's disease. See Remicade® Label [Exhibit E81] at page 1. Remicade currently generates annual sales in excess

of $6 billion across all of its indications. Johnson & Johnson Annual Report (2012) at 5 [Exhibit E102].

16. In 2000, Remicade® was recognized with the Prix Galien, one of the most prestigious international awards presented for pharmaceutical research and innovation. In 2013, President Obama honored Jan Vilček, another named inventor on the '471 patent, with the National Medal of Technology and Innovation. *See* http://communications.med.nyu.edu/media-relations/news/jan-vilcek-md-phd-honored-white-house-awards-ceremony [Exhibit E80].

17. Across its approved indications, which currently include adult and pediatric Crohn's disease, rheumatoid arthritis, adult and pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (*see* Remicade® Label [Exhibit E81]), Remicade® has been used to treat over two million patients.

III. BIOLOGICS DEVELOPED AT CENTOCOR THAT SHOWED PROMISING RESULTS BUT ULTIMATELY FAILED

A. Anti-TNFα Monoclonal Antibody cA2 Failed to Treat Sepsis

18. We initially tested cA2 at Centocor as a treatment for sepsis, which is a systemic response to severe bacterial, viral, or fungal infection associated with high serum TNFα levels.

19. Experiments conducted in the 1980s had demonstrated that sepsis correlated with a systemic release of TNF into the blood. *See* A. Waage *et al.*, "Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease," *Lancet* 1:355-57 (1987) [Exhibit E28]. In addition, animal studies had shown that TNF caused a wide variety of acute toxic effects, many of which were features of bacterial endotoxin poisoning. *See* B. Beutler & A. Cerami, "Tumor necrosis, cachexia, shock, and inflammation: A common mediator," *Ann. Rev. Biochem.* 57:505-18, at 509 (1988) [Exhibit E82]; K.J. Tracey *et al.*, "Shock and tissue injury induced by recombinant human cachectin," *Science* 234:470-74 (1986)

[Exhibit E26]; K.J. Tracey *et al.*, "Cachectin/tumor necrosis factor induces lethal shock and stress hormone responses in the dog," *Surg. Gyn. Obstet.* 164:415-422 (1987) [Exhibit E27].

20. Thus, in the late 1980s, there had been reasons to believe that anti-TNFα antibodies could provide an effective treatment option for protecting against or preventing sepsis.

21. Researchers tested this hypothesis in animal models and obtained initial results that were encouraging. In 1985, for example, it was reported that passive immunization against TNF protected mice from the effects of the endotoxin lipopolysaccharide (LPS), a lethal toxin present on bacterial cell walls that is used to induce septic shock in animal models. *See* B. Beutler *et al.*, "Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin," *Science* 229:869-71 (Aug. 30, 1985) [Exhibit E33]. These data suggested that TNF could be one of the principal mediators of endotoxin-caused shock, and the study's authors concluded that the "potential utility of passive immunization with antisera to TNF in animals with shock induced by septicemia (or possibly other causes) needs further exploration." B. Beutler *et al.* (1985), at 871 [Exhibit E33]. It was noted that mice are "relatively resistant to the effects of LPS when compared to most other mammals," such that "TNF may play a more prominent role as a mediator of shock" in other mammals and "[i]mmunization against TNF might then be expected to yield a higher level of protection." Beutler *et al.* (1985), at 871 [Exhibit E33].

22. In 1987, it was reported that anti-TNF antibodies could prevent septic shock associated with lethal bacteremia in primates. K.J. Tracey *et al.*, "Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia," *Nature* 330:662-664 (Dec. 23, 1987) [Exhibit E36]. In that experiment, researchers administered doses of the anti-TNF antibodies to baboons, and then challenged the baboons with injections of the bacteria. K.J.

Tracey *et al.* (Dec. 1987), at 663 [Exhibit E36]. The experiment showed a moderate degree of protection from the challenge. K.J. Tracey *et al.* (Dec. 1987), at 664 [Exhibit E36].

23. Based on the success reported in these animal models, human trials were performed with the expectation that anti-TNFα antibodies could be as effective at treating sepsis in humans, if not more so. That expectation proved incorrect.

24. From 1991 to 1992, Centocor conducted a Phase I-II clinical trial with the anti-TNFα antibody cA2 in several dozen patients with sepsis, and that trial failed to confirm the results reported in animal models. This early failure is recounted in several review articles. *See, e.g.*, M. Feldmann, "Translating Molecular Insights in Autoimmunity into Effective Therapy," *Annu. Rev. Immunol.* 2009. 27:1–27 at 17 (2009) [Exhibit E43]; J. Vilček, "From IFN to TNF: a journey into realms of lore," *Nature Immunology* 10:555-557 at 557 (Jun. 2009) [Exhibit E44] (observing that even at a dose as high as 10 mg/kg, "no substantial therapeutic benefit could be demonstrated"); J. Vilček & M. Feldmann, "Historical review: Cytokines as therapeutics and targets of therapeutics," *TRENDS in Pharmacological Sciences* 25:201-209, at 204-05, Table 4 (Apr. 2004) [Exhibit E45] (observing that treatment of patients with sepsis with cA2 conferred "no significant benefit").

25. Five years later, a clinical trial exploring the effect of cA2 in severe sepsis reached a similar outcome. *See* M. Clark *et al.*, "Effect of a chimeric antibody to tumor necrosis factor-alpha on cytokine and physiologic responses in patients with severe sepsis-a randomized, clinical trial," *Crit. Care Med.* 26:1650-59 (Oct. 1998) [Exhibit E83]. The study's authors concluded that "a single dose of cA2 did not alter the overall pattern of cytokine activation or the profound derangements in physiologic function that accompany severe sepsis." Clark *et al.*, at 1650 [Exhibit E83].

26. A 2001 review article confirmed that there was no significant benefit to treatment with four different anti-TNFα antibodies, as shown in eight clinical sepsis trials:

Table 1. Clinical trials of monoclonal antibodies and soluble tumor necrosis factor (TNF) receptor fusion proteins directed against TNF-α during sepsis

Agent	Study	Control Mortality (%)	Anti-TNF Mortality (%)	Benefit (%)
Monoclonal antibodies				
CB0006	Fisher et al. (13)	6/19 (32)	27/61 (44)	−12
CDP571	Dhainaut et al. (14)	6/10 (60)	20/32 (63)	−3
Ray 1351	Abraham et al. (15)	108/326 (33)	196/645 (30)	+3
Ray 1351	Cohen et al. (16)	66/167 (40)	144/336 (37)	+3
Ray 1351	Abraham et al. (17)	388/938 (33)	382/948 (40)	+3
MAK195F (afelimomab)	Reinhart et al. (18)	12/29 (41)	44/93 (47)	−6
MAK195F (afelimomab)	Reinhart et al. (19)	128/222 (58)	121/224 (54)	+4
MAK195F (afelimomab)	Panacek et al. (20)	243/519 (46)	213/488 (44)	+4*
Soluble receptors				
p75 fusion protein	Fisher et al. (21)	16/33 (36)	49/106 (45)	−15
p55 fusion protein	Abraham et al. (22)	54/148 (36)	136/358 (38)	−1
p55 fusion protein	Abraham et al. (17)	192/530 (36)	177/532 (27)	+1

*The 4% benefit was seen in septic patients with IL-6 > 1000 pg/mL, the target population of this study. Risk adjusted benefit was 6.9%.

K. Reinhart, "Anti-tumor necrosis factor therapy in sepsis: Update on clinical trials and lessons learned," *Crit. Care Med.* 29:S121-S125 (2001) [Exhibit E54].

27. Thus, although initial *in vitro* and animal studies indicated that anti-TNFα antibody therapy would be a promising treatment option for sepsis, early stage clinical trials failed to confirm the result in humans and, to this day, no one has been able to develop an anti-TNFα antibody that can effectively and safely treat sepsis in humans.

B. Anti-CD4 Monoclonal Antibody cM-T412 Failed to Treat Rheumatoid Arthritis

28. Another failed monoclonal antibody target was CD4. Just as anti-TNFα antibodies had been viewed as promising candidates to treat sepsis in the early 1990s, anti-CD4 antibodies were thought to be promising candidates in the treatment of rheumatoid arthritis based on *in vitro* and animal studies.

29. CD4 is a glycoprotein found on the surface of certain T cells. It was believed that an antibody targeting the CD4 protein on T cells would enable one to deplete the population of T cells that expressed CD4 selectively.

30. Initial studies in mouse and other animal models for rheumatoid arthritis had shown promise. Type II collagen-induced arthritis in mice, for example, displays disease characteristics that are similar to human rheumatoid arthritis. *See, e.g.*, J.M. Stuart *et al.*, "Collagen autoimmune arthritis," *Annu. Rev. Immunol.* 2:199 (1984) [Exhibit E84]; J.S. Courtenay *et al.*, "Immunization against heterologous type II collagen induces arthritis in mice," *Nature (Lond.)* 283:666 (1980) [Exhibit E85]. Early animal studies had shown that collagen-induced arthritis could be prevented with antibodies targeting CD4+ T cells. *See, e.g.*, G.E. Ranges *et al.*, "Prevention of type II collagen-induced arthritis by in vivo treatment with anti-L3T4," *J. Exp. Med.* 162:1105-1110 (Sept. 1985) [Exhibit E86]; H. Waldmann *et al.*, "Manipulation of T cell responses with monoclonal antibodies," *Annu. Rev. Immunol.* 7:407 (1989) [Exhibit E87].

31. Early human trials with cM-T412, an anti-CD4 antibody we developed at Centocor, suggested that the antibody could be a promising treatment option, showing that it was safe for human use and that it also decreased the number of circulated CD4+ T cells. *See* J.E. Looney *et al.*, "High-level expression and characterization of a mouse-human chimeric CD4 antibody with therapeutic potential," *Hum Antibodies Hybridomas* 3:191-200 (Oct. 1992) [Exhibit E88]; L.W. Moreland *et al.*, "Use of a chimeric monoclonal anti-CD4 antibody in patients with refractory rheumatoid arthritis," *Arthritis & Rheumatism* 36:307-318 (Mar. 1993) [Exhibit E89]; E.H. Choy *et al.*, "Treatment of rheumatoid arthritis with single dose or weekly pulses of chimaeric anti-CD4 monoclonal antibody," *Scand. J. Immunol.* 36:291-98 (Aug. 1992) [Exhibit E90].

32. Even as late as 1994, T-cell-focused therapies remained the prevalent approach to using antibodies to treat RA. Elliott *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric

Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis & Rheumatism*, 36:1681-1690, at 1681 (Dec. 1993) [Exhibit E73] (noting that, "in most cases" up to that point in time, efforts to use "monoclonal antibodies as therapeutic agents in" the treatment of RA were "targeted specifically to the T cell, a strategy based on evidence that T cells are involved in the initiation and maintenance of RA").

33. However, T-cell-focused antibody therapies quickly proved to be unsatisfactory. The problem with cM-T412, for example, was that it turned out to be "more efficient in eliminating naïve and circulating T cells than it was at eliminating activated, memory pathogenic T cells resident in the joint." E.H. Choy *et al.*, "Monoclonal antibody therapy in rheumatoid arthritis, " *Brit. J. Rheum.* 37:484-490, at 488 (1998) [Exhibit E91]. Further compounding the problem was the fact that when administered intravenously, cM-T412 primarily bound peripheral blood CD4 targets, which do not contribute significantly to synovitis, rather than CD4+ lymphocytes in the joints. Choy *et al.*, at 488 [Exhibit E91]. Thus, to obtain a sufficient concentration at the joint to treat RA, a high dose of cM-T412 was required, which resulted in an "unacceptable level of immunosuppression." Choy *et al.*, at 488 [Exhibit E91]. Similar effects were observed with other anti-T-cell monoclonal antibodies. The antibody cM-T412 and other T-cell-depleting monoclonal antibodies, were ultimately abandoned as a result. Choy *et al.*, at 488 [Exhibit E91].

34. Subsequent CD4 targeting efforts were directed toward non-immune-cell-depleting monoclonal antibodies. *See, e.g.*, M.F. Van den Broek *et al.*, "Treatment of rats with monoclonal anti-CD4 induces long-term resistance to streptococcal cell wall-induced arthritis," Eur. J. Immunol 22:57-61 (1992) [Exhibit E92]; G.S. Panayi *et al.*, "T cell hypothesis in rheumatoid arthritis (RA) tested by humanized non-depleting anti-CD4 monoclonal antibody

(mAb) treatment I: Suppression of disease activity and acute phase response," *Arthritis Rheum.* 39:S244 (1996) [Exhibit E93]; R. Levy *et al.*, "Results of a placebo-controlled, multicenter trial using a primatized non-depleting, anti-CD4 monoclonal antibody in the treatment of rheumatoid arthritis," *Arthritis Rheum.* 39:S122 (1996) [Exhibit E94]. But even these so-called "non-depleting" antibodies were clinically unsatisfactory, showing modest efficacy at best, and only at intolerably high doses. *See* H. Scheerens *et al.*, "MTRX1011A, a humanized anti-CD4 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a Phase I randomized, double-blind, placebo-controlled study incorporating pharmacodynamic biomarker assessments," *Arthritis Res. & Ther.* 13:R177, at 2 (2011) [Exhibit E95].

35. To this day, anti-CD4 monoclonal antibody therapies remain ineffective at treating RA. *See* Scheerens *et al.*, at 10 [Exhibit E95]. That paper, which reported the failure of a recent Phase I clinical trial of the nondepleting humanized anti-CD4 monoclonal antibody MTRX1011A, concluded that although "CD4 T cells are certainly involved in the pathogenesis of RA, data from this study and those published by others have shown that targeting CD4 T cells with an anti-CD4 antibody is associated with at best a modest improvement in clinical parameters," even at dosages far in excess of those considered tolerable by patients. Scheerens *et al.*, at 10 [Exhibit E95].

36. Thus, despite the promise shown in preclinical and early clinical studies, anti-CD4 monoclonal antibody therapy ultimately failed to become a treatment option for rheumatoid arthritis.

37. The failure of these promising preclinical candidates to translate into effective therapeutics exemplifies and underscores the lack of predictability in the field of antibody-based

treatment for disease in the March 1991 time frame. This unpredictability led one reviewer to observe, in reflecting on the challenges of translational medicine:

> [A]nimal models of disease are notoriously poor predictors of the response of human disease . . . . Many drugs are effective in animals but not in humans. Thus, anti-CD-4 antibody proved to be very effective in suppressing collagen-induced arthritis but not when applied in patients with RA.

M. Feldmann *et al.*, "The transfer of a laboratory based hypothesis to a clinically useful therapy: the development of anti-TNF therapy of rheumatoid arthritis," *Best Practice & Res. Clin. Rheumatol.* 18:59-80, at 63-64 (2004) [Exhibit E96].

C. Monoclonal Antibodies cM-T412 and cA2 Both Failed to Treat Multiple Sclerosis

38. Because both TNFα and CD4+ T cells were implicated in the disease progression of multiple sclerosis, it had been thought that anti-TNFα and anti-CD4 monoclonal antibodies could provide a therapeutic option in human patients suffering from that disease. *See* K. Selmaj *et al.*, "Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions," *J. Clin. Invest.* 87:949-954 (Mar. 1991) [Exhibit E63]; M.K. Waldor *et al.*, "Reversal of experimental allergic encephalomyelitis with monoclonal antibody to a T cell subset marker," *Science* 22:415-417 (1985) [Exhibit E97]. Both treatments, however, failed to produce a viable human therapeutic for multiple sclerosis.

39. Initial results in a mouse model of multiple sclerosis, for example, indicated that anti-TNFα antibodies prevented the development of symptoms. *See* K. Selmaj *et al.*, "Anti-tumor necrosis factor therapy abrogates autoimmune demyelination," *Ann. Neurol.* 30:694–700 (Nov. 1991) [Exhibit E64]. Nevertheless, early human trials exploring the use of cA2 as a treatment for multiple sclerosis had to be cancelled when researchers determined that the patients' symptoms became worse. B.W. van Oosten *et al.*, "Increased MRI activity and

immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2," *Neurology* 47:1531-1534 (Dec. 1996) [Exhibit E65].

40. Anti-CD4 antibodies used to treat experimental allergic encephalomyelitis, an animal model of multiple sclerosis, similarly provided encouraging results in the late 1980s. *See* M.K. Waldor *et al.*, "Reversal of experimental allergic encephalomyelitis with monoclonal antibody to a T cell subset marker," *Science* 22:415-417 (1985) [Exhibit E97]. A Phase I trial of the anti-CD4 antibody cM-T412 even showed promising results in humans. *See* J.W. Lindsey *et al.*, "Phase 1 clinical trial of chimeric monoclonal anti-CD4 antibody in multiple sclerosis," *Neurology* 44:413-19 (Mar. 1994) [Exhibit E98] (concluding that "treatment of MS patients with cM-T412 chimeric anti-CD4 antibody is well tolerated at the doses tested and produces a long-lasting, selective depletion of CD4 lymphocytes"). However, development of cM-T412 as a treatment option for multiple sclerosis was ultimately halted after a Phase II clinical trial reported that, although cM-T412 therapy produced a "long-lasting reduction of circulating CD4-positive T cells," there was "no effect on the primary measure of efficacy" and cM-T412 was "unlikely to have a beneficial effect on the clinical disease course." B.W. van Oosten *et al.*, "Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial," *Neurology* 49:351-57 (Aug. 1997) [Exhibit E99].

41. Thus, although initial preclinical and, in the case of cM-T412, early clinical studies indicated that anti-TNFα and anti-CD4 antibody therapies would be promising treatment options for multiple sclerosis, early stage clinical trials failed to confirm the result in humans.

IV. CONCLUSION

42. Although monoclonal antibody therapies developed at Centocor, such as cA2 for treating sepsis or multiple sclerosis, and cM-T412 for treating rheumatoid arthritis or multiple

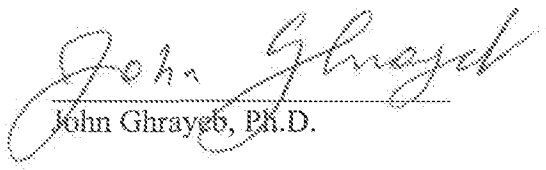
sclerosis, showed initial promise in preclinical models (and, in the case of cM-T412, in early clinical studies), each of these antibodies failed to produce viable treatment options for these indications in humans.

43. I believe that these experiences are relevant to the question of whether a person working in the field of treatment of RA or Crohn's disease would have had an expectation that that a particular antibody shown to be effective *in vitro* and/or in animal models would work when given to human patients. My personal experiences are contrary to that assumption. Specifically, as I explained above, examples of projects with which I had personal involvement showed very strong preclinical results in animal models and other studies. In each instance, the antibody treatment failed to make the transition to a viable human therapeutic product.

44. Based on these experiences, and given the level of unpredictability in the field, I would disagree with the proposition that it would have been obvious to one skilled in the art that a person, having knowledge or possession of the cA2 antibody in March of 1991 could successfully treat sepsis, multiple sclerosis, rheumatoid arthritis, or Crohn's disease in humans.

I, John Ghrayeb, do hereby declare and state, that all statements made herein of my own knowledge are true to the best of my knowledge, information, and belief, formed after reasonable inquire under the circumstances; and further that these statements were made with the knowledge that willfull false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,



John Ghrayeb, Ph.D.

Date: December 19, 2013.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: *Ex Parte* Reexamination of U.S. Patent No. 6,284,471	)	Reexamination Control No. 90/012,851
Originally Filed: Feb. 4, 1994 Originally Issued: Sept. 4, 2001	)	Filing Date of Reexamination: April 29, 2013
Inventors: Le *et al.*	)	Examiner: Padmashri Ponnaluri
For: ANTI-TNFα ANTIBODIES AND ASSAYS EMPLOYING ANTI-TNFα ANTIBODIES	)	Group Art Unit: 3991 Confirmation No.: 4111

DECLARATION OF PROFESSOR SANDER JAN HENDRIK VAN DEVENTER UNDER 37 C.F.R. § 1.132

I. INTRODUCTION

A. Background and Expertise

1. I have been retained by counsel for Janssen Biotech, Inc. ("Janssen") to provide my opinions on topics raised in the above-captioned *ex parte* reexamination proceeding. I understand that Janssen is the successor company of Centocor, Inc. ("Centocor").

2. In connection with this engagement, I am being compensated for my time at a rate of $300.00 per hour. My *curriculum vitae* is attached as Exhibit A.

3. I am a Professor of Translational Gastroenterology at Leiden University Medical Center. Prior to that position, I was a Professor of Experimental Medicine at The Academic Medical Centre ("AMC") at the University of Amsterdam, a Professor and Head of the Department of Gastroenterology at the AMC, and a research associate at Rockefeller University, New York. I was a Fellow of the Dutch Royal Academy of Sciences.

4. I received my Medical Degree from the University of Amsterdam in 1978 and completed my Ph.D. there in 1988 on the importance of Gram-negative bacterial endotoxins in

sepsis. Afterwards, I was trained and board-certified by the Royal Dutch Society of Physicians as an internist and a gastroenterologist.

5. After completing my Ph.D. thesis, I worked as a research associate at Rockefeller University, in the laboratory of Professor Anthony Cerami. During my time at Rockefeller University, I was involved in several preclinical studies on the biology and neutralization of TNFα. I started my research group at the AMC in 1991.

6. I have been extensively involved in the characterization of several monoclonal antibodies (anti-endotoxin, anti-CD4, and anti-TNFα). Some of these studies were performed in collaboration with Centocor, including a study of the use of anti-TNFα antibodies in Crohn's disease in 1993/1994. I have also worked with other anti-TNFα antibody manufacturers.

B. Materials Considered

7. I reviewed U.S. Patent No. 6,284,471 (the "'471 patent") which I understand is being reexamined in *ex parte* reexamination Control No. 90/012,851. I also reviewed the "Office Action" dated September 6, 2013 in that reexamination proceeding.

8. I also reviewed a number of publications, all listed in Exhibit B to this declaration. Copies of these publications are attached to my declaration as Exhibits E1-E77 and E100.

C. Legal Standards and Bases for this Declaration

9. I understand that the PTO has decided to institute a reexamination of claims 1-9 of the '471 patent in light of allegations that the claims are unpatentable for "double patenting" based on other patents granted to Centocor or Janssen.

10. I have been asked to provide my opinion about whether a person of ordinary skill in the art would have believed that knowledge of a particular anti-TNFα antibody would have made obvious the use of that antibody to treat humans suffering from either rheumatoid arthritis

("RA") or Crohn's disease ("Crohn's") in approximately March of 1991. For the reasons I present below, I do not believe that such a person would have found it obvious to use an anti-TNFα antibody to treat either RA or Crohn's.

11. I believe that a person of ordinary skill in the art in the field of the '471 patent would be someone who had at least a Ph.D. and two years of post-doctoral experience in the field of immunology. I believe that I can accurately describe how this person would have considered the state of the art of the '471 patent in March of 1991, given my education, training and experience at that time.

II. THE STATE OF THE ART IN 1991

A. The Causes of Rheumatoid Arthritis and Crohn's Disease Were Not Well Known in March of 1991

12. Rheumatoid arthritis is a disease characterized by pain, stiffness, swelling, and loss of function in joints. The disease is progressive and chronic. This much was understood long before 1991. I recall that in 1991, the causes of RA were not well understood. See, for example, Edward D. Harris, Jr., "Rheumatoid Arthritis: Pathophysiology and Implications for Therapy," *New. Engl. J. Med.*, 322:1277-1289 (1990) [Exhibit E1] ("The cause of rheumatoid arthritis is unknown."). In particular, researchers (such as myself) did not understand the mechanisms by which RA caused its symptoms, which made the search for effective treatments difficult. All of this is reflected by scientific literature published at the time, which I discuss below.

13. Crohn's disease is a type of inflammatory bowel disease ("IBD"). It is a chronic disorder which causes abdominal pain, weight loss, fatigue, and diarrhea. About 70% of all patients undergo one or more surgical procedures in the course of this disease. Like other chronic diseases it is highly debilitating and distressing for patients. I recall that in 1991, the

causes of Crohn's were not well understood. See, for example, Joseph B. Kirsner, "Inflammatory Bowel Disease Part I: Nature and Pathogenesis," *Disease-a-Month*, 37:610-666, at 632 (Oct. 1991) [Exhibit E2] ("The persistence of the IBD inflammatory reaction and its tendency to recur remains unexplained."). One of the hypotheses regarding the pathogenesis was that Crohn's disease results from an inappropriate immune response in the gastrointestinal tract, but the exact mechanism had not been elucidated. Others hypothesized that Crohn's disease resulted from mycobacterial infection, in particular M. paratuberculosis. Gary Gitnick *et al.*, "Preliminary report on isolation of mycobacteria from patients with Crohn's disease," *Digestive Diseases & Sciences* 34:925-932 (June 1989) [Exhibit E3]. Because the mechanism was not known, effective treatments were difficult to develop and immune-suppressive interventions could have deleterious effects. For example, if Crohn's disease indeed would be caused by mycobacterial infections, immune suppressive therapies would be strongly contra-indicated. This is reflected in scientific publications at the time, which I discuss below.

B. There Was Very Little Experience in 1991 Using Antibodies to Treat Diseases in Humans

14. I believe that it is important to recognize that the perspectives people working in the field of pharmaceutical development had about the prospects of antibody treatment in March of 1991 were very different from those they have today. It would be a mistake to equate today's perspectives on the feasibility of using antibodies to treat disease, particularly chronic diseases, with the beliefs of people working in the field in March of 1991.

15. In March of 1991, only one antibody product had been approved for human use; namely, Orthoclone (also called OKT3). OKT3 was the first antibody product ever approved, which occurred in the U.S. in 1986,[1] and subsequently in Europe in around 1988.

16. OKT3 is a murine IgG2a antibody that targets the CD3 antigen on human T-cells. See, for example, A. Benedict Cosimi *et al.*, "Use of Monoclonal Antibodies to T-Cell Subsets for Immunologic Monitoring and Treatment in Recipients of Renal Allografts," *N. Engl. J. Med.* 305:308-314 (Aug. 6, 1981) [Exhibit E4]; Ortho Multicenter Transplant Study Group, "A Randomized Clinical Trial of OKT3 Monoclonal Antibody for Acute Rejection of Cadaveric Renal Transplants," *N. Engl. J. Med.* 313:337-342 (Aug. 8, 1985) [Exhibit E5]. The antibody was used to prevent graft rejections in patients that had undergone an organ transplant operation (typically a kidney transplant). See Ortho Multicenter Transplant Study Group. The antibody worked basically by suppressing the person's immune system before and shortly after the person underwent the transplant operation. *Id.* The antibody product was given over a relatively short duration (10 to 14 days), and was administered in conjunction with other immunosuppressive agents. *Id.* That was important because OKT3 was a mouse monoclonal antibody, which would trigger an immunogenic response with production of human anti-mouse antibodies (HAMA). *Id.*

17. OKT3 was designed for use in acute care settings only. *Id.* It was not designed or approved for multiple administrations.[2] This is an important distinction from Remicade®, which

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[1] "Ortho Gets First FDA Okay for Therapeutic Monoclonal: Orthoclone OKT3 Approved for Renal Transplants, Target Population of 4,000 per Year," *Pink Sheet* (June 23, 1986) [Exhibit E6].

[2] In fact, OKT3 could have severe side effects that would lead to patients being admitted to the intensive care unit. See, for example, Heather Vallhonrat *et al.*, "In vivo generation of C4d, Bb, iC3b, and SC5b-9 after OKT3 administration in kidney and lung transplant recipients," *Transplantation* 67:253-258 (Jan. 27, 1999) [Exhibit E7].

has been approved for treating chronic diseases such as RA and Crohn's disease. Chronic diseases require the patient to be given the product multiple times.

18. It is fair to say that in March of 1991, many people had great hopes for using antibodies to treat human diseases. Indeed, this hope had existed from almost before the time antibodies had been fully characterized. For example, at the turn of the 20th century, Dr. Paul Ehrlich had advanced the concept of a "magic bullet" where an immunological agent could be used for targeted delivery of a drug to a cell in a patient.[3] Hope, however, was very different from having an expectation that an antibody-based pharmaceutical product would be safe and effective when used to treat humans, particularly in a chronic disease setting. For this, many targets needed to be met, including achieving a lack of immunogenicity, monoclonality, high binding affinity, lack of cross-reactivity and manufacturability.

19. As a result, I believe that a person of ordinary skill in the art would not have considered it to be routine, predictable, or assured that an antibody product would provide a safe and effective method of treating any human disease, even in view of pre-clinical experimental evidence. Instead, I believe people working in the field of antibody development in March of 1991 believed that there were substantial risks and uncertainty in any antibody-based therapeutic candidate, and that this was true regardless of the strength of the pre-clinical experimental evidence. This uncertainty would have been amplified for treating complex, chronic diseases, such as RA and Crohn's disease.

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[3] See, for example, Klaus Strebhardt & Axel Ullrich, "Paul Ehrlich's magic bullet concept: 100 years of progress," *Nature Reviews Cancer* 8:473-480 (June 2008) [Exhibit E8].

C. In 1991, Researchers Did Not Know Whether Human Diseases Could Be Treated By Targeting Cytokines

20. By March of 1991, there were a number of reports in the literature that identified the presence in patients afflicted with a wide range of disorders of atypical or abnormal levels of inflammatory mediators, including one important group of mediators called "cytokines." See, for example, A.M. Nouri *et al.*, "Cytokines and the chronic inflammation of rheumatic disease: I. The presence of interleukin-1 in synovial fluids," *Clin. Exp. Immunol.* 55:295–302 (Feb. 1984) [Exhibit E9]; J.T. Whicher & S.W. Evans, "Cytokines in disease," *Clin. Chem.* 36:1269-1281 (July 1990) [Exhibit E10]; Brian J. Nickoloff *et al.*, "The Role of Adhesion Molecules, Chemotactic Factors, and Cytokines in Inflammatory and Neoplastic Skin Disease—1990 Update," *J. Investigative Dermatology* 94:151s–157s (1990) [Exhibit E11]; C.I. Westacott, "Synovial fluid concentration of five different cytokines in rheumatic diseases," *Ann. Rheum. Dis.* 49:676-681 (1990) [Exhibit E12].

21. Cytokines are a diverse group of molecules, which includes interleukins and interferons. TNFα is one example of a cytokine.

22. Cytokines interact with receptors on the surfaces of cells. They are generally specific to one or a small number of such receptors. At a very simple level, when the receptor binds a cytokine, it will often induce the cell to respond in some manner.

23. In the body, the actions of any individual cytokine can be very complex and varied. For example, a single type of cytokine may cause different effects or responses when that cytokine is bound by a receptor on different types of cells, or when the binding occurs in the presence or absence of other molecules. A single cytokine thus may produce several different responses (a phenomenon termed "pleiotropism"). In addition, the binding of a cytokine by a

particular receptor often causes downstream effects on one or more other cytokines, and sometimes on itself, as well, resulting in a complex web of interactions.

24. Around the March 1991 timeframe, there was intense research interest in cytokines and the roles they play in disease progression. Yet it is safe to say that very little was known at that time about the roles that different cytokines play in the progression or prevention of disease.

25. Also, given what was known at that time about the complexity of cytokine interactions, it was unclear whether cytokines could even serve as viable therapeutic targets. For example, in March of 1991, it was not known whether targeting one particular cytokine would be effective in treatment, given that other cytokines could compensate for the removal of the targeted cytokine. The cytokine network was known to be redundant in that many cytokines could achieve the same function. Blocking the action of one cytokine might not have any clinical effect as a secondary cytokine may be able to assume its function.

26. It also was not known whether targeting one particular cytokine would lead to unforeseen consequences due to unknown relationships with other cytokines or cellular factors, or due to roles that the cytokines play in modulating different types of cellular responses or activities. Complicating things further, without a more complete understanding of the mechanism of a given human disease, one could not reliably predict what role the overexpression or underexpression of a single cytokine would play in the progression or amelioration of that human disease. Even today it remains difficult to predict whether targeting a single cytokine or inflammatory mediator will have a therapeutic effect in inflammatory diseases. For example, despite extensive evidence that the cytokine interleukin-17 ("IL-17") is involved in the inflammatory response in several immune-mediated diseases, including Crohn's disease,

administration of secukinumab, an anti-IL-17 antibody, to patients with Crohn's disease had no effect on disease activity and increased the incidence of adverse effects. Wolfgang Hueber, "Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial," *Gut* 61:1693–1700 (2012) [Exhibit E13].

27. A good summary of this complex landscape associated with cytokines was provided by Gabrielle Kingsley *et al.*, in "Immunotherapy of rheumatic diseases - practice and prospects," *Immunology Today* (1991) 12:177-179 ("Kinglsey, 1991") [Exhibit E14]. As these authors explained at page 177:

> [T]he most important question regarding cytokine intervention in rheumatic disease lies not in its technical feasibility but in the likely effect of interfering with only one cytokine with what is undoubtedly a very complex network. It seems highly improbable that a single cytokine holds the key to RA synovitis.

28. Another example of this perspective was provided by Dr. Rafael Fernandez-Botron in his August 1991 paper in the FASEB Journal, where he explained:

> In vivo, cytokines do not act alone but in combination with other cytokines and stimuli. Different cytokines can have redundant effects on certain cells, and combinations of cytokines can be synergistic or antagonistic in their effects depending on the target cells (1-3). Because of such complexity and because much of the knowledge of the biologic activities of cytokines has been derived from in vitro studies, actual roles played by cytokines and regulation of their activity in vivo are not completely clear. Moreover, understanding mechanisms that regulate cytokine activity in vivo requires consideration of other parameters such as

> different microenvironments and anatomical compartmentalization.

Rafael Fernandez-Botran, "Soluble cytokine receptors: their role in immunoregulation," *FASEB Journal*, 5:2567-74, 2567 (Aug. 1991) [Exhibit E15]. See also, e.g., Beutler and Cerami, "The History, Properties, and Biological Effects of Cachectin," *Biochemistry*, 27(2):7575-7582 [Exhibit E16] ("Redundancy of the type seen in the lymphotoxin/cachectin 'family' is not unknown.").

29. A similar perspective was described by David E. Trentham in "Immunotherapy and other novel therapies," *Current Opinion in Rheumatology* 3:369-372 at 371 (Jun. 1991) [Exhibit E17]. As he explained,

> Unidimensional attacks on aberrant immune pathways might have a limited effect on the underlying disease process.

30. Trentham also noted that while "the relevance of tumor necrosis factor and the biologic outcome of its banishment by a monospecific inhibitor remain in doubt, the isolation of interleukin inhibitors strengthens the probability that interleukin-mediated processes all involve precise cell surface receptors, and abrogation of the activity can be achieved by intervening with either the factor or its surface receptor." *Id.* at 370.

31. Trentham also captured the belief of many at the time that the human body naturally would produce antibodies in an attempt to fight RA, and, thus, attempts at "treatment with 'designer molecules' would be superfluous and therefore ineffective." *Id.* at 371.

32. Cytokines were also understood to be just a piece of a larger puzzle, and there was nothing that suggested that cytokines would prove to be better targets than other components of the immune system. As Kingsley *et al.* observed:

> The greatest obstacle to developing specific effective therapy for rheumatoid arthritis (RA) has been lack of understanding of aetiology.

See Kingsley, 1991 at 177 [Exhibit E14].

33. These authors then explained:

> [B]ased on present knowledge, a pathogenetic model can be constructed in which rheumatoid antigen(s) is presented in the context of a limited range of major histocompatibility complex (MHC) class II structures to the disease-promoting $CD4^+$ T cells that become activated. These, in turn, activate other cells including macrophages, B cells, other T cells and synoviocytes to release effector molecules such as cytokines, growth factors, antibodies and degradative enzymes. This leads to synovial inflammation and proliferation which cause joint destruction. It is likely that this immune activation will trigger a variety of immunoregulatory mechanisms but these are as yet ill-defined. Whether the critical MHC-antigenic peptide-T-cell receptor interactions occur in central lymphoid organs or whether this activation occurs primarily in situ after migration of T cells to the synovium is not known. In either case migration of T cells must play an important role in generating synovitis. Each component of this pathogenetic pyramid is a potential target for immunotherapeutic intervention.

Id. (citations omitted).

34. Kingsley *et al*. also noted that there was "consensus that the monokines interleukin 1 (IL-1), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor α (TNF- α) are present within the joint in rheumatoid arthritis patients at high concentrations." *Id.* But then, they observed that the relationship of RA to "T-cell-derived

cytokines such as IL-2, IL-4 and gamma-interferon (IFN-γ)," as well as "IL-7, IL-8, IL-9, and IL-10," was not well understood. *Id.*

35. In the March 1991 timeframe, there was even less known about the role of cytokines in other inflammatory diseases. For example, researchers were just beginning to understand that increased levels of cytokines were associated with inflammatory bowel diseases. See, e.g., J. Brynskov *et al.*, "Increased concentrations of interleukin-1β, interleukin-2 and soluble interleukin-2 receptors in endoscopical mucosal biopsy specimens with active inflammatory bowel disease," *Gut* 33:55-58 (1992) [Exhibit E18].

D. In 1991, Researchers Did Not Know Whether Human Diseases Could Be Treated by Agents that Target the Cytokine TNFα

36. Although work had been done on murine (and, to some extent, CDR-grafted) anti-TNFα antibodies before 1991, it was not clear in the March 1991 timeframe whether an anti-TNFα antibody would be of therapeutic benefit in treating human disease.

37. Originally, TNFα had been identified as a tumour-necrosis-inducing factor.[4] Carswell, "An endotoxin-induced serum factor that causes necrosis of tumors," *Proc. Nat'l Acad. Sci. USA* 72:3666 (1975) [Exhibit E19]. Thus, at first, TNFα itself was thought to be a potentially useful target or agent in the treatment of cancer. See, e.g., Creasey *et al.*, "Cures and Partial Regression of Murine and Human Tumors by Recombinant Human Tumor Necrosis Factor," *Cancer Res.*, 46:5687-5690 (1986) [Exhibit E22]; Selby *et al.*, "Tumour necrosis factor in man: Clinical and biological observations," *Br. J. Cancer* 56:803-808 (1987) [Exhibit E23]; Borden *et al.*, "Lymphokines and Cytokines as Cancer Treatment: Immunotherapy Realized,"

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[4] TNFα was also referred to in the scientific literature as "cachectin." See, for example, Bruce Beutler *et al.*, "Purification of cachectin, a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced raw 264.7 cells," *J. Exp. Med.*, 161:984-995 (1985) [Exhibit E20]; Kevin J. Tracey *et al.*, "Cachectin/Tumor Necrosis Factor Induces Cachexia, Anemia, and Inflammation," *J. Exp. Med.*, 167:1211-1227 (Mar. 1988) [Exhibit E21].

Cancer, 65.3 Suppl. 800-814 (1990) [Exhibit E24]. There also was some concern that targeting TNFα may increase the incidence of cancer, given its perceived role in suppressing tumor growth.

38. In the cancer setting, like other disease settings, the role of TNFα was poorly understood in the early 1990s. See, e.g., Borden at 808 ("Although it is tempting to ascribe antitumor activity to the direct antiproliferative effects, the situation is more complex. Antitumor effects *in vivo* for cells resistant to the antiproliferative effects in vitro have been demonstrated. These findings suggest an effect of TNF on host response.").

39. In some initial studies TNF was administered to cancer patients to explore whether it would provide therapeutic benefits. It did not. M.L. Sherman *et al.*, "Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: Phase I toxicity and effects on lipid metabolism," *J. Clin. Oncol.* 6:344-350 (1986) [Exhibit E25]; Christopher E. Spooner *et al.*, "The Role of Tumor Necrosis Factor in Sepsis," *Clin. Immunol. & Immunopath.* 62:S11-S17 (1992) at S12 [Exhibit E39] ("Attempts to utilize rhTNF as therapy for cancer have been unsuccessful due to the occurrence of systemic toxicity before therapeutic levels can be reached.").

40. Research performed in the late 1980s had also identified a potential role of TNFα in sepsis. Around 1986, Bruce Beutler's group injected TNFα into rats and dogs, and found that doing so caused symptoms that resembled sepsis, such as hypotension, metabolic acidosis, hemoconcentration, and, eventually, death from respiratory arrest. K.J. Tracey *et al.*, "Shock and tissue injury induced by recombinant human cachectin," *Science* 234:470-474 (Oct. 24, 1986) [Exhibit E26]; K.J. Tracey *et al.*, "Cachectin/tumor necrosis factor induces lethal shock and

stress hormone responses in the dog," *Surg. Gynecol. Obstet.* 164:415-22 (May 1987) [Exhibit E27]. Beutler hypothesized that TNFα was a mediator of sepsis. *Id.*

41. Clinical research also showed that higher levels of TNF were associated with more severe (and often fatal) cases of sepsis. See A. Waage *et al.*, "Association between tumor necrosis factor in serum and fatal outcome in patients with meningococcal disease," *Lancet* 319:355-357 (1987) [Exhibit E28]; Eric Girardin *et al.*, "Tumor Necrosis Factor and Interleukin-1 in the Serum of Children with Severe Infectious Purpura," *N. Engl. J. Med.* 319:397-400 (Aug. 18, 1988) [Exhibit E29]; J.M. Debets *et al.*, "Plasma tumor necrosis factor and mortality in critically ill septic patients," *Crit. Care Med.* 17:489-494 (Jun. 1989) [Exhibit E30]; Pierre Damas *et al.*, "Tumor necrosis factor and interleukin-1 serum levels during severe sepsis in humans," *Crit. Care Med.* 17:975-978 (Oct. 1989) [Exhibit E31]; James D. Marks, "Plasma Tumor Necrosis Factor in Patients with Septic Shock: Mortality Rate, Incidence of Adult Respiratory Distress Syndrome, and Effects of Methylprednisolone Administration," *American Review of Respiratory Disease*, 141:94-97 (1990) [Exhibit E32].

42. In preliminary animal experiments, anti-TNFα antibodies showed some potential to protect against the effects of sepsis, but only under fairly limited experimental conditions. See, for example, Bruce Beutler *et al.*, "Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin," *Science* 229:869-871 (Aug. 30 1985) [Exhibit E33]; Steven M. Opal, "Efficacy of a Monoclonal Antibody Directed against Tumor Necrosis Factor in Protecting Neutropenic Rats from Lethal Infection with *Pseudomonas aeruginosa*," *J. Infect. Dis.* 161:1148-1152 (1990) [Exhibit E34].

43. Anti-TNFα antibodies were shown to be capable of protecting animals from infusions of bacteria only if the antibodies were given before the bacterial challenge. See Ayona

T. Silva *et al.*, "Prophylactic and Therapeutic Effects of a Monoclonal Antibody to Tumor Necrosis Factor-α in Experimental Gram-Negative Shock," *J. Infect. Dis.* 162:421-427 (1990) [Exhibit E35]. This same protective effect was seen with baboons when large amounts of bacteria were infused into the animals. See, e.g., Kevin J. Tracey, "Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia," *Nature* 330:662-664 (Dec. 23, 1987) [Exhibit E36]; Yuman Fong *et al.*, "Antibodies to Cachectin/Tumor Necrosis Factor Reduce Interleukin 1β and Interleukin 6 Appearance During Lethal Bacteremia," *J. Exp. Med.* 170:1627-1633 (1989) [Exhibit E37]; L.B. Hinshaw, "Survival of primates in LD100 septic shock following therapy with antibody to tumor necrosis factor (TNF alpha)," *Circ. Shock.* 30:279-292 (Mar. 1990) [Exhibit E38]. Because the animals had been pre-treated with the antibody before the infection was introduced, it was not known whether the antibody would work in patients who were already suffering from sepsis. Later work confirmed that administering anti-TNFα antibodies was not a viable method of treating sepsis in human patients (as discussed below).

44. Before 1991, there was intense interest in identifying new treatments for sepsis, due to the large number of cases; septicemia was "the 13th leading cause of death in the United States" and "the most common cause of death among intensive care patients in the United States." Christopher E. Spooner *et al.*, "The Role of Tumor Necrosis Factor in Sepsis," *Clin. Immunol. & Immunopath.* 62:S11-S17 (1992) [Exhibit E39]. The initial TNFα studies in animal models led many to believe that TNFα played a key role in sepsis, and this led to a number of groups initiating clinical investigations to test anti-TNFα antibodies.

45. The initial work in treating baboons with anti-TNFα antibodies led to a number of other sepsis trials being carried out in humans using anti-TNFα murine antibodies. However,

these trials were either neutral or negative. For example, Exley *et al.*, reported on a Phase I trial where a murine anti-TNF antibody was given to sepsis patients. See A.R. Exley *et al.*, "Monoclonal Antibody to TNF in Severe Septic Shock," *Lancet*, 335:1275-1277 (1990) [Exhibit E40]. The results of this trial showed no benefit to the patients administered the antibody. The mortality rate was higher than one would have expected in patients with severe septic shock that received standard support therapy.

46. Not only were these early investigations not successful, some pre-clinical data showed increased mortality on treatment, which suggested again that anti-TNFα antibodies might be harmful. For example, Echtenacher *et al*, showed a beneficial effect of the presence of TNFα on septic peritonitis in rats. See Bernd Echtenacher *et al.*, "Requirement of endogenous tumour necrosis factor/cachectin for recovery from experimental peritonitis," *J. Immunol.* 145:3762-3766 (Dec. 1, 1990) [Exhibit E41].

47. Thus, while there was intense interest and hope that anti-TNFα antibodies would be effective in treating sepsis in patients by March of 1991, the initial reports of the early clinical investigations were not as promising. This suggested that the picture involving TNFα was complicated and still unknown, even for sepsis for which extensive pre-clinical work had preceded the clinical investigations.

48. Centocor also obtained approval to investigate its anti-endotoxin antibody HA-1A for sepsis, but did not proceed in those investigations because a second trial failed to confirm evidence of efficacy found in some patients in the initial trial. See, e.g., Fisher, "Investors Punish Centocor for More Bad News," N.Y. *Times* (Jan. 19, 1993) [Exhibit E42].

49. Beginning in 1991, Centocor also performed a phase I-II clinical trial for sepsis using the anti-TNF antibody cA2 (later know as infliximab and eventually commercialized as

Remicade®), but that trial did not show positive results from cA2 treatment. M. Feldmann, "Translating Molecular Insights in Autoimmunity into Effective Therapy," *Annu. Rev. Immunol.* 2009. 27:1–27 at 17 (2009) [Exhibit E43]. Even at a cA2 dose as high as 10 mg/kg, "no substantial therapeutic benefit could be demonstrated." J. Vilček, "From IFN to TNF: a journey into realms of lore," *Nature Immunology* 10:555-557 at 557 (Jun. 2009) [Exhibit E44]; *see also* J. Vilček & M. Feldmann, "Historical review: Cytokines as therapeutics and targets of therapeutics," *TRENDS in Pharmacological Sciences* 25:201-209, at 204-05, table 4 (Apr. 2004) [Exhibit E45] (treatment with cA2 conferred "no significant benefit").

50. Other anti-TNFα trials for sepsis likewise failed. Celltech's CB00006 antibody showed a 12% increase in mortality vs. control. Fisher *et al.*, "Influence of an anti-tumor necrosis factor monoclonal antibody on cytokine levels in patients with sepsis: The CB0006 Sepsis Syndrome Study Group," *Crit. Care Med.* 21:318-327 (1993) [Exhibit E46]. Celltech's anti-TNFα antibody CDP571 also showed no survival benefit versus a control. Dhainaut *et al.*, "CDP571, a humanized antibody to human tumor necrosis factor-α: Safety, pharmacokinetics, immune response, and influence of the antibody on cytokine concentrations in patients with septic shock," *Crit. Care Med.* 23: 1461-1469 (1995) [Exhibit E47].

51. Yet another anti-TNFα antibody, Bay x 1351, showed no survival benefit vs. control. Edward Abraham *et al.*, "Efficacy and safety of monoclonal antibody to human tumor necrosis factor a in patients with sepsis syndrome: A randomized, controlled, double-blind, multicenter clinical trial," *JAMA* 273:934-941 (1995) [Exhibit E48]; Jonathan Cohen & Jean Carlet, "INTERSEPT: An international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-α in patients with sepsis," *Crit. Care Med.* 24:1431–1440 (1996) [Exhibit E49]; Edward Abraham *et al.*, "Double-blind randomized controlled trial of

monoclonal antibody to human tumour necrosis factor in treatment of septic shock," *Lancet* 351:929–933 (1998) [Exhibit E50].

52. Trials with the anti-TNFα antibody fragment MAK195F failed as well. Konrad Reinhart *et al.*, "Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK195F, in patients with sepsis and septic shock: A multicenter, randomized, placebo-controlled, dose-ranging study," *Crit. Care Med.* 24:733–742 (1996) [Exhibit E51]; Konrad Reinhart *et al.*, "Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES study," *Crit. Care Med.* 29:765–769 (2001) [Exhibit E52]; Edward Panacek *et al.*, "Neutralization of TNF by a monoclonal antibody improves survival and reduces organ dysfunction in human sepsis: Results of the MONARCS trial," *Chest* 118:88S (2000) [Exhibit E53].

53. In short, by March of 1991, researchers' views about the use of anti-TNFα antibodies to treat sepsis were shifting. The experimental evidence that had motivated people to start clinical testing of sepsis had not translated into benefits in human patients. Subsequent to March of 1991, the results of several clinical investigations showed that anti-TNFα antibodies did not have the benefits expected of them from the pre-clinical experimental studies. *See* K. Reinhart, "Anti-tumor necrosis factor therapy in sepsis: Update on clinical trials and lessons learned," *Crit. Care Med.* 29:S121-S125 (2001) [Exhibit E54]. This confirmed the perspectives that I and others had in March of 1991 that the role of TNFα was very complex and still to be elucidated, despite years of experimental investigations prior to that date.

E. Even if Early Trials of Anti-TNFα Antibodies Had Shown Success in Treating Sepsis, Researchers in 1991 Would Not Have Been Motivated to Use Anti-TNFα Antibodies to Treat Chronic Inflammatory Diseases

54. In the March 1991 timeframe, I do not believe that a person of ordinary skill would have found a reason to use anti-TNFα antibodies to treat chronic, inflammatory diseases based on the work that was being done at that time in connection with testing TNFα-targeting antibodies in the treatment of sepsis.

55. First, sepsis differs significantly from other diseases that result in increased levels of TNFα, particularly chronic inflammatory diseases such as RA and Crohn's. These differences are relevant to considering whether an antibody-based regimen would be considered viable. For example, sepsis is an acute clinical condition for which a single application of a murine antibody was thought to be feasible. Sepsis involves the activation of the innate immune system, which functions to remove foreign substances from the body but does not depend on specific targeting mechanisms to do so. Autoimmune-mediated inflammatory diseases, on the other hand, involve a malfunction of the adaptive immune system, causing the body to specifically target itself in an inappropriate manner. Thus success using an anti-TNFα approach to treating sepsis would not have pointed to using the same approach to treat chronic disease because the underlying mechanisms of disease were very different.

56. Further, the role of TNFα in patients exhibiting sepsis was not well understood, even at the time that trials were being conducted with anti-TNFα antibodies in sepsis patients. The limited understanding of the role of TNFα in the progression of sepsis would not have made obvious the potential use of these anti-TNFα antibodies for diseases other than sepsis, and particularly not for chronic (rather than acute) inflammatory diseases. In the March 1991 timeframe, a person of ordinary skill simply would not have extrapolated the results of these limited clinical tests of anti-TNFα antibodies in sepsis to likely results of other tests, even for the

treatment of sepsis, and would certainly not extrapolate to the treatment of chronic inflammatory diseases.

57. A more accurate picture of the state of the art based on the results of these early clinical investigations in March of 1991 was that (i) the role of TNFα in even heavily studied disease like sepsis remained unclear, (ii) whether anti-TNFα antibodies could provide effective and safe treatments by altering TNFα levels or activity even in sepsis was not clear, and (iii) there was very little knowledge about the role of TNFα in RA and Crohn's disease. Given all of this, I do not believe a person of ordinary skill in March of 1991 would have had any basis for believing that anti-TNFα antibodies could relieve symptoms of these chronic diseases.

F. The Presence of TNFα in RA Patients Did Not Suggest, in 1991, that RA Could be Treated with Anti-TNFα Antibodies

58. I recall that there was much debate in the March 1991 timeframe about which cytokine or cytokines were the primary drivers of various disease processes and whether targeting each such cytokine would result in a viable treatment. For example, in March of 1991, TNFα was not seen as a natural target for treating RA, as other cytokines were known to be present in greater quantities in RA patients.

59. Several researchers believed different cytokines were more important targets than TNFα. See, for example, Shizuo Akira *et al.*, "A nuclear factor for IL-6 expression (NF-IL6) is a member of a C/EBP family," *EMBO J.* 9:1897-1906 (1990) [Exhibit E55] ("IL-6 may be one of the principal cytokines for generalized autoimmune disease."); Frédéric A. Houssiau *et al.*, "Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides," *Arthritis & Rheumatism* 31:784-788 (Jun. 1988) [Exhibit E56] ("in the group of patients with RA, a striking correlation between serum IL-6 activity and serum levels of C-reactive protein, α1-acid glycoprotein, α1-antitrypsin, fibrinogen, and haptoglobin was

found"); G. Buchan *et al.*, "Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1α," *Clin. Exp. Immunol.* 73:449-455 (1988) [Exhibit E57] ("There has been much speculation about the role of immune mediators in the pathogenesis of RA, especially interleukin-1 (IL-1)."); B. Combe *et al.*, "Interleukin-2 in rheumatoid arthritis: production of and response to interleukin-2 in rheumatoid synovial fluid, synovial tissue and peripheral blood," *Clin. Exp. Immunol.* 59:520-528 (1985) [Exhibit E58] ("It is possible that inadequate production of IL-2 may lead to defective T suppressor and NK activity in the rheumatoid joint. These defects could be, in part, responsible for the B cell hyperactivity with resultant immunological injury that is apparent in the rheumatoid joint."); Michael Seitz *et al.*, "Enhanced Production of Neutrophil-activating Peptide-1/Interleukin-8 in Rheumatoid Arthritis," *J. Clin. Invest.* 87:463-469 (Feb. 1991) [Exhibit E59] ("This study suggests a role for NAP-1/IL-8 in the recruitment and activation of neutrophils in rheumatoid joints . . . ."). IL-6 was also believed to play a significant role in Crohn's. Yasuo Suzuki *et al.*, "Significant increase of interleukin 6 production in blood mononuclear leukocytes obtained from patients with active inflammatory bowel disease," *Life Sciences* 47:2193-2197 (1990) [Exhibit E60] ("The present results, therefore, may indicate some important role of interleukin 6 in the pathogenesis of inflammatory bowel disease and also the potency of interleukin 6 production in mononuclear leukocytes can be an indicator of the activity of inflammatory bowel disease," and noting "no significant difference in interleukin 6 production between ulcerative colitis and Crohn's disease.").

60. It was also not apparent that specifically targeting TNFα would mediate the role or activity of other cytokines in a way that could be useful in therapy because TNFα affected

other important cytokines such as interleukin-1, and TNFα could contribute to both anti-inflammatory and pro-inflammatory effects.

61. Simply put, based on available literature at the time, a person of ordinary skill in the art would not have thought that a chronic disease such as RA or Crohn's disease could be successfully treated by administering an anti-TNFα antibody. Even in March of 1991, there was significant pessimism as to whether targeting a cytokine *in vivo* would have any beneficial effect. See, for example, Trentham *et al.*, [Exhibit E17] as discussed in paragraph 30, above.

62. Indeed, before March of 1991, while it was known that TNFα levels were elevated in certain chronic inflammatory diseases, it was not known whether TNFα caused the disease, resulted from the disease, or had some other relationship to the disease. For example, as Beutler observed when discussing TNFα in the context of HIV infection:

> It may thus be reasonably concluded that markedly elevated cachectin/TNF levels are indicative of disease. But indicative of what disease? And does the hormone cause disease, combat disease, or merely serve as an indicator? These and many other questions raised by the finding of association between elevated cachectin/TNF levels and HIV infection beg to be addressed.
>
> . . . .
>
> What is the stimulus for cachectin/TNF production? Does HIV itself provoke cachectin/TNF secretion? Or, alternatively, is cachectin/TNF produced in response to the many secondary infections that occur in such immunocompromised patients?
>
> . . . .
>
> If cachectin/TNF is, indeed, produced in response to HIV, what is its function? Does its presence retard viral proliferation, or does it

> (as in endotoxic shock) work chiefly to the detriment of its host? The latter possibility must not be discounted. The immune system and its components are imperfect in design, and abundant examples of immune-mediated injury to the host may be cited. It would be unsafe to assume that this cytokine, or any other, must fulfill a beneficial function just because it is produced.

See Beutler, "The presence of cachectin/tumor necrosis factor in human disease states," *Am. J. Med.* 85:287-288 at 287 (Sept. 1988) [Exhibit E61].

63. It was not until many years after March of 1991 that the relationship between TNFα and other cytokines in connection with RA became clear. It is now known, based on the work of Marc Feldmann and others, that TNFα plays a central role in the immune response mediated by IL-1 and other cytokines, as well as other components of the immune system. See, e.g., Marc Feldmann, "Translating Molecular Insights in Autoimmunity into Effective Therapy," *Annu. Rev. Immunol.* 27:1–27 (2009) [Exhibit E43].

64. Even with these additional insights, experiences have shown that targeting high levels of TNFα in autoimmune disorders using anti-TNFα antibodies is not straightforward. For example, elevated TNFα levels are seen in multiple sclerosis ("MS") patients. K. Selmaj *et al.*, "Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions," *J. Clin. Invest.* 87:949-954 (Mar. 1991) [Exhibit E63]. Researchers using a mouse model of MS found that anti-TNFα antibodies prevented symptoms. K. Selmaj *et al.*, "Anti-tumor necrosis factor therapy abrogates autoimmune demyelination," *Ann. Neurol.* 30:694–700 (Nov. 1991) [Exhibit E64]. But early human trials of cA2 therapy for MS were cancelled because cA2 therapy made MS symptoms worse. B.W. van Oosten, "Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2," *Neurology*, 47:1531-1534 (Dec. 1996) [Exhibit E65].

65. In sum, one of ordinary skill in the art in March 1991 would not have expected that an antibody to TNFα should be or could be used as an effective therapy for RA.

G. The Presence of TNFα in Crohn's Disease Patients Did Not Suggest, in 1991, that Crohn's Could be Treated with Anti-TNFα Antibodies

66. By March of 1991, research had suggested that T-cells were inappropriately active in Crohn's disease. See, e.g., C. Mueller *et al.*, "T-cell activation in Crohn's disease: Increased levels of soluble interleukin-2 receptor in serum and in supernatants of stimulated peripheral blood mononuclear cells," *Gastroenterology*, 98:639-46 (Mar. 1990) [Exhibit E66]. However, the link between Crohn's and elevated TNFα levels was not understood at that time. For example, in discussing the presence of elevated TNFα levels in these patients, Murch *et al.*, stated that "it is clear that further work is required to determine the site of TNFα production in chronic inflammatory bowel disease and to establish whether its excess production does play a part in mucosal inflammation." S.H. Murch *et al.*, "Serum concentrations of tumour necrosis factor α in childhood chronic inflammatory bowel disease," *Gut* 32:913-917 (Aug. 1991) [Exhibit E67].

67. Even after March 1991, there was substantial disagreement in the community about the role, if any, of TNFα in Crohn's disease. For example, one group observed:

> Although the generation of cytotoxic and antimicrobial functions by neutrophils and monocytes contributes to the host defenses, the release of tumor necrosis factor, free oxygen radicals, and IL-1 by activated neutrophils and monocytes may also contribute to mucosal damage in IBD.

Pullman *et al.*, "Enhanced Mucosal Cytokine Production in Inflammatory Bowel Disease," *Gastroenterology* 102:529-537 at 535 (1992) [Exhibit E68].

68. Other groups, however, were still focusing work on different cytokines. See e.g., J. Brynskov *et al.*, "Increased concentrations of interleukin-1β, interleukin-2 and soluble interleukin-2 receptors in endoscopical mucosal biopsy specimens with active inflammatory bowel disease," *Gut* 33:55-58 (1992) [Exhibit E18]. Further, there was speculation that TNFα found in the gut of Crohn's disease patients actually resulted from lysis of cells containing TNFα that had passed into the gut, such as neutrophils or macrophages. See C.P. Braegger *et al.*, "Tumour necrosis factor alpha in stool as a marker of intestinal inflammation," *Lancet* 339:89-91 at 90 (Jan. 11, 1992) [Exhibit E69]. This suggested that while TNFα could be an indication of Crohn's/IBD, it was not believed to be a cause of IBD.

69. In short, a person of ordinary skill in the art in March 1991 would not have expected that an antibody to TNFα would have been an effective therapy for Crohn's disease. This skepticism persisted even after 1991. I recall that during a presentation I made regarding using anti-TNFα therapy using cA2 to treat Crohn's at a meeting of the Dutch Society of Gastroenterology, several people in attendance became upset that we were using an approach which they believed was not only not helpful, but was genuinely harmful to patients. Some people in attendance even went so far as to claim that use of anti-TNFα therapy for Crohn's was unethical. I obviously disagreed, although I was cautious about the approach. Another anti-inflammatory approach, by using anti-CD-4 antibodies, had caused patient's T-cells to disappear for a at least a year, indicating that such therapies may have serious side effects. A. Stronkhorst, G.N. Tytgat, S.J. van Deventer, "CD4 antibody treatment in Crohn's disease, *Scand. J. Gastroenterol. Suppl.*194:61-65 (1992) [Exhibit E70].

70. I also note that while some TNFα-targeting therapeutics, such as Remicade®, have been shown to be effective for both Crohn's disease and RA, others have been approved

only for one of these diseases. For example, Enbrel has been approved for RA but not Crohn's disease. All of this suggests that targeting TNF to achieve a therapeutic effect must be considered in the context of a specific disease, and one cannot expect that an approach that works for one disease will work for another.

H. Prior to 1991, Researchers Had Tried But Failed to Develop Effective Treatments for RA and Crohn's Disease

1. Prior RA Treatments Had Not Been Successful

71. In March 1991, treatment for RA was generally not effective in the long term. A review article by Asherton, *et al.*, noted that aggressive treatment "certainly benefitted" RA patients "for the first few months and 'probably' for the first few years" after beginning aggressive therapies, but that patients typically could take such drugs for a few years at most. Ronald A. Asherson *et al.*, "Rheumatology," *Postgrad. Med. J.* 67:114-139 at 117 (1991) [Exhibit E71]. Asherson, *et al.*, also explained that:

> The outlook is indeed depressing in the absence of the availability of any 'targetted' therapy. It appears that despite a plethora of NSAIDs and increasing numbers of so-called 'disease modifying drugs', we are unable to influence the long term outcome of radiological progression, diminished earning capacity and increased mortality in our patients with RA in 1991.

72. This view was shared by others. See, e.g., M.J. Elliott, *et al.*, "TNFα Blockade in Rheumatoid Arthritis: Rationale, Clinical Outcomes and Mechanisms of Action," *Int'l J. Immunopharmacology* 17:141-145 (Feb. 1995) [Exhibit E72] ("Many patients remain refractory to such conventional treatments or are unable to tolerate them in the long term because of side-effects. In addition, the evidence that most of these therapies alter the progression of disease is poor, and new treatments are urgently needed.").

73. Standard RA treatments being used in the March 1991 time frame were based on non-steroidal anti-inflammatory drugs ("NSAIDs"). Asherson at 117-118 [Exhibit E71]. Other treatments used included gold compounds, penicillamine, sulphasalazine, azathioprine, and methotrexate, although these were not always effective and often came with severe side effects. *Id.* at 118-120. Experimental treatments at the time included cyclosporin A, fish oil, granulocyte colony stimulating factor, anti-lymphocyte immunotoxin, anti-interleukin receptor antibody, interleukin-2 toxin, anti-CD4 antibodies, anti-thymocyte globulin, an *E. coli* extract called "OM.8980," thymopoetin, podophyllum derivatives, thalidomide, and therafectin. *Id.* at 120-121.

74. The general goal of all of these therapies is to remove or suppress T-cells. Indeed, in March of 1991, the prevailing wisdom in RA treatment was that one had to target T-cells to provide a viable therapeutic intervention. This view is reflected in an article published in June of 1991. See, for example, Kingsley, 1991 at 178 [Exhibit E14] ("T-cell therapy is currently favored."). As these authors explained:

> [t]here is overwhelming evidence that supports a central position for the T cell in rheumatoid synovitis: immunohistological studies of RA synovium demonstrate perivascular aggregates of activated CD4 + T cells closely applied to antigen-presenting cells; T cells specific for the inducing agent from animals with experimental arthritides, such as adjuvant arthritis and streptococcal cell wall arthritis, can transfer disease; in human inflammatory arthritides of known cause (reactive arthritis) T cells specific to the inciting antigen are found in the joint. The critical role of T cells in RA is corroborated by the striking association of particular HLA class II alleles with the disease, given that these molecules restrict the presentation of antigenic peptides to $CD4^+$ T cells. Most

> convincingly, early attempts at T-cell-directed immunotherapy in humans, such as thoracic duct drainage, total lymphoid irradiation and lymphocytapheresis, while neither practical nor safe as routine therapy, resulted in disease remission. The recent beneficial use of cyclosporin A, which, primarily, interferes with T-cell function, in RA further supports their importance.

Id.

75. Kingsley *et al.* also identified a number of "studies of monoclonal antibodies directed against T-cell targets" that showed promise at the time, such as antibodies to CD4 and the IL-2 receptor. *Id.*

76. Even as late as 1993, antibodies targeting T-cells to treat RA were being pursued. See, for example, Elliott, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis & Rheumatism*, 36:1681-1690, at 1681 (Dec. 1993) [Exhibit E73], which stated that, "in most cases" up to that point in time, efforts to use "monoclonal antibodies as therapeutic agents in" the treatment of RA were "targeted specifically to the T cell, a strategy based on evidence that T cells are involved in the initiation and maintenance of RA." These T-cell-focused approaches ultimately did not prove successful.

2. Prior Crohn's Treatments Had Not Been Successful

77. Before anti-TNFα antibodies were used to treat chronic inflammatory diseases, conventional treatment consisted of administration of high dose mesalazine (in mild cases), corticosteroids (in moderate to severe disease) and immunosuppressives such as azathioprine and methotrexate.

78. None of these drugs is an ideal therapeutic for treating Crohn's. Mesalazine has a limited ability to induce remissions, and corticosteroids have many side effects and do not heal mucosal lesions in Crohn's patients. The response to treatment with azathioprine is slow and the

therapeutic efficacy of methotrexate in Crohn's disease tends to decrease with prolonged administration. Many patients do not respond to treatment with azathioprine or methotrexate. Furthermore, one of the major problems with conventional medical treatment was the inability to change the natural course of the disease. See, for example, Kirsner at 620 [Exhibit E2] ("Because none of the current therapeutic measures cures ulcerative colitis or Crohn's disease, medical treatment is never completely discontinued. Medical supervision is continued indefinitely . . . .").

79. Thus, there was a long-felt need for a treatment for Crohn's disease which overcame the problems and side effects of conventional treatments.

80. As was the case with RA, discussed above, some groups considered targeting T-cells as a way to treat Crohn's disease. A. Stronkhorst *et al.*, "CD4 antibody treatment in Crohn's disease," *Scand. J. Gastroenterol. Suppl.* 194:61-65 (1992) [Exhibit E70]. However, this approach unexpectedly removed T-cells for about a year, which caused concerns.

I. Researchers Were Surprised that RA and Crohn's Could Be Effectively Treated With Anti-TNFα Antibodies

81. Prior to the publication of the initial successes of cA2, there was widespread skepticism that targeting TNFα using anti-TNFα antibodies could be a successful treatment method for RA. However, the successes of cA2 changed the attitudes of those working in the field.

82. These views started to change when the results of the clinical investigations involving trials with cA2 were published at the end of 1993. For example, Michael Elliott *et al.*'s paper on the treatment of rheumatoid arthritis concluded:

> The results obtained . . . have important implications, both scientifically and clinically. At a scientific level, the ability of the neutralizing antibody, cA2, to reduce acute-phase protein

> synthesis, reduce the production of other cytokines such as IL-6, and significantly improve the clinical state demonstrates that it is possible to interfere with the cytokine network in a useful manner without untoward effects. Due to the many functions and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce the production of other cytokines and of themselves, there had been some pessimism as to whether targeting a single cytokine in vivo would have any beneficial effect. This view is clearly refuted.

"Treatment of Rheumatoid Arthritis with chimeric monoclonal antibodies to tumour necrosis factor α," *Arthritis & Rheumatism*, 36:1681-1690 (Dec. 1993) [Exhibit E73].

83. Another paper by Elliott's group, published in 1994, noted that "[t]he data show that patients with flares of rheumatoid arthritis can be successfully managed with cA2, which provides an alternative to traditional treatments such as hospital admission, high-dose corticosteroids, or cytotoxic therapy." Michael Elliott *et al.*, "Repeated therapy with monoclonal antibody to tumor necrosis factor α (cA2) in patients with rheumatoid arthritis," *Lancet* 344:1125-27 (Oct. 22, 1994) [Exhibit E74].

84. Even with these clinical results involving RA, skepticism remained regarding the feasibility of using antibodies to TNFα to treat Crohn's disease For example, according to Breese *et al.*:

> There are conflicting reports in the literature on the production of TNF-α in inflamed mucosa. TNF-α levels are elevated in the serum and stools of patients with active inflammatory bowel disease; in inactive disease, levels decrease to those of control patients. By spot enzyme-linked immunosorbent assay, a higher frequency of mucosal mononuclear cells from patients with Crohn's disease and ulcerative colitis secrete TNF-α than from control patients.

> Immunohistochemistry shows an increase in TNF-α-immunoreactive cells in Crohn's disease and ulcerative colitis, which is confined to the mucosa in the latter. However, in contrast, Capello et al. showed by in situ hybridization that 11 of 15 patients with inflammatory bowel disease had messenger RNA for TNF-α in colonic mucosa, as did 4 of 9 control patients. Using polymerase chain reaction (PCR), Stevens et al. detected TNF-α transcripts in all samples, regardless of disease, whereas Isaacs et at. could not detect TNF-α messenger RNA in biopsy specimens from most patients with inflammatory- bowel disease or controls.

See Emma J. Breese *et al.*, "Tumor necrosis factor α-producing cells in the intestinal mucosa of children with inflammatory bowel disease," *Gastroenterology* 106:1455-1466 (Jun. 1994) [Exhibit E75].

85. Breese *et al.* then observed:

> In summary, we have documented an increase in the frequency of TNF-α-secreting cells in gut inflammation with the largest increase found in active Crohn's disease. There was no relationship between the effect of treatment or histological improvement and the frequency of TNF-α-secreting cells. We have also shown that clinical remission may be accompanied by underlying immunologic activity.

Id. at 1465.

86. In other words, while many of the *in vivo* activities of TNFα match the changes found in IBD, researchers continued to consider use of anti-TNFα antibodies to treat Crohn's controversial.

87. I was involved in the first use of cA2 to treat Crohn's disease in a human. *See* Bert Derkx *et al.*, "Tumour-necrosis-factor antibody treatment in Crohn's disease," *Lancet*

342:173-74 (July 17, 1993) [Exhibit E76]. My team and I were treating a young patient at the AMC who was suffering from debilitating Crohn's. *Id.* She had not responded well to what was standard therapy at the time of prednisone, mesalazine, aspirin, azathioprine, and beclomethasone. *Id.* We administered two doses of cA2 to her, which relieved her symptoms for three months. *Id.* A striking and unexpected finding in this first patient and in subsequent patients treated with cA2 was the rapid induction of the clinical response, with an immediate reduction of other inflammatory mediators such as IL-6 and CRP. It was also for the first time that a therapy in Crohn's disease showed a significant effect on mucosal lesions (mucosal healing is now known as "deep remission").

88. Based on this positive result, we conducted a ten-patient trial using cA2 to treat Crohn's. *See* Hendrik M. van Dullemen, "Treatment of Crohn's Disease with Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)," *Gastroenterology* 109:129-135 (1995) [Exhibit E77].[5] The induction of mucosal healing was considered to be so spectacular and unexpected, that a leading journal, *Gastroenterology*, placed the endoscopic photographs on the cover. *Gastroenterology*, 109 (Jul. 1995). Mucosal healing later was proved to be strongly correlated to long-term outcome such as exacerbations, hospital admissions and surgeries, completely changing the long-term quality of life of Crohn's disease patients. These successes quickly dispelled doubts about the feasibility of targeting TNFα. cA2 was the first therapeutic that provided an effective treatment for Crohn's and altered the progression of the disease, rather than simply partial amelioration of symptoms.

89. Ultimately, larger studies confirmed the value of targeting TNFα. The FDA approved cA2 for treatment of moderate-to-severe Crohn's in August 1998, and for treatment of

[5] This paper has subsequently become one of the most cited papers regarding treatment of Crohn's.

RA on November 10, 1999. See FDA Approval Letter for Infliximab (Aug. 24, 1998) [Exhibit E62]; FDA Approval Letter for Infliximab (Nov. 10, 1999) [Exhibit E100]. As with Crohn's, treatment with cA2 altered the progression of RA, instead of just providing partial amelioration of symptoms.

III. CONCLUSIONS

90. Based on my knowledge in the field of treatments of RA and Crohn's in March of 1991, I do not believe that a person of ordinary skill in the art would have believed that the effective treatment of either RA or Crohn's using an anti-TNFα antibody would have been possible. Instead, I believe that such a person would have been skeptical that an intervention targeting TNF-α would prove to be effective in treating either of these diseases.

91. I also believe that the person of ordinary skill in the art would have had substantial doubts in March of 1991 as to the viability of treatment of these chronic diseases using an anti-TNFα antibody. The factors that support my conclusion include:

- the complexity that was known to exist in these diseases, and the lack of any clear indication that TNFα played a defined or conclusive role in the progression or amelioration of either RA or Crohn's;
- the complexity that was known to exist in the relationship between cytokines such as TNFα and other cytokines present at elevated or altered levels in patients afflicted with RA and Crohn's, and the known redundancy in these systems of cytokines;
- the prevailing wisdom that interventions in treatment of RA should target T-cells or other factors, rather than TNFα; and
- the failure of clinical interventions using anti-TNFα antibodies in other diseases where a more express linkage between TNFα and the disease was believed to exist (*e.g.*, sepsis, cancer).

92. I, therefore, do not believe that a method of treating RA or Crohn's would have been obvious to a person of ordinary skill in the art in March of 1991, based on knowledge or possession by that person of any particular anti-TNF-α antibody.

I, Sander van Deventer, do hereby declare and state, that all statements made herein of my own knowledge are true to the best of my knowledge, information, and belief, formed after reasonable inquire under the circumstances; and further that these statements were made with the knowledge that willfull false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Professor Sander van Deventer

Date: December 18, 2013.

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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TABLE OF EVIDENCE INCLUDED WITH BRIEF

In accordance with MPEP § 1205.02, the following items of evidence previously made of record are cited in this Appeal Brief and are being transmitted to the Patent Trial and Appeal Board (PTAB) concurrently with this Appeal Brief.

Document	Originally Submitted
Declaration of John Ghrayeb, Ph.D. under 37 C.F.R. § 1.132	December 19, 2013
Declaration of Professor Sander Jan Hendrik van Deventer under 37 C.F.R. § 1.132	December 19, 2013

Also pursuant to MPEP § 1205.02, Patent Owner has included as Appendix B Patent Owner's Listing of Undisputed or Admitted Facts (cited herein as "SOF") with numbered paragraphs and references to the record in this proceeding.

So that family relations may be easily visualized, Patent Owner has included in Appendix C a graphical representation of the '471 Patent and other related patents and applications which are relevant to this appeal.

I. REAL PARTY IN INTEREST [37 C.F.R. § 41.37(c)(1)(i)]

Pursuant to 37 C.F.R. § 41.37(c)(1)(i), the real parties in interest are identified as the owners of U.S. Patent No. 6,284,471 ("the '471 Patent"), Janssen Biotech, Inc. and New York University (collectively referred to as "Patent Owner").

II. RELATED PROCEEDINGS [37 C.F.R. § 41.37(c)(1)(ii)]

Pursuant to 37 C.F.R. § 41.37(c)(1)(ii), related appeals, interferences, and trials are identified as follows.

The '471 Patent is the subject of litigation pending in the United States District Court for the District of Massachusetts. *See Janssen Biotech, Inc. et al v. Celltrion Healthcare Co., Ltd. et al.*, Civil Action No. 1:15-cv-10698-MLW (D. Mass. 2015) (the "2015 Massachusetts Action"). Specifically, on March 6, 2015, Janssen Biotech, Inc. and New York University (collectively, the Patent Owner of the '471 Patent) filed a complaint for patent infringement (including of the '471 Patent) against Celltrion Healthcare Co., Ltd.; Celltrion, Inc.; and Hospira, Inc. *See* D.I. No. 1, 1:15-cv-10698 (Mar. 6, 2015).

On March 16, 2015, Patent Owner filed a motion to stay the 2015 Massachusetts Action with respect to the '471 Patent pending resolution of the present reexamination proceeding involving the '471 Patent. *See* D.I. No. 8, 1:15-cv-10698 (Mar. 16, 2015). On April 9, 2015, the defendants filed an opposition to the motion to stay. *See* D.I. No. 41, 1:15-cv-10698 (Apr. 8, 2015).

On April 8, 2015 in the 2015 Massachusetts Action, Patent Owner moved for partial summary judgment that the "notice of commercial marketing" provided by Celltrion Healthcare Co., Ltd. and Celltrion, Inc. (collectively "Celltrion") is legally ineffective under the Biologics Price Competition and Innovation Act ("BPCIA"), 42 U.S.C. § 262(*l*)(8)(A), and also for a preliminary and permanent injunction precluding Celltrion from entering the market for at least 180 days after approval of its proposed biosimilar to Remicade® (infliximab) and after a legally effective notice of commercial marketing. *See* D.I. No. 34, 1:15-cv-10698 (Apr. 8, 2015).

On April 29, 2015 in the 2015 Massachusetts Action, Celltrion filed a combined opposition to Patent Owner's motion for partial summary judgment, opposition to Patent Owner's motion for a preliminary injunction, and cross-motion for summary judgment that Celltrion had properly provided "notice of commercial marketing" under the BPCIA. As of June 15, 2015, the motions were fully briefed.

The '471 Patent was previously the subject of a declaratory judgment action filed in the United States District Court for the District of Massachusetts by two of the defendants in the

2015 Massachusetts Action (*i.e.*, Celltrion Healthcare Co., Ltd. and Celltrion, Inc.). *See Celltrion Healthcare Co. Ltd., et al. v. Janssen Biotech, Inc.*, Civil Action No. 1:14-cv-11613 (D. Mass., filed Mar. 31, 2014). The plaintiffs voluntarily dismissed that action without prejudice on October 23, 2014. *See* D.I. No. 33, 1:14-cv-11613 (Oct. 23, 2014).

The '471 Patent also was previously the subject of a declaratory judgment action filed by the third of the three defendants in 2015 Massachusetts Action (*i.e.*, Hospira, Inc.). *See Hospira, Inc. v. Janssen Biotech, Inc., et al.*, Civil Action No. 14-cv-07049 (S.D.N.Y., filed Aug. 29, 2014). The court dismissed that action based on its holding that the plaintiff lacked standing. *See* D.I. No. 60, 14-cv-07049 (Dec. 1, 2014).

Pursuant to the BPCIA, on February 5, 2015, Celltrion served Patent Owner with a Detailed Statement Pursuant to the BPCIA (42 U.S.C. § 262(*l*)(3)(B)(ii)(I)) that included invalidity contentions relating to the '471 Patent. Patent Owner requested authorization from Celltrion to provide the invalidity contentions in the Detailed Statement to the Office in this proceeding, but Celltrion declined to give Patent Owner the authorization to do so, stating that provision of the Detailed Statement to the Office would violate the BPCIA and that the prior art references cited in the Detailed Statement had previously been submitted to the Office in Information Disclosure Statements.

III. SUMMARY OF THE CLAIMED SUBJECT MATTER [37 C.F.R. § 41.37(c)(1)(iii)]

Pursuant to 37 C.F.R. § 41.37(c)(1)(iii), the claimed subject matter of each independent claim of the '471 Patent involved in this appeal is identified as follows.

Claim 1 relates to a chimeric antibody having a human constant region, and a non-human variable region with the amino acid sequence set forth in either SEQ ID NO: 3 or 5. Support for claim 1 can be found, for example, in the current specification[1] of the '471 Patent at pages 15-25 of the October 2014 Amendment, as modified by paragraphs 12-13 on page 6 of the April 2015 Amendment;[2] SEQ ID NO:3; SEQ ID NO:5; Figures 16A and B.[3]

Claim 3 relates to a chimeric antibody having a human constant region, and a non-human variable region comprising a polypeptide encoded by the nucleic acid sequence set forth in either SEQ ID NO: 2 or 4. Support for claim 3 can be found, for example, in the current specification of the '471 Patent at pages 15-25 of the October 2014 Amendment, as modified by paragraphs 12-13 on page 6 of the April 2015 Amendment; SEQ ID NO: 2; SEQ ID NO: 4; Example XIV (at pages 78-79 of the October 2014 Amendment);[4] Figures 16A and B.

Claim 5 relates to a chimeric antibody having a human constant region, and a non-human variable region with the light chain variable regions having the amino acid sequence set forth in SEQ ID NO: 3 and the heavy chains variable regions having the amino acid sequence set forth in SEQ ID NO: 5. Support for claim 5 can be found, for example, in the current specification of the '471 Patent at pages 15-25 of the October 2014 Amendment, as modified by paragraphs 12-13 on page 6 of the April 2015 Amendment; SEQ ID NO: 3; SEQ ID NO: 5; Figures 16A and B.

Claim 7 relates to a chimeric antibody of subtype IgG1 having a human constant region, and a non-human variable region comprising a polypeptide encoded by the nucleic acid sequence

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[1] The current specification of the '471 Patent is set forth on pages 3 to 99 of Reexamination Control No. 90/012,851 ("the '851 Reexamination") File Wrapper, Amendment After Final Rejection under 37 C.F.R. § 1.116 dated October 10, 2014 ("October 2014 Amendment"), and was slightly modified in response to issues raised by the Examiners under 35 U.S.C. § 112, as shown on pages 3 to 8 of the Amendment After Final Rejection under 37 C.F.R. § 1.116 dated April 13, 2015 ("April 2015 Amendment").

[2] The corresponding disclosure in the '471 Patent as originally issued appears at 9:36-15:45.

[3] The sequence IDs and figures are the same in the specification as originally issued and the current specification. The current figures are found at Attachment A to the April 2015 Amendment.

[4] The corresponding disclosure in the '471 Patent as originally issued is Example XIII (at 46:1-56).

set forth in SEQ ID NO: 2 or 4. Support for claim 7 can be found, for example, in the current specification of the '471 Patent at pages 15-25 of the October 2014 Amendment, as modified by paragraphs 12-13 on page 6 of the April 2015 Amendment; the first full paragraph on page 30 of the October 2014 Amendment;[5] SEQ ID NO:2; SEQ ID NO:4; Figures 16A and B.

The '471 Patent disclosure as amended thus provides a sufficient written description of each of the claims of the '471 Patent, and fully enables one skilled in the art to practice the invention defined by these claims.

[5] The corresponding disclosure in the '471 Patent as originally issued appears at 18:21-36.

IV. ARGUMENT [37 C.F.R. § 41.37(c)(1)(iv)]

A. Summary of the Argument

This appeal seeks reversal of the erroneous obviousness-type double patenting ("ODP") rejections of claims in U.S. Patent No. 6,284,471 (hereinafter "the '471 Patent") over claims in two related patents, U.S. Patent No. 5,698,195 ("the '195 Reference Patent") and U.S. Patent No. 5,656,272 ("the '272 Reference Patent") (collectively the "Reference Patents").

The '471 Patent issued from U.S. Application No. 08/192,093 (hereinafter "the '093 Application"), filed on February 4, 1994. Although originally designated a continuation-in-part application, the '093 Application is now properly denominated as a divisional application of U.S. Application Serial No. 08/013,413 (hereinafter the "Parent Application"), filed on February 2, 1993.[6] The '093 Application claims the benefit of and incorporates by reference the entire disclosure of the Parent Application. *Id.* The Reference Patents also claim, *inter alia*, the benefit of the Parent Application, and each incorporates by reference the entire disclosure of the Parent Application.

The rejections should be reversed for two independent reasons:

First, the obviousness-type double patenting rejections of the claims of the '471 Patent based upon the Reference Patents are precluded by 35 U.S.C. § 121, and must be reversed. During the examination of the Parent Application, the Office applied a five-way restriction requirement. In response to that restriction, the Patent Owner prosecuted claims within non-elected Group I of the restriction in the '093 Application, which is now properly denominated as a divisional of the Parent Application, and which issued as the '471 Patent. Appendix B, Patent Owner's Listing of Undisputed or Admitted Facts (cited herein as "SOF ¶ <no.>") ¶¶ F1-F2, F24-F26, F62-F73. Each of the applications issuing as the Reference Patents was in turn prosecuted to secure examination and allowance of claims in elected Group IV of the restriction applied during examination of the Parent Application. *Id.* ¶¶ F1-F2, F9-F10, F12-F13, F19. As such,

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[6] The '093 Application as originally filed included certain information unnecessary to support any of the claims of the '471 Patent, but by amendments entered during this reexamination, that unnecessary disclosure was removed. *See* Appendix B, Statement of Admitted or Undisputed Facts ("SOF") ¶¶ F27-F28, F62-F73. The Examiners now agree that the '093 Application is properly designated a divisional application. *See* '851 Reexamination, October 2014 Amendment at 3; SOF ¶ F73.

each Reference Patent stems from an application "with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement," as specified in Section 121. As it is undisputed that consonance with the restriction requirement applied in the Parent Application has been maintained in both the Reference Patents and the '471 Patent, therefore the safe harbor of Section 121 precludes use of the claims of such Reference Patents against the claims of the '471 Patent to support any ODP rejection. *Id.* ¶¶ F1-F2, F15, F21, F55.

The Examiners' refusal to give effect to Section 121 rests upon two errors of law. The first error is their contention that Section 121 applies only if the reference patent claims issue from "divisional applications." The second error is their contention that the '471 Patent claims are not subject to Section 121 because the '093 Application, as filed, was not denominated a "divisional application." However, nothing in the language of or law governing Section 121 requires either of these as a condition of finding that the safe harbor of Section 121 applies.

Second, independent of Patent Owner's entitlement to the Section 121 safe harbor, the ODP rejections should be reversed because the Examiners have erroneously refused to apply the appropriate two-way test for determining whether the claims of the '471 Patent and the Reference Patents are obvious in view of each other. It was the restriction requirement imposed by the Office in the Parent Application—not any voluntary action taken by Patent Owner—that precluded Patent Owner from securing examination of both groups of claims in a single application, leaving Patent Owner with no choice but to pursue them in separate applications. Consistent with that restriction requirement, Patent Owner diligently and reasonably prosecuted the Group I claims in the '093 Application leading to the '471 Patent, and the Group IV claims in the applications leading to the Reference Patents, ultimately prevailing in its effort to gain commercially significant protection for these revolutionary new antibody products and treatment methods. While it took longer to gain allowance of the antibody claims of Group I of the restriction, and for the '471 Patent to issue, than to obtain issuance of the treatment claims of Group IV of the Reference Patents, the length of the '471 Patent's prosecution was due to the actions taken by the Office, not the Patent Owner. After first requiring restriction, the Office took strikingly different positions during examination on the patentability of the antibody claims of Group I leading to the '471 Patent than it did on the patentability of the therapeutic methods of the Group IV applications leading to the Reference Patents. Because the later issuance of the

'471 Patent relative to the Reference Patents was solely due to the positions and actions taken by the Office during the examinations that led to the '471 Patent, Patent Owner is entitled to have the two-way test used to determine all ODP issues as to the '471 Patent. And here, when that test is applied, it is beyond dispute that no ODP rejection is proper, as the Examiners have not taken issue with the nonobviousness evidence of record that demonstrates that one with knowledge of the claimed antibodies of the '471 Patent would have had no way of expecting that they could serve as effective treatments in humans, much less that they could serve as revolutionary treatments for rheumatoid arthritis or Crohn's disease, as claimed in the Reference Patents.[7]

In this case, where Patent Owner has complied with both the letter and spirit of the law, there is no legitimate basis for denying Patent Owner the benefit of Section 121's safe harbor for the '471 Patent claims, or for refusing to evaluate ODP issues as to those claims under the two-way test. Accordingly, Patent Owner respectfully requests that the Board reverse the rejections for ODP and direct the Examiners to issue a reexamination certificate confirming the patentability of the '471 Patent's claims 1-7.

B. Statement of Issues Presented in this Appeal

The issues presented in this appeal are as follows:

(1) Whether, notwithstanding the prohibitions of 35 U.S.C. § 121, the Examiners erred in using the claims of the Reference Patents, which claims are all consonant with the originally-elected Group IV of the restriction in the Parent Application, to reject the claims of the divisional '471 Patent, which was filed as a result of the restriction in the Parent Application and whose claims are all consonant with non-elected Group I of that restriction?

(2) Whether under the facts of this case, where it is undisputed that the claims of the Reference Patents are not rendered obvious by the claims of the '471 Patent, the Examiners erred in declining to apply the two-way test for determining obviousness-type double patenting, when the claims of the Reference Patents and of the '471 Patent could not have been prosecuted in a single application due to

[7] *See* Declaration of John Ghrayeb, Ph.D. under 37 C.F.R. § 1.132 ¶¶ 18-44; Declaration of Professor Sander Jan Hendrik van Deventer under 37 C.F.R. § 1.132 ¶¶ 14-70.

the imposition of a restriction requirement in the Parent Application, and when the Patent Owner diligently filed and reasonably prosecuted the application leading to the '471 Patent?

C. Brief Summary of Relevant Facts

Nearly all of the operative facts implicated in this appeal are undisputed and support reversal of the rejections for obviousness-type double patenting. A Patent Owner's Statement of Undisputed or Admitted Facts from the record of this reexamination proceeding is presented in Appendix B hereto.

1. Summary of Facts Relevant to Entitlement of the '471 Patent Claims to Section 121

During examination of the Parent Application, the Office applied a five-way restriction requirement. In response to that restriction, Patent Owner elected to prosecute claims in Group IV,[8] first in the Parent Application itself, and then in the continuing applications leading to the Reference Patents.[9] The claims that issued in the Reference Patents all fall within Group IV of the restriction in the Parent Application.[10] Patent Owner prosecuted claims falling within the non-elected Group I invention of this restriction in the '093 Application that issued as the '471 Patent.[11] The issued claims of the '471 Patent all fall within Group I.[12]

During this reexamination proceeding, the claims that are the subject of this appeal were repeatedly rejected for obviousness-type double patenting in view of claims 1-16 of the '195 Reference Patent and claims 1-7 of the '272 Reference Patent, either alone or in conjunction with certain secondary references. These rejections were premised on the Examiners' position that, because the applications issuing as the Reference Patents were continuation-in-part applications—and not "divisionals" of either the Parent Application or of the '093 Application—they were "not filed as a result of restriction requirement made between the claims of these

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[8] *See* SOF ¶¶ F1-F6.

[9] *See, inter alia*, SOF ¶¶ F17, F23.

[10] *See* SOF ¶¶ F15-F16, F21-F22.

[11] *See* SOF ¶¶ F25-F26.

[12] *See* SOF ¶¶ F55-F56.

patents," and are thus are not precluded from being used as references against the '471 Patent claims, notwithstanding 35 U.S.C. § 121.[13]

In response, the Patent Owner explained that the plain language of 35 U.S.C. § 121 does not require a reference patent to issue from a divisional application. A reference patent may issue from the original application subject to the restriction, or from a continuing application of that application, such as those that led to the '195 and '272 Reference Patents, that is filed to obtain examination of claims directed to the originally elected invention (here Group IV), provided, as here, the issued claims stemming from those applications maintain consonance with their original restriction groups.[14]

The final rejection also took the position that the '471 Patent claims do not qualify under the safe harbor of Section 121 because, when the '093 Application was filed, it was not denominated a "divisional" application. In response, Patent Owner explained the record was replete with evidence showing the '093 Application, which was filed after the restriction had been applied in the Parent Application, was prosecuted to secure examination of claims to the non-elected Group I invention in response to the restriction applied in the Parent Application.[15]

The record shows that Patent Owner and the Examiners agree that:

(a) the Office applied a restriction requirement in the Parent Application and never withdrew or modified that requirement; SOF ¶¶ F1-F2, F8;

(b) Patent Owner prosecuted the applications leading to the Reference Patents to gain allowance of claims falling only within originally elected Group IV of the restriction in the Parent Application; *id.* ¶¶ F12-F17, F19-F23;

(c) Patent Owner prosecuted the '093 Application that led to the '471 Patent to gain allowance of claims falling only within Group I of the restriction in the Parent Application; *id.* ¶¶ F24-F26, F55-F56;

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[13] '851 Reexamination, Non-Final Action dated Sept. 6, 2013 at 5-7; '851 Reexamination, Final Action dated Aug. 26, 2014 at 9, 15-16, 18-20; '851 Reexamination, Final Action dated Feb. 12, 2015 ("Final Action") at 9-20; '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2.

[14] *See* '851 Reexamination, Interview Summary of Nov. 1, 2013 at 8; '851 Reexamination, Amendment dated Dec. 19, 2013 at 45-52; '851 Reexamination, October 2014 Amendment at 128-138.

[15] '851 Reexamination, October 2014 Amendment at 136-137.

(d) each of the applications resulting in the Reference Patents and the '471 Patent as filed contained subject matter not contained in the Parent Application, and hence were designated on filing as "continuation-in-part" applications; *id.* ¶ F27;

(e) none of the added matter in the '093 Application relative to the Parent Application was necessary to support any claim of the '471 Patent as issued, or was ever the subject of a claim in the '471 Patent or the Reference Patents; *id.* ¶¶ F28, F63-F64;

(e) amendments entered during this reexamination delete the additional subject matter added to the '093 Application that was unnecessary to support any claim of the '471 Patent, so that the disclosure of the '471 Patent now conforms to that of the Parent Application; *id.* ¶¶ F62-F73;

(f) the '093 Application is now properly denominated a divisional of the Parent Application; *id.* ¶ F73;

(g) the claims of the Reference Patents that are being relied upon to support the outstanding ODP rejections are consonant with Group IV of the restriction requirement applied in the Parent Application; *id.* ¶¶ F15, F21; and

(h) the claims of the '471 Patent now being rejected on the basis of ODP are consonant with Group I of the restriction requirement applied in the Parent Application; *id.* ¶ F55.

2. Summary of Facts Relevant to Patentability Distinct Natures of the '471 Patent Claims and the Claims in the Reference Patents

As noted above, the ODP rejections of the claims under appeal rest on the Examiners' conclusions that Section 121 does not preclude use of the Reference Patents against the '471 Patent, and that if a one-way test is used, the claims of the '471 Patent represent obvious variations of those of the Reference Patents.[16] In response, the Patent Owner demonstrated that, even without the benefit of the safe harbor, the record supports Patent Owner's position that it is entitled to the use of the two-way test, and that probative, uncontested evidence shows that under this test the claims in the '471 Patent and those in the Reference Patents are clearly not obvious in view of each other. *Id.* ¶ F61.

[16] '851 Reexamination, Non-Final Action dated Sept. 6, 2013 at 5-9; '851 Reexamination, Final Action dated Aug. 26, 2014 at 20-23; Final Action at 24-25.

In particular, the record also shows that the '471 Patent claims must be evaluated relative to the claims in the Reference Patents under the two-way test. The '471 Patent claims issued later than the claims in the Reference Patents because the Office compelled Patent Owner to prosecute these claims in a separate application, and then took positions in the prosecution of that application (the '093 Application) that ended up resulting in a later issuance of the '471 Patent. SOF ¶¶ F1-F2, F9-F10, F12-F13, F19, F24-F26. The Patent Owner did not delay issuance of the '471 Patent's claims, but to the contrary, followed standard Office procedures to promptly and diligently prosecute these claims to allowance. *Id.* ¶¶ F24-F54. Thus, the fact that the '471 Patent claims issued later than the Reference Patent claims is entirely a consequence of the positions and actions taken by the Office.

When the proper two-way test is applied, it cannot be fairly concluded from the claims of the '471 Patent that it would be obvious to use the claimed "methods for treating an animal by administering a pharmaceutical composition containing an antibody" to treat rheumatoid arthritis or Crohn's disease, as required by the claims of the Reference Patents. *See* § IV.E.3, *infra*. This evidence includes declarations from qualified experts and confirms the independent and distinct natures of the Group IV inventions claimed in the Reference Patents as compared to the Group I inventions claimed in the '471 Patent. SOF ¶ F61; *see also* § IV.E.3(a), *infra*. This evidence is also consistent with the original determination by the Office that the inventions claimed in the '471 Patent are patentably distinct from the inventions claimed in the Reference Patents, which was the predicate justifying the Office's original requirement for restriction in the Parent Application. Indeed, the Examiners have not disputed that the evidence of record shows that under the two-way test for obviousness-type double patenting, the claims of the '471 Patent are patentably distinct from the claims in the Reference Patents.

Therefore, even if the '471 Patent claims are not found subject to Section 121, they are not unpatentable based on the claims of the Reference Patents for reasons of obviousness-type double patenting.

D. The Claims of the '471 Patent are Protected from Obviousness-Type Double Patenting Rejections by the Safe Harbor of 35 U.S.C. § 121

Section 121 of title 35, United States Code, provides a safe harbor from obviousness-type double patenting rejections to inventors required to restrict an application claiming multiple

"independent and distinct" inventions into separate applications to secure examination of each invention. *See Applied Materials v. Advanced Semiconductor Materials*, 98 F.3d 1563, 1568-69 (Fed. Cir. 1996) ("Section 121, viewed overall, assures that the technicalities of restriction practice are not elevated from their purpose of examination convenience to a potential taint on the validity of the ensuing patents."). As explained below, the '471 Patent is a divisional of the Parent Application, and enjoys the protections of the Section 121 safe harbor relative to the claims in each of the Reference Patents.

1. The '471 Patent is a Divisional that Qualifies for the Statutory Safe Harbor

(a) The Office Has Confirmed the '471 Patent's Status as a Divisional of the Parent Application

There is no dispute that the '471 Patent, which issued from the '093 Application, is a divisional of the Parent Application. The record shows that Patent Owner presented claims to the non-elected Group I invention for examination in the '093 Application in response to the restriction and the guidance of the Office to do so. SOF ¶¶ F1-F2, F25-F26, F33. The '471 Patent also was amended during this proceeding, in full compliance with rules applicable to this proceeding, to conform its disclosure to that of the Parent Application. Indeed, the Director of the Central Reexamination Unit has confirmed the propriety of the amendments and the designation of the '093 Application as a divisional, and the Examiners have expressly recognized its status as such.[17] *See id.* ¶¶ F62-F73. Consequently, the '093 Application is now properly denominated a divisional of the Parent Application in correspondence with the evidence in the record that it was prosecuted to secure examination of the non-elected Group I invention in response to the restriction in the Parent Application. *See id.* ¶¶ F1-F2, F24-F26.

(b) As a Divisional Resulting from the Restriction in the Parent Application, the '471 Patent Falls within the Safe Harbor of 35 U.S.C. § 121

The patent law, through 35 U.S.C. § 121, provides safe harbor to divisional patents such as the '471 Patent. To determine whether a patent falls within the safe harbor, one necessarily begins with the text of the statute. *BP Am. Prod. Co. v. Burton*, 549 U.S. 84, 91 (2006) ("We

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[17] *See* '851 Reexamination, Decision Granting Petition Under 37 C.F.R. § 1.181 dated Nov. 25, 2014; *see also* 37 C.F.R. § 1.530(d)-(e); MPEP § 2234.

start, of course, with the statutory text."); *Wyeth v. Kappos*, 591 F.3d 1364, 1369 (Fed. Cir. 2010). Here, the statute provides:

> [1] If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. [2] If the other invention is made the subject of a divisional application which complies with the requirements of section 120 it shall be entitled to the benefit of the filing date of the original application. [3] [a] A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts [b] against a divisional application or against the original application or any patent issued on either of them, [c] if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. § 121 (bracketed parsing designations added).

Sentence [3] of Section 121 specifies the circumstances under which the safe harbor applies. It begins by identifying in clause [a] the following two categories of patents that may not be used against an eligible safe harbor patent for ODP purposes:

(i) patents issuing on the "application with respect to which a requirement for restriction under this section has been made;" and

(ii) patents issuing "on an application filed as a result of such a requirement."

The Reference Patents in this appeal—the '195 and '272 Reference Patents—fall within both categories. To begin, they constitute patents issuing on "application[s] with respect to which a requirement for restriction under this section has been made" because they arise from continuing applications of the Parent Application in which the Office required restriction. *See* SOF ¶¶ F1-F2, F9-F10; *see also Geneva Pharms. v. GlaxoSmithKline, PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003) ("Section 121 states: A patent issuing on an application with respect to which a requirement for restriction under this section has been made . . . shall not be used as a reference . . . . Thus, if the [challenged] patents and the [reference] patent trace their lineage back to a common parent which was subject to a restriction requirement, then § 121 intervenes to prevent a nonstatutory double patenting rejection.") (quotation marks omitted).

They also qualify as patents issuing on "application[s] filed as a result of such a requirement" (*i.e.*, the restriction requirement) because the words "as a result of" in Section 121 are construed broadly to cover any application filed "due to the administrative requirements imposed by the Patent and Trademark Office." *See Boehringer Ingelheim Int'l GmbH v. Barr Labs. Inc.*, 592 F.3d 1340, 1352 (Fed. Cir. 2005) ("the 'as a result of' requirement applies to the challenged patent as well as the reference patent"); *id.* at 1353 n.3 ("We believe that this interpretation of the 'as a result of' requirement is too narrow. The child application was 'due to the administrative requirements imposed by the Patent and Trademark Office.'") (internal citation omitted).

Clause [b] of the third sentence of Section 121 defines the categories of applications and patents against which the Reference Patents may not be used: (i) divisional applications; (ii) original applications; or (iii) any patents issued on either. Clause [b] provides safe harbor to the claims of the '471 Patent because the evidence demonstrates the '093 Application was prosecuted to secure examination of the non-elected Group I invention in response to the restriction, and has been, by a duly authorized amendment conforming the '471 Patent's disclosure to that of the Parent Application, designated a divisional application. In other words, the '093 Application is a divisional application, and the '471 Patent is a patent that issued from the '093 Divisional Application.[18] SOF ¶¶ F62-F73. Thus, in the absence of any exception (and, as explained below, no exceptions are present here), the plain language of Section 121 precludes the Reference Patents from being used against the '471 Patent to support any proper ODP rejection.

2. The MPEP's Limited Exceptions to the Safe Harbor's Protections Do Not Apply to This Case

MPEP § 804.01 sets forth a limited number of "situations where the safe harbor of 35 U.S.C. 121 does not apply." As shown in the table below, none of the exceptions set forth in MPEP § 804.01 exists here.

[18] Clause [c] requires only that the divisional application be "filed before the issuance of the patent on the other application," *i.e.*, the non-elected invention. There is no dispute that the '093 Application meets this requirement because it was filed before the issuance of the Reference Patents.

MPEP § 804.01 provision	*The '471 Patent*
(A) The applicant voluntarily files two or more applications without a restriction requirement by the Examiner.	**Not applicable**: Examiner issued a restriction requirement in the Parent Application that led to filing of the applications for the '471 Patent and the Reference Patents. SOF ¶¶ F1-F2, F9-F10, F24-F26.
(B) The claims of the different applications or patents are not consonant with the restriction requirement made by the Examiner, since the claims have been changed in material respects from the claims at the time the requirement was made.	**Not applicable**: As explained in detail in § IV.D.3(b), *infra*, Examiners have acknowledged that the claims of the '471 Patent and the Reference Patents maintained consonance with the restriction groups in the Parent Application. *See also* SOF ¶¶ F15, F21, F55.
(C) The restriction requirement was written in a manner which made it clear to applicant that the requirement was made subject to the nonallowance of generic or other linking claims and such generic or linking claims are subsequently allowed.	**Not applicable**: The restriction requirement contained no mention of generic or linking claims, and no such claims were allowed. *Id.* ¶¶ F1-F2.
(D) The requirement for restriction (holding of lack of unity of invention) was only made in an international application by the International Searching Authority or the International Preliminary Examining Authority.	**Not applicable**: The Office issued the restriction requirement as part of a domestic filing, not as part of an international application. *Id.* ¶¶ F1-F2.
(E) The requirement for restriction was withdrawn by the Examiner before the patent issues.	**Not applicable:** The Examiner never withdrew the restriction requirement. *Id.* ¶ F8.
(F) The claims of the second application are drawn to the "same invention" as the first application or patent.	**Not applicable**: The claims of the '471 Patent are directed to the antibodies and immunoassays of Group I, while the claims of the '195 and '272 Reference Patents are directed to the methods of treatment of Group IV.[19] *Id.* ¶¶ F1-F2, F15, F21, F55.
(G) Where a requirement for restriction between a product, a process of making the product, and a process of using the product was made subject to the non-allowance of the product and the product is subsequently allowed.	**Not applicable:** There was no such contingency in the restriction requirement. *Id.* ¶¶ F1-F2.

[19] The Examiner has acknowledged the claims of the '471 Patent (the "second application" described in MPEP § 804.01(F)) are not drawn to the "same invention" as the Parent Application. *See* Final Action at 9 (". . . the claims at issue are not identical . . . ."), 11 (same).

During this reexamination, Patent Owner pointed out the Examiners' failure to identify any Office policy that supported the ODP rejections and that the Examiners were refusing to adhere to MPEP § 804.01. *See* October 2014 Amendment at 133-36; April 2015 Amendment at 24-27. The Examiners did not attempt to show, in either the Final Action or the Advisory Action, how any provision in the MPEP (§ 804.01 or otherwise) or other published Office policy authorizes the present rejections. *See, e.g.*, Final Action at 9, 11, 13, 19 (citing "MPEP 804.01" without reference to specific paragraph and without explanation of significance of MPEP § 804.01). The Examiners also did not identify any change in the law governing double patenting that called into question any published Office policy on application of the safe harbor of Section 121. In view of the Examiners' tacit concession that no such provisions, policies or changes in the law exist, the Board should reverse the ODP rejections as being imposed in contravention to the published examination standards of the Office.

3. The '471 Patent and the Reference Patents Maintained Consonance with the Restriction in the Parent Application

(a) The Law Governing Consonance Focuses on Not Crossing a Line of Demarcation Set by the Restriction

A central focus of the inquiry for eligibility of patent claims for the safe harbor of Section 121 is whether those issued claims, along with those issued in the reference patent, maintained consonance with the restriction requirement that compelled the patent owner to prosecute the claimed inventions in separate applications. Under well-established authority, consonance exists where the subject matter claimed in the patent does not cross the line of demarcation set in the restriction requirement. *See Gerber Garment Tech. v. Lectra Sys.*, 916 F.2d 683, 688 (Fed. Cir. 1990) ("Consonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction requirement be maintained."). Also, the consonance inquiry necessarily focuses on the claims in *issued patents*—not on the disclosure in the patents, not on claims presented during examination of applications that never issue, and not on the designation or type of patent containing those claims. *See* 35 U.S.C. § 121 ("A patent issuing on an application . . . shall not be used as a reference . . . ."); *Geneva Pharms. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1381 (Fed. Cir. 2003) ("Section 121 shields *claims* against a double patenting challenge if consonance exists between the divided groups of *claims* and an earlier restriction requirement.") (emphasis added); *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569,

1579 (Fed. Cir. 1991) ("new or amended *claims* in a divisional application are entitled to the benefit of § 121 if the *claims* do not cross the line of demarcation drawn around the invention elected in the restriction requirement").[20]

Consonance exists as long as the claims of the patents resulting from the restriction requirement do not violate the subject matter boundaries of the restriction groups. Consonance exists if the issued claims in the *different* patents do not claim subject matter spanning more than one of the restriction groups. As the Federal Circuit has explained, "*new or amended claims* in a divisional application are entitled to the benefit of § 121 if the claims do not cross the line of demarcation drawn around the invention elected in the restriction requirement." *Symbol Techs.*, 935 F.2d at 1579; *Gerber*, 916 F.2d at 688 (inquiry is whether claim has crossed "the line of demarcation between the independent and distinct inventions.") (quotation marks omitted).

(b) Patent Owner Has Maintained Consonance in the '471 and Reference Patents[21]

The facts established during the present reexamination proceeding demonstrate that the

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[20] The consonance inquiry's focus on *issued* claims accords with the similar focus on issued claims for the underlying question of whether non-statutory double patenting exists. *See* MPEP § 804 ("The second is the 'nonstatutory-type' double patenting rejection . . . which is primarily intended to prevent prolongation of the patent term by prohibiting *claims in a second patent* not patentably distinguishing from *claims in a first patent*.") (emphasis added). Until there is an issued patent, it is impossible to have improper prolongation of patent term. The Office's practice of imposing "provisional" double patenting rejections is consistent with this well-settled law. Under that practice, the Office will identify potential double patenting concerns when two applications with potentially conflicting claims are pending. Where the Office determines a potential double patenting situation exists between pending claims, Office policy calls for the issuance of a "provisional" ODP rejection. *See* MPEP § 804.I.B. If the earlier-filed application is determined to be allowable, Office policy calls for "the Examiner [to] withdraw the ODP rejection in the earlier-filed application thereby permitting that application to issue." MPEP § 804.I.B.1. Issuance of such a patent would then lead to a non-provisional obviousness-type double patenting rejection in the application that remained pending, in light of the issued patent. *See* MPEP § 804.I.A.

[21] As shown in Appendix D, all of the claims of the '471 Patent fall within *non-elected Group I* of the restriction requirement imposed in the Parent Application because each claim is directed either to a chimeric antibody or to a method of using such an antibody in immunoassays. *See also* SOF ¶¶ F1-F2, F55. Appendix D also shows that claims in each of the '195 and '272 Reference Patents define subject matter falling within *elected Group IV* of the restriction requirement, as each is directed to a method of treating a particular disease in a human—either Crohn's disease ('272 Reference Patent) or rheumatoid arthritis ('195 Reference Patent)—by administering to the human an anti-TNF chimeric antibody. *See* SOF ¶¶ F1-F2, F15, F21. Patent Owner notes that Appendix D to this Appeal Brief has the identical content as Appendix D to Patent Owner's Amendment dated December 19, 2013, but corrects a typographical error (*i.e.*, the '195 patent was shown as "the '193 patent").

claims in the '471 Patent and the claims in each of the '272 and '195 Reference Patents maintained consonance with the restriction applied in the Parent Application. In the Parent Application, the Examiner imposed a five-way restriction requirement. SOF ¶¶ F1-F2. This restriction requirement was never withdrawn, modified or superseded. *Id.* ¶ F8; *see also* § IV.D.4, *infra*. Among the restriction groups were a Group I invention ("monoclonal antibodies, detectably labeled monoclonal antibodies, chimeric antibodies, pharmaceutical compositions, and assay methods") and a Group IV invention ("methods for treating an animal by administering a pharmaceutical composition containing an antibody"). SOF ¶ F1-F2. The Examiner stated that, if the Patent Owner elected to examine the Group IV invention, a further election of species would be required within the Group IV invention. *Id.* ¶ F4.

In response to the restriction requirement, Patent Owner elected the Group IV invention, and further elected the species of "chronic inflammatory pathology." *Id.* ¶ F5. The Examiner withdrew from consideration claims to other inventions identified in the restriction, *id.* ¶ F6, and subsequently rejected all pending claims drawn to the elected Group IV invention on October 27, 1993. *Id.* ¶ F7.

Patent Owner then filed several continuing applications, including the '093 Application (leading to the '471 Patent), U.S. Application No. 08/192,102 ("the '102 Application") (leading to the '272 Reference Patent) and U.S. Application No. 08/324,799 ("the '799 Application") (leading to the '195 Reference Patent). *Id.* ¶¶ F9-F10, F24. The record of prosecution of the '093 Application and related applications reflects that this course of prosecuting these different inventions in different applications was undertaken in consultation with the Examiner to adhere to the restriction applied in the Parent Application.[22]

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[22] For example, at an interview held on December 1, 1995, Patent Owner and the Examiner discussed at least U.S. Application No. 08/192,861 Application and the '102 Application. *See* '861 Application File Wrapper, Interview Summary; '102 Application File Wrapper, Interview Summary; SOF ¶ F12. Shortly thereafter, Patent Owner filed amendments across a number of pending applications—including the '093 Application—addressing the restriction applied in the Parent Application. *See* SOF ¶¶ F12-F13, F33 (noting that that claims were being "amended as suggested by the Examiner" and that Patent Owner was pursuing "non-elected subject matter" of the Parent Application); *see also* '102 Application, Preliminary Amendment dated Dec. 5, 1995 at 3 ("Entry of the Preliminary Amendment prior to examination of the application is respectfully requested pursuant to the telephone conversation between Examiner Nisbet and the undersigned on December 1, 1995.").

i. Consonant with the Restriction Requirement, Patent Owner Prosecuted the Group I Invention in the Application Leading to the '471 Patent

Through a preliminary amendment filed on December 23, 1994, Patent Owner limited the claims presented for examination in the '093 Application to the subject matter of Group I of the restriction in the Parent Application. *Id.* ¶¶ F25-F26. Group I specifies "monoclonal antibodies, detectably labelled monoclonal antibodies, chimeric antibodies, pharmaceutical compositions, and assay methods." *Id.* ¶ F1-F2. In that same amendment, Patent Owner stated that it made the amendment "pursuant to the restriction requirement set forth in parent application Serial No. 08/013,413." *Id.* ¶ F26. Consistent with Patent Owner's statement, the claims examined in the '093 Application all fall within Group I of the restriction requirement. *Id.* ¶¶ F24-F56. More particularly, the issued claims of the '471 Patent all recite chimeric antibodies or immunoassay methods using chimeric antibodies. *Id.* ¶ F55.

The record thus demonstrates that the Patent Owner prosecuted the '093 Application to secure examination of the non-elected Group I invention in response to the restriction applied in the Parent Application. These facts are not in dispute—the Examiners agree that the record establishes that: (1) the claims presented in the '093 Application correspond to the Group I invention of the restriction in the Parent Application, and (2) the Patent Owner used the '093 Application to pursue examination of this non-elected Group I invention. *See* SOF ¶¶ F1-F2, F24-F26, F55-F56.

ii. Consonant with the Restriction Requirement, Patent Owner Prosecuted the Group IV Invention in the Applications Leading to the '272 and '195 Reference Patents

The claims in the Reference Patents are limited to the same Group IV invention elected for examination in response to the restriction imposed in the Parent Application. SOF ¶¶ F1-F2, F15, F21. With respect to the '272 Reference Patent, Patent Owner presented a preliminary amendment in the '102 Application that limited the claims to methods of treating Crohn's disease using chimeric anti-TNF antibodies, and the issued claims all recite "method[s] of treating TNFα-mediated Crohn's disease in a human" by administering anti-TNF chimeric antibodies. *Id.* ¶ F13. With respect to the '195 Reference Patent, Patent Owner presented a preliminary amendment in the '799 Application limiting the claims to methods for treating rheumatoid

arthritis using chimeric anti-TNF antibodies, and the issued claims all recite "method[s] of treating rheumatoid arthritis" using anti-TNF chimeric antibodies. *Id.* ¶ F19. Thus, all of the Reference Patents' claims are limited to the Group IV invention defined by the restriction in the Parent Application. *Id.* ¶¶ F1, F15-F16, F21-F22.

These facts, again, are not in dispute. The Examiners confirmed not only that the Reference Patent claims correspond to the Group IV invention elected for examination in the Parent Application, but also that the Patent Owner used the '102 and '799 Applications to continue examination of the Group IV invention elected for examination in response to the restriction in the Parent Application. *Id.* ¶¶ F16-F17, F22-F23.

4. The Observations in Footnote 5 of the Final Action Are Believed to Have Been Withdrawn, But If Not, Are Erroneous

In footnote 5 of the Final Action, the Examiners suggested that Patent Owner crossed the line of demarcation by bringing certain claims into the '093 Application, and that another Examiner's restriction in a related application may have operated as a withdrawal or modification of the Parent Application's restriction. *See* Final Action at 17 n.5. During the interview conducted on March 31, 2015, Patent Owner explained why both assertions in footnote 5 were erroneous. *See* April 2015 Amendment at 14. Based on that discussion, Patent Owner understands that the Examiners have abandoned their footnote 5 assertions. *See id.* (summary of interview, noting that "Representatives of the Office acknowledged the clarifications made by Patent Owner's representative" with regard to footnote 5). Consistent with Patent Owner's understanding, the Examiners also did not advance any position in the Advisory Action based on the arguments presented in footnote 5. *See* '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2 (not mentioning consonance).

While Patent Owner continues to believe that footnote 5 arguments stand withdrawn, because the Advisory Action states that the Examiners are maintaining the ODP rejection "for the reasons of record set forth in the final office action," *i.e.*, the Final Action that includes footnote 5, in an abundance of caution these arguments are again responded to here. As explained below, the observations in footnote 5 lack any merit.

(a) Patent Owner Did Not Present Claims that Crossed the Line of Demarcation in the '093 Application

Footnote 5 of the Final Action suggests that consonance was lost during prosecution of the '093 Application based on the false premise that the '093 Application included "polypeptides" claims whose subject matter falls within Group III, as opposed to Group I.[23] *See* Final Action at 17 n.5. The August 8, 1998 amendment referenced in footnote 5 did not cross a line of demarcation because that amendment introduced claims defining particular *antibody* polypeptides, which is the precise subject matter of Group I (*i.e.*,". . . monoclonal antibodies, detectably labeled monoclonal antibodies, *chimeric antibodies*, pharmaceutical compositions and *assay methods* . . . ."). For example, claim 140 recited "A polypeptide comprising the amino acid sequence selected from the group consisting of **SEQ ID NO: 3** and **SEQ ID NO: 5** . . . ." '093 Application File Wrapper, Amendment dated Aug. 3, 1998 at 3. These two recited sequences define the heavy and light chains of *the chimeric c42 antibody*. Claims 140-159 thus clearly fell within Group I of the restriction applied in the Parent Application, and their addition did not deprive the '093 Application claims of consonance. SOF ¶¶ F1-F2.

(b) Actions During Examination of the '674 Application the Office Did Not Withdraw or Modify the Restriction Applied in the Parent Application

Footnote 5 of the Final Action also refers to a restriction requirement applied in a related, but ultimately abandoned, application (*i.e.*, Application No. 08/570,674) ("the '674 Application"). *See* Final Action at 17 n.5. Here, the Examiners incorrectly suggest that the restriction required in the '674 Application was "different" from the restriction required in the Parent Application, so that the '674 Application's restriction requirement effectively withdrew or modified the restriction requirement imposed in the Parent Application. This suggestion has no basis in, and is in fact contrary to, the record of the '674 Application.

The restriction applied in the '674 Application had three, rather than five, groups. But these three groups corresponded precisely to Groups I, II and IV of the restriction applied in the

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[23] As an initial matter, footnote 5 wrongly associates "TNF polypeptides" with Group III. The TNF receptor "polypeptide" invention is the Group II, not Group III, invention. *See* SOF ¶ F2 ("TNF polypeptides"). Group III was directed to "polynucleotides encoding chimeric antibodies, transformed hosts, and processes for preparing antibodies by culturing transformed/transfected hosts . . . ." *Id.*

Parent Application. SOF ¶ F2; '674 File Wrapper, Requirement for Restriction/Election dated Sept. 18, 1996 at 2. The reason why the '674 Application restriction contained only three, rather than five groups, was simply that there were no claims presented in the '674 Application that corresponded to the remaining two groups of the Parent Application restriction. The Office, thus, had no reason to address these additional invention groups (Groups III and V of the Parent Application restriction) when it required restriction in the '674 Application.

In fact, the restriction applied in the '674 Application was *fully consistent* with the lines of demarcation first established in the Parent Application. *Id.* Specifically, the Examiner in that case identified the *same patentable distinctions* between *chimeric antibodies* (*i.e.*, Group I in both the Parent and '674 Applications), *TNF polypeptides* (*i.e.*, Group II in both the Parent and '674 Applications) and methods of treatment *using antibodies* (*i.e.*, Group IV of the Parent Application and Group III of the '674 Application) as the Examiner who applied the restriction in the Parent Application. The table below illustrates this fact:

'413 Restriction	'674 Restriction
Group I: "monoclonal antibodies, detectably labeled monoclonal antibodies, *chimeric antibodies*, pharmaceutical compositions and *assay methods*"	Group I: "chimeric antibodies"
Group II: "TNF polypeptides"	Group II: "peptide compositions" (TNFα receptor peptides)
Group III: "polynucleotides encoding antibodies, transformed hosts, transfected hosts, and processes for preparing antibodies . . . "	[No claims to this subject matter]
Group IV: "methods for treating an animal by administering a pharmaceutical composition containing an antibody . . ."	Group III: Methods of treating TNF-mediated diseases [using composition comprising anti-TNF chimeric antibody chain]
Group V: "methods for removing TNF-alpha from a sample and treatment methods involving removal of TNF-alpha from a body fluid and returning said body fluid to an animal . . ."	[No claims to this subject matter]

Thus, even if the restriction required in the '674 Application had some legal significance to the status of the restriction required in the Parent Application (which it does not), that restriction requirement provides no support for the suggestion that it in any way operated to withdraw or alter the restriction applied in the Parent Application or to otherwise suggest the claims of the '471 Patent or the Reference Patents lack consonance.

5. The Examiners' Arguments against the Application of Safe Harbor Find No Support from the Language of § 121 or the Limited Exceptions to the Safe Harbor Protections Set Forth in the MPEP

"Prior to the 1952 Patent Act, courts and patentees were aware of the unfairness that resulted when the Patent Office required restriction or division between claims in a patent application, thus requiring that a second patent application be carved out of the first, and then rejected the second application on the basis of the first." *Boehringer*, 592 F.3d at 1350. The statutory "safe harbor is provided to protect an applicant from being penalized for *dividing* an application." *Id.* at 1353-54 (emphasis in original).

Here, because Patent Owner honored the Office's restriction requirement, it divided the Parent Application and maintained consonance with the restriction in the resulting patents (*i.e.*, the '471 Patent, and the '272 and '195 Reference Patents, respectively). The '471 Patent disclosure—both the original and as amended—fully supports all of the issued claims in the '471 Patent. Also, the amendment denominating the '093 Application a division of the Parent Application was expressly found proper under the Office's rules applicable to this proceeding. Further, as explained below, the facts of this case are legally indistinguishable from those in another reexamination in which the Office granted safe harbor to an application originally designated a continuation-in-part that was re-designated a division after amendments in a reexamination proceeding. In short, there is no principled reason for denying safe harbor to the '471 Patent's claims. The Board should grant safe harbor to the '471 Patent notwithstanding the '093 Application's pre-amendment denomination.

(a) A Divisional Is Not Denied Section 121's Safe Harbor Merely Because It Was Designated a CIP When It Was Filed

Effectively ignoring the determination that the '471 Patent is a proper divisional of the Parent Application, the Examiners erroneously contend that the '471 Patent does not qualify for the safe harbor of Section 121 because the '093 Application (*i.e.*, the application from which the

'471 Patent issued) was designated a "continuation-in-part" when it was filed. *See* '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2; Final Action at 19. Section 121 does not require the application resulting in the safe harbor patent to meet any particular timing for when it is formally designated a divisional, and the Examiners' argument to the contrary conflicts with the law governing Section 121, the Office's prior actions, and the very purpose of the safe harbor provision.

As previously explained, Section 121 does not, under its express terms, condition eligibility for safe harbor on the original designation of the safe harbor patent. It requires only: (i) that the application issuing as the safe harbor patent contain a disclosure sufficient to support the claimed, non-elected invention in the manner specified by Section 120, (ii) that the application ***is*** a divisional application of the application that was the subject of a restriction requirement, and (iii) that the application was filed "before the issuance of the other application," *i.e.*, the reference patent(s). *See* 35 U.S.C. § 121 (requiring a "divisional application which complies with the requirements of section 120" and noting that reference patents "shall not be used as a reference . . . against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application"). The '093 Application meets each of these requirements:

- First, there is no dispute that the '093 Application as filed supports '471 Patent claims because it incorporated by reference the entirety of the Parent Application as of its filing date. *See* SOF ¶ F27.
- Second, the '093 Application is a divisional of the Parent Application. It was amended by a preliminary amendment to present claims to the non-elected Group I invention for examination and thereafter was used to prosecute the non-elected Group I invention, as the Office has duly and officially recognized. *Id.* ¶¶ F25-F28, F62-F73. The amendment that denominated the '093 Application as a "divisional" merely conformed the name and form of the application to recognize its proper status.
- Finally, the '093 Application was filed before the issuance of the Reference Patents. *See id.* ¶¶ F14, F20, F24.

Consequently, the '471 Patent, which issued from the '093 Application, falls squarely within the safe harbor of Section 121.

(b) In Legally Indistinguishable Circumstances, the Office Gave Safe Harbor to a Continuation-in-Part that Was Re-Designated a Divisional

In Reexamination Control No. 90/009,659 ("the Martek Reexamination"), the Office determined that an application originally filed with the designation "continuation-in-part" was properly amended to be designated a divisional application and consequently enjoyed safe harbor against earlier issued patents in the same family as the reexamined patent. As explained below, the facts of Martek are legally indistinguishable from the instant case.

The Martek Reexamination was directed to a patent—the '244 Patent—that issued from an application that was originally designated a "continuation-in-part" from, and contained disclosure not found within an original application. *See* U.S. Application No. 08/483,477 File Wrapper, Specification at p. 1, ll. 2-4. During the Martek Reexamination, the Office rejected the '244 Patent claims for obviousness-type double patenting in view of claims that issued in two other patents in the same patent family. *See* Martek Reexamination, Office Action dated Aug. 5, 2010 at 33-38. Specifically, the Office took the position that:

> The safe harbor provision of 35 USC 121 is unavailable here since the present patent is a continuation and continuation-in-part of the [reference] patent.

Martek Reexamination, Decision Granting Ex Parte Reexamination dated Mar. 5, 2010 at 21 (citing *Pfizer Inc. v. Teva Pharms. USA*, 518 F.3d 1353, 1363 (Fed. Cir. 2008)).

The Martek patent owner responded by amending the reexamined patent's specification to conform the patent's disclosure to match that of its parent, and by expressly designating the application from which the patent issued to be a "divisional application." *See* Martek Reexamination, Amendment by Patent Owner Under 37 C.F.R. § 1.530 dated Oct. 5, 2010 at 3 ("This application is a [continuation-in-part] divisional application of U.S. patent application [Ser.] No. 08/292,736, filed Aug. 18, 1994, now U.S. Pat. No. 5,656,319 . . . .") (brackets and underlining in original).

In the next Office Action, the Office withdrew the obviousness-type double patenting rejections in view of the amendment that re-designated the application a divisional:

> Patent Owner has *amended the benefit claim such that the instant patent is a divisional* of the '319 patent, which is a divisional of the '594 patent, which in turn is a divisional of the '242 patent. Restriction requirements were issued in each of the application [sic] that matured into the '242 patent, the '594 patent and the '319 patent. *As such, the safe harbor of U.S.C. 121 is available*, and the *obviousness-type double patenting rejections* over the '242 patent and the '594 patent are hereby *withdrawn.*

Martek Reexamination, Non-Final Action dated Mar. 4, 2011 at 12 (emphasis added).

The Examiners' ODP rejections in this proceeding cannot be reconciled with the Office's practice in the Martek Reexamination.[24] In this case, Patent Owner amended the '471 Patent to: (i) conform its disclosure to that of the Parent Application in which the restriction was applied, and (ii) changed the designation of the '093 Application to a "divisional" of the Parent Application. SOF ¶¶ F62-F73. The Examiners' rejection under these circumstances conflicts directly with the Office's[25] determination in the Martek Reexamination that the same changes were effective to place the '244 Patent within Section 121's safe harbor and necessitate the withdrawal of ODP rejections. Consistent treatment of the '471 Patent claims in the present reexamination requires withdrawal of the rejections for double patenting over the '272 and '195 Reference Patent claims.

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[24] Under established Office practices, an Examiner is required to specifically address a deviation from Office practice where the Examiner advances a new interpretation of the law. For example, MPEP § 1207.02 (9th ed.) (March 2014) provides:

> If an examiner's answer is believed to contain a new interpretation or application of the existing patent law, the examiner's answer, application file, and an explanatory memorandum should be forwarded to the TC Director for consideration. See MPEP §1003. If approved by the TC Director, the examiner's answer should be forwarded to the Office of the Associate Commissioner for Patent Examination Policy for final approval.

The Examiners in this proceeding have not done so at any point in this proceeding.

[25] Patent Owner also observes the panel in both this proceeding and the Martek proceeding included Examiners Ponnaluri and Huang, who are also participating in this reexamination proceeding. *See* Martek Reexamination, Non-Final Action dated Mar. 4, 2011 at 21.

(c) The Recently Issued *Searle* Decision Does Not Support the Examiners' ODP Rejection

After Patent Owner filed its notice of appeal in this proceeding, the Federal Circuit issued *G.D. Searle LLC v. Lupin Pharmaceuticals, Inc.*, ___ F.3d ___, No. 2014-1476 (Fed. Cir. June 23, 2015), a case in which it found that the safe harbor of Section 121 inapplicable. Although *Searle* also concerns a continuation-in-part that was re-designated a divisional, the facts and equities in *Searle* differ materially from those found in this case, and *Searle* provide no basis for denying safe harbor to '471 Patent claims.

In *Searle*, the Federal Circuit considered, *inter alia*, "whether the safe harbor provision of 35 U.S.C. § 121 applies to the RE '048 patent and protects it from invalidation based on the '165 patent." *Searle*, slip op. at 7. The *Searle* court ultimately concluded that the RE '048 patent did not qualify for safe harbor despite the application for the reissued patent[26] having been re-designated a divisional and having removed from it portions of the specification that were not in the patent in which the restriction was required. *Id.* at 7-8.

The Federal Circuit reached its conclusion in *Searle*, however, because of facts that are materially different from those present in this case. In *Searle*, the patent owner introduced claims directed to new matter added in the continuation-in-part that (a) were unsupported in the disclosure of the parent application, and (b) were allowed to issue. Accordingly, when Searle filed a reissue application that conformed its disclosure to that of its parent and denominated it as a divisional, Searle needed to, and did, cancel a number of claims from that patent that lacked support in the original application in which the restriction was applied. This distinction from the facts presented in this appeal is critical.

As the Federal Circuit observed, the reissued patent—the '068 patent ('113 application) that reissued as the RE '048 patent—initially issued with, and for years enjoyed the benefit of, claims dependent on the subject matter in the '068 patent but removed from the RE '048 patent. *Id.* at 9. Although the patent owner Pfizer cancelled those claims from the RE '048 patent, the Federal Circuit determined that "[f]airness to the public does not permit Pfizer to convert the '113

[26] That is, the '113 application for the '068 patent that reissued as the RE '048 patent.

application into a division of the original '594 application, and thereby take advantage of the safe harbor provision." *Id.* As the court succinctly explained:

> Pfizer cannot now identify the '113 application as a divisional of the '594 application … and retroactively relinquish the new matter in the '113 application, after having enjoyed years of patent protection for it.

Id. No such equitable considerations exist in this case because, as previously explained, there is no dispute that every issued claim of the '471 Patent is supported by the disclosure of the Parent Application alone, to which the amended specification now corresponds.

The Federal Circuit also denied the RE '048 patent the benefit of safe harbor because the "RE '048 patent (the challenged patent) and the '165 patent (the reference patent) are not 'derived from the same restriction requirement.'" *Id.* at 11. This again is a materially different fact relative to the present proceeding. In *Searle*, the reference patent was a divisional of the original '594 Application in which the Office imposed a three-way restriction requirement, while the challenged patent claimed priority through a continuation-in-part of the '594 Application filed *before* the Office imposed restriction on the '594 Application. *Id.* at 3-4. Consequently, the *Searle* Court held that the challenged patent and reference patent "are not derived from the same restriction requirement." In contrast, and as previously explained, the '471 Patent and the Reference Patents here *are* derived from the *same* restriction requirement imposed in the Parent Application, and they maintained consonance with that restriction requirement. SOF ¶¶ F1-F2, F15, F21, F55. In view of the material differences between the *Searle* and the instant case, *Searle* cannot justify a denial of safe harbor to the '471 Patent claims.

(d) The Examiners' Contention that Reference Patents Must Issue from Divisional Applications Has No Merit

The Examiners' argument that the '471 Patent does not qualify for the safe harbor because the '272 and '195 Reference Patents must issue from divisional applications[27] conflicts with the plain language of Section 121, standard Office procedures, and applicable law. As previously explained, the '272 Patent and the '195 Patent each qualify as reference patents under Section 121 because they constitute: (i) patents issuing on "application[s] with respect to which a requirement

[27] *See* Final Action at 20-21 (Examiner's argument); '851 Reexamination, Advisory Action dated Oct. 31, 2014 at 2 (same).

for restriction under this section has been made" because they arise from continuing applications of the Parent Application; and (ii) constitute patents issuing on "application[s] filed as a result of such a requirement." *See* § IV.D.1(a), *supra*. Nothing in Section 121 requires reference patents to arise from divisional applications. *See* 35 U.S.C. § 121.

The Examiners' argument makes no sense in view of the fact that the '272 and '195 Reference Patents issued from applications prosecuting the same Group IV invention elected for examination in the Parent Application. SOF ¶¶ F1-F5, F9-F23. Under the Office's own policies, it would have been improper to denominate continuing applications directed to the *elected* Group IV invention "divisionals" because divisional applications may be used only for pursuing *non-elected* inventions. *See* MPEP § 201.06 (5th ed., rev. 15) (Aug. 1993) ("A later application for a distinct or independent invention . . . is known as a divisional application or 'division.'"). It was entirely appropriate, on the other hand, to pursue the Group IV invention in continuing applications. As the Examiners' interpretation conflicts with the clear language of Section 121, and would require Patent Owner to have performed an impermissible procedure for compliance, that interpretation should be rejected.

The Examiners position also ignores the Office's long-established and statutorily authorized continuing application practice. *See, e.g.*, 35 U.S.C. § 120 ("[a]n application for patent for an invention" that properly claims priority to an earlier application "shall have *the same effect, as to such invention*, as though filed on the date of the prior application.") (emphasis added). Under this practice, an applicant may continue examination begun in an earlier-filed application, and have that later application be considered the same application in substance as the earlier application.

Substantial precedent supports this continuing application practice. For example, the Supreme Court has held that a continuing application and its parent "are to be considered *as parts of the same transaction, and both as constituting one continuous application*, within the meaning of the law." *Godfrey v. Eames*, 68 U.S. 317, 326 (1864) (italics added).[28] The CCPA

[28] Although *Godfrey* predated the partial codification of continuation practice in the Patent Act of 1952, the Federal Circuit has noted that the legislative history "does not indicate any congressional intent to alter the Supreme Court's interpretation of continuing application practice." *Transco Prods. v. Performance Contracting*, 38 F.3d 551, 557 (Fed. Cir. 1994).

and the Federal Circuit have followed this rule faithfully. *See, e.g., Teter v. Kearby*, 169 F.2d 808, 813 (CCPA 1948) (considering series of divisional applications to be "parts of the same transaction making one continuous application."); *Applied Materials v. Advanced Semi. Materials*, 98 F.3d 1563, 1567 (Fed. Cir. 1996) (finding reference and safe harbor patents remained within scope of § 121 despite complicated prosecution histories and the filing of several continuing applications). The Federal Circuit also has found distinctions among members of the same family of patent applications to be generally unimportant and that the labels "'continuation,' 'divisional,' and 'continuation-in-part' are merely terms used for administrative convenience." *Transco Prods. v. Performance Contracting*, 38 F.3d 551, 556 (Fed. Cir. 1994) (citing MPEP § 201.11).

Consistent with this long-standing precedent, the Federal Circuit has found patents issuing from continuing applications derived from a divisional application eligible for the safe harbor of Section 121:

> [I]f the [safe harbor patent] and the [reference patent] trace their lineage back to a common parent which was subject to a restriction requirement, then § 121 intervenes to prevent a double patenting rejection.

Boehringer Ingelheim Int'l v. Barr Labs., 592 F.3d. 1340, 1352 (Fed. Cir. 2010) (quoting *Geneva Pharms.*, 349 F.3d at 1378) (brackets as in *Boehringer*); *Applied Materials*, 98 F.3d at 1567. These holdings are entirely consistent with "the purpose of § 121," which is "to prevent a patentee who divides an application in which a restriction requirement has been made from risking invalidity due to double patenting." *Boehringer*, 592 F.3d at 1350 ("the safe harbor [of § 121] is provided to protect an applicant from being penalized for dividing an application. Section 121 is not concerned with any overlap in non-elected inventions prosecuted within any particular divisional application *or in how any such applications are filed.*") (emphasis added); *see also Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1354 (Fed. Cir. 2009) ("Our decisions in *Applied Materials* and *Symbol Technologies* thus establish that a patent need not have issued directly from a divisional application to receive § 121 protection. In other words, intervening continuation applications do not render a patent ineligible for § 121 protection so long as they descended from a divisional application filed as a result of a restriction requirement.").

The Federal Circuit has also explained that the language of Section 121 compels this conclusion:

> [Section] 121 refers broadly to "a divisional application," and does not state that the divisional must be a direct divisional of the original application. Had Congress intended to limit the safe harbor only to a divisional of the application in which the restriction requirement was entered, it could have said "a divisional application of the original application," rather than simply "a divisional application."

Boehringer, 592 F.3d at 1351. The Federal Circuit thus has consistently held Section 121 applies to a patent issuing from a continuing application that descends from a divisional application. *See, e.g., Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991); *Boehringer*, 592 F.3d. at 1352 (finding patent issuing from "a divisional of a divisional" to be within safe harbor). Indeed, in *Applied Materials*, 98 F.3d at 1567, the Federal Circuit found Section 121 to apply to a reference patent that issued from a continuing application having both intervening continuation and *continuation-in-part* applications.[29] The Examiners' proposition that a patent application may not change its disclosure in any manner relative to a previously filed application and still remain within Section 121 is contrary to this well-established law.

Under the logic of these cases and the statutory purpose of Section 121, the Examiners' proposition that reference patents issuing from continuing applications derived from and claiming the invention elected for examination in response to a restriction fall outside Section 121 can simply not be sustained. Indeed, no reported decision of the Federal Circuit or its predecessor court has held that a "reference" patent falls outside of the Section 121 if it issues from a continuing application derived from an otherwise eligible application (*i.e.*, the application used to prosecute the invention elected for examination in response to the restriction, or an

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[29] The court explained the complicated lineage of the patents at issue in *Applied Materials* in a related case. *See Applied Materials*, 98 F.3d at 1567 (citing *Applied Materials, Inc. v. Gemini Research Corp.*, 835 F.2d 279, 280 (Fed. Cir. 1988)). As described in the *Gemini Research* decision, the "safe harbor" patent [the '609 patent] issued from a continuation application that had followed (i) an earlier continuation application, (ii) a continuation-in-part application, and (iii) an additional intervening restriction related to the added matter of the continuation-in-part application. *Gemini Research* at 280. The court found the resulting patent within the safe harbor as against (i) a patent issuing with claims to the elected invention [the '712 patent] and (ii) a patent issuing from two consecutive continuation applications filed after a divisional application [the '496 patent].

application filed in response to that restriction to pursue examination of a non-elected invention).[30] Consequently, "reference patents" are covered by Section 121 regardless of whether the patent issued from the original application subjected to the restriction, an application filed in response to the restriction, or from a continuing application of either, provided the latter claims the same invention as its parent original or parent divisional application.

(e) The Examiners' Contention that the Precise Claims that Were Subject to Restriction Were Required to Have Been Presented in the Reference Patents Has No Merit

The Examiners' assertion that the safe harbor does not apply because "the original claims which were subjected to restriction in the parent were not present (at the time of the filing of the applications) in [the '102 and '799] applications" is also without merit. *See* Final Action at 20. To begin, the Examiners' argument appears to rely on the premise that the Reference Patents must be divisionals. As explained in the preceding section, that premise is wrong.

Furthermore, nothing in Section 121 or the law governing application of its safe harbor provision requires the filing of applications for reference patents with, and only with, verbatim copies of claims subjected to restriction in the parent application. *See* 35 U.S.C. § 121. Indeed, the Federal Circuit has specifically rejected that theory in several cases. For example, in *Symbol Technologies*, the accused infringer argued that the patentee violated consonance by adding apparatus claims in a divisional application that had not appeared in the parent application at the time the parent was restricted between a method and other inventions. 935 F.2d at 1580. The Federal Circuit held that consonance was not violated (*i.e.*, there was no "breach of the restriction requirement") because both the pre-existing method claims and the "new" apparatus claims were directed to the same invention. *Id.*

The proper inquiry thus focuses on whether the reference patents arose from the same restriction requirement as the challenged patent and whether the *subject matter* of the issued claims in the patents maintained consonance with the restriction requirement. *See* §§ IV.D.1(b), IV.D.3, *supra*. As previously explained, both points are true for the '471 Patent and Reference

[30] The *Applied Materials* decision clearly held that a patent issuing from an application that was not denominated a "divisional" application remained subject to Section 121. The '712 patent in that case issued from the application that was subject to the restriction, which was not a "divisional" application. *See Applied Research*, 98 F.3d at 1567-68; *Gemini Research* at 835 F.2d at 280.

Patent claims at issue in this proceeding, and the claims of the '471 Patent thus qualify for the safe harbor. *Id.*

To the extent the Examiners intended to imply that Patent Owner violated consonance by presenting claims in the '471 Patent or the Reference Patents that encompass subject matter beyond what the claims in the Parent Application cover, the Examiners are again wrong. Indeed, the Federal Circuit, in *Applied Materials*, rejected that precise theory. There the court found a patent remained subject to Section 121 even though it traced its path through a sequence of filings which included the addition of claims to subject matter not in the original application that were restricted from the intervening application. *Applied Materials*, 98 F.3d at 1568. As that court made crystal clear, "[a] restriction requirement does not prohibit subsequent amendments to the claims." *Id.*

Moreover, it is well-established that the proper inquiry for maintaining consonance is to determine if the issued claims encompass subject matter in a *different* restriction group, not whether the issued claims encompass subject matter not at issue in any group. *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1380 (Fed. Cir. 2013). And, as previously explained, claims presented during examination but which do not issue in a patent are irrelevant to the double patenting analysis and the question of eligibility for the safe harbor of Section 121. Consequently, the claims issued in the Reference Patents do not in any way preclude the claims of the '471 Patent from Section 121's safe harbor.

(f) The Examiners' Contention that the Challenged and Reference Patents Must Have Had at All Times the Same Disclosure as the Parent Application Has No Merit

The Examiners' assertion that the safe harbor does not apply because the applications leading to the '471 Patent and the '195 and '272 Reference Patents had disclosures that "were different from the parent '413 application specification" is without merit. *See* Final Action at 19-20. Like the argument addressed in the preceding section of this brief, the Examiners' argument here appears to rely on the false premise that the Reference Patents must be divisionals and that both the Reference and safe harbor patent must contain an identical disclosure as the Parent Application subjected to the restriction. *See id.*

Nothing in Section 121 or the law governing application of its safe harbor conditions the safe harbor on the involved patents having a disclosure identical to that of the parent application.

Although the second sentence of Section 121 requires that "the other [non-elected] invention" be "made the subject of a divisional application which complies with the requirements of section 120," that sentence relates to the ability claim the benefit of an earlier filing date, not the availability of safe harbor. Moreover, this sentence actually contemplates that divisional applications may have different disclosures than their parent applications by virtue of its reference to compliance "with the requirements of section 120"—such clause would be meaningless if Section 121 required the disclosures of the various applications to be identical.[31] Further to this point, the MPEP specifically contemplates that a divisional application and its parent might *not* have identical written descriptions. *See* MPEP § 201.06 ("divisional application should set forth *at least the portion* of the earlier disclosure that is germane to the invention"[32]) (emphasis added).

Similarly, there is no requirement in Section 121, or in any reported case, for a reference patent and its parent application to have identical disclosures. Indeed, Section 121 does not require *any* type of comparison between the disclosure of a reference patent and the disclosure of the parent application. Nor does it restrict the type of application that gives rise to a reference patent—it merely requires reference patents to either: (i) issue from "application[s] with respect to which a requirement for restriction under this section has been made"; or (ii) issue from "application[s] filed as a result of such a requirement." *See* § IV.D.1(b), *supra*. As previously explained, the Reference Patents meet both of these criteria. *See id.*

Thus, there is no legal or principled reason to deny the '471 Patent claims safe harbor from the Reference Patents, and the Examiners' ODP rejections should be reversed.

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[31] The evaluations mandated by Section 121 necessarily are considered through the lens of the claimed invention, rather than the disclosures of the applications in the abstract. It is well-settled that the content of the specification is not controlling of obviousness-type double patenting assessment. *In re Braat*, 937 F.2d 589, 594 n.5 (Fed. Cir. 1991); *In re Kaplan*, 789 F.2d 1574, 1579 (Fed. Cir. 1986). The inquiry specified in Section 121 thus must start with the claims, and then determine if the claimed invention is supported by the disclosure in the manner required by § 120, and, thereby, by § 112. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1560 (Fed. Cir. 1991) ("[T]he 'written description' requirement most often comes into play where claims not presented in the application when filed are presented thereafter . . . . [P]atent applicants often seek the benefit of the filing date of an earlier-filed foreign or United States application under 35 U.S.C. § 119 or 35 U.S.C. § 120, respectively, for claims of a later-filed application. The question raised by these situations is most often phrased as whether the application provides 'adequate support' for the claim(s) at issue.").

[32] *See also* discussion of March 2014 change to MPEP § 201.06, above.

E. Even Without the Benefit of Safe Harbor, the Obviousness-Type Double Patenting Rejections Must be Overturned Because the '471 Patent Claims Are Not Unpatentable Under the Two-Way Obviousness Test

Independent of the safe harbor, the Examiners' ODP rejections must be reversed because they rest on the application of the wrong test for obviousness-type double patenting, the "one-way" test. Because it was the restriction requirement imposed by the Office that caused the '471 Patent claims to be examined in a separate application from the applications which issued as the Reference Patents, and because Patent Owner engaged in only conventional prosecution activities to secure issuance of the '471 Patent claims. It was the Office, not the Patent Owner, that controlled the rate of prosecution of these claims, and the later issuance of the '471 Patent claims was due solely to the actions and positions taken the Office, not the Patent Owner. The Examiners therefore should have employed the "two-way" test for assessing ODP.[33] As explained below, application of the two-way test mandates reversal of Examiners' ODP rejections because it is undisputed that the '471 Patent claims do not render either of the claimed methods defined by the '272 and '195 Reference Patents obvious, thereby precluding a finding of two-way obviousness of the involved sets of claims.

1. The Two-Way Test for Obviousness-Type Double Patenting is the Proper Test

The Examiners rely heavily on the Federal Circuit's decision in *In re Berg* to contend that the one-way test applies, but in so doing ignore the *Berg* court's primary focus: whether the patentee improperly controlled how the challenged patent claims were prosecuted and whether both sets of claims could have been pursued in a single application. *See In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998). Although the *Berg* court concluded that the one-way test applied in that case, it did so because the patentee there could have but did not file the claims of its separate applications in a single application. *See id.* at 1433 ("we base our affirmance on the second stated rationale of the Board: because Berg could have filed the claims of its separate

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[33] Under a one-way test, "the examiner asks whether the application claims [*i.e.*, the challenged claims] are obvious over the [Reference] patent claims. . . . Under the two-way test, the examiner also asks whether the patent claims are obvious over the application claims. If not, the application claims later may be allowed." *In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998).

applications in a single application, and it simply chose to file two applications despite nearly identical disclosures, Berg is not entitled to the two-way test.").

In stark contrast to the *Berg* facts, the Office's restriction requirement in the Parent Application precluded Patent Owner from pursing examination of the claims of the '471 Patent in the same application as claims issuing in the Reference Patents.[34] SOF ¶¶ F1-F2. In other words, unlike *Berg*, Patent Owner did not voluntarily prosecute the '471 Patent claims in a separate application from the claims issuing in the Reference Patents—it was *compelled* to prosecute the claims to the Group I and Group IV inventions separately.

Indeed, the *Berg* court identified as one action a patentee could have taken to avoid application of the one-way test filing all of its related claims together in a single application, and thereby force the Office to require restriction in that application. A patentee that did so, according to the *Berg* court, would not face the severities of one-way test because it would receive safe harbor from Section 121. *See id.* at 1435-36 ("by filing all of its related claims in one application, such an applicant is protected from an obviousness-type double patenting rejection if the PTO later determines the applicant has submitted claims to more than one patentable invention"). That is precisely what Patent Owner did here: it filed claims for separate inventions together in the Parent Application, in response to which the Office then required restriction, which in turn forced Patent Owner to file separate applications to prosecute claims to the Group I and Group IV inventions in the '093 Application and the applications resulting in the Reference Patents, respectively.[35] *See* § IV.D.1(b), *supra*; SOF ¶¶ F1-F2, F13, F19, F26.

The two-way test is to be employed unless there is evidence that the Office was not solely responsible for the delays in examination of the challenged patent, and such delays result in the

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[34] Examiner's assertion that Patent Owner's "arguments regarding the two-way test have no merit since the applicants voluntarily chose to file '471, '272 and '195 patent' applications as CIP applications" is inexplicable. Final Action at 24. As explained in detail in connection with its discussion of consonance, Patent Owner did not *voluntarily* file separate applications to pursue the Group I and Group IV inventions—the Office compelled it to do so by requiring restriction in the Parent Application. *See* § IV.D.3, *supra*; *see also* SOF ¶¶ F1-F2, F13, F19, F26.

[35] That the '093 Application was originally denominated a continuation-in-part should be irrelevant because, regardless of the application's denomination, the Office precluded its claims from being prosecuted in the '413 Application. Stated differently, Patent Owner filed the '093 Application "as a result of" the restriction requirement imposed by the Office—an application need only be filed "due to the administrative requirements imposed by the Patent and Trademark Office" to be filed "as a result of" a restriction requirement. *Boehringer*, 592 F.3d at 1353 n.3.

improper extension of the patent right. *See In re Braat*, 937 F. 2d 589, 592 (Fed. Cir. 1991) ("Obviousness-type double patenting is a judicially created doctrine intended to prevent *improper* timewise extension of the patent right.") (emphasis in original); *In re Berg*, 140 F.3d at 1434 n.6 ("where the inventions could not have been filed in a single application, if the applicant thereafter controlled the respective rates of prosecution to cause the species or improvement claims to issue prior to the genus or basic invention claims as could have been done by, *e.g.*, filing the genus claims long after the species claims even though the two were invented at nearly the same time or the genus claims were invented first, or by filing numerous continuations in the genus application while failing to respond substantively to PTO Office actions, such applicant seems not to be entitled to the two-way test").

Although the two-way test has been characterized as an "exception" to the use of the one-way test in measuring ODP, that exception should apply when a patentee has been forced to file separate applications and thereafter took no actions intended to delay examination of the presented claims. Indeed, the examples of improper control identified in *Berg* ("*e.g.*, filing the genus claims long after the species claims even though the two were invented at nearly the same time" or "filing numerous continuations in the genus application while failing to respond substantively to PTO Office actions") make clear that conventional prosecution activities (*i.e.*, presenting amendments and/or arguments) are not the type of actions that "control" the pace of prosecution and thereby disqualify the patent claims from being considered under the two-way obviousness test. *Id.*; *see also In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1376 (Fed. Cir. 2008) ("patentees repeatedly submitted claims directed to claims covering other inventions, urged the examiner to declare interferences for unrelated inventions, and repeatedly filed continuing applications without appeal").

For patentees forced by the Office to file separate applications to secure claims to inventions which the Office has found to be patentably distinct, the two-way test should be employed except in those situations where it can be shown the patentee took actions other than engaging in conventional prosecution of the claims. That result accords with the fact that, but for the Office's requirement for restriction, all of the claims could have issued from the same application, and with the Federal Circuit's recognition that patentees do not have control over conventional prosecution activities. *See Braat*, 937 F.2d at 593 ("The rationale behind this proposition is that an applicant (or applicants), who files applications for basic and improvement

patents should not be penalized by the rate of progress of the applications through the PTO, a matter over which the applicant does not have complete control.").

In this case, there is no suggestion, much less evidence, showing that Patent Owner engaged in anything other than conventional prosecution activities in relation to the '093 Application, and took no actions to improperly control the rate of prosecution of the claims or to otherwise cause any improper delay in the issuance of those claims. At the outset, Patent Owner promptly filed the '093 Application—on the same day it filed the application for the first of the Reference Patents, *see* SOF ¶¶ F10, F24—and, as explained below, it reasonably and timely prosecuted the '093 Application in full conformity with applicable provisions of the patent law and the Office's regulations. Accordingly, the two-way test for obviousness is the appropriate test to employ to measure the '471 Patent claims relative to the claims in the Reference Patents.

The Examiners further cite the following passage from MPEP § 804 in support of their erroneous assertion that use of the one-way test is appropriate:

> If the application at issue is the later filed application or both are filed on the same day, only a one-way determination of obviousness is needed in resolving the issue of double patenting . . . . See, e.g., *In re Berg*, 140 F.3d 1438, 46 USPQ2d 1226 (Fed. Cir. 1998) (the court applied a one-way test where both applications were filed the same day).

Final Action at 24 (quoting MPEP § 804.II.B.1) (underlining added in Final Action). But, contrary to the Examiner's assertion, neither MPEP § 804 nor *Berg* stand for the proposition that the one-way test applies whenever two applications are filed on the same day, especially when those two applications are continuing and/or divisional applications claiming the benefit of the same parent application. As previously explained, the *Berg* court affirmed the use of the one-way test because "Berg *could have* filed the claims of its separate applications in a single application, *and it simply chose*" not do so. *Berg*, 140 F.3d at 1433 (emphasis added).

Patent Owner here could not file the '471 Patent Group I claims in the same application as the Group IV claims that issued in the Reference Patents—when it did so in the Parent Application, the Office required restriction between these groups, compelling Patent Owner to file and pursue examination of those claims in separate applications. The *Berg* court certainly did not suggest, much less hold, that the one-way test should be applied if the Office itself

compelled an applicant to file two separate applications. Accordingly, Patent Owner should not be penalized for promptly filing the '093 Application, and the two-way test should be employed to evaluate obviousness-type double patenting in this proceeding.

2. Patent Owner's Proper Use of Conventional Examination Procedures Does Not Extinguish the Right to Use the Two-Way Test

As previously explained, the Office was solely responsible for causing the '471 Patent to issue in a separate patent and to do so after the Reference Patents issued because, but for the Office's restriction requirement in the Parent Application, Patent Owner could have prosecuted the elected and non-elected subject matter in the same application, thereby obviating any potential ODP issue. Moreover, as explained below, the Office was the sole source of delays in issuance of the '471 Patent claims, as it incorrectly refused to find the claims presented in the '093 Application allowable, even after finding comparable elements of these claims allowable in the '272 and '195 Reference Patents, and by failing to expeditiously examine the '093 Application.

In support of their contention that the Patent Owner was a source of delay, the Examiners cite to nothing more than Patent Owner's use of conventional prosecution and authorized procedures that are enshrined in the patent law and the Office's own regulations. As explained in more detail below, Patent Owner followed routine procedures to prosecute the '093 Application, and reasonably secured allowance of its claims by doing so. Such actions do not constitute any "improper" delay of examination. They are the precise opposite—they are by definition appropriate under the statute and the Office's own regulations. Use of these authorized and conventional examination procedures cannot justify depriving Patent Owner the benefit of the two-way test, and doing so would be manifestly unfair in view of the record of examination of the '471 Patent.

Under the Examiners' theory, any patentee who persists in the assertion that a claim is patentable or who needs to request statutorily authorized extensions of time would suffer the severities of the one-way test, because in the Examiners' view, the patentee would have exercised some control over the length of the prosecution. Such a result would make no sense. Had the Patent Owner performed the actions with which Examiners now finds fault (*i.e.*, amending the claims, obtaining routine duly-authorized extensions, and filing 37 C.F.R. § 1.129(a)

submissions) in prosecuting all of the claims in its originally filed Parent Application, there would have been no negative impact to the validities of any of those claims. There is no principled reason why Patent Owner should be penalized for performing those same actions just because the Office required restriction in the Parent Application, thereby causing the claims of the '471 Patent be prosecuted in and to issue from a separate application. As explained below, Patent Owner followed conventional and authorized prosecution procedures during examination of the '093 Application, and did not engage in conduct to improperly control the rate of the prosecution of that application.

(a) Patent Owner Used Authorized Procedures to Reasonably Pursue Allowance of the '471 Patent Claims

Patent Owner diligently pursued issuance of the Group I claims using statutorily prescribed procedures to convince the Office that the claims issuing in the '471 Patent are patentable. For example, Patent Owner responded to each Office action within statutorily defined time limits,[36] generally responding in significantly less time than the maximum time allowed by statute. *See* SOF ¶¶ F29-F54. Patent Owner also properly used the Congressionally authorized procedure specified in 37 C.F.R. § 1.129(a) to withdraw the finality of previously imposed Office actions to secure reconsideration of the merits of its application.[37] *See id.* ¶¶ F35, F45. Patent Owner took no actions to control the rate at which the '093 Application was examined—it did not seek to suspend examination of the '093 Application, nor did it allow the application to go abandoned and then revive it. *Id.* ¶¶ F24-F55. To the contrary, Patent Owner worked diligently to secure issuance of claims directed to the non-elected Group I invention, an invention it could not have pursued in the Parent Application or the applications for the Reference Patents due to the restriction requirement imposed in the Parent Application. *Id.* ¶¶ F1-F2.

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[36] Pursuant to 35 U.S.C. § 133, an applicant may respond to an Office Action within up to six months of the date it was mailed by the Office.

[37] 37 C.F.R. § 1.129(a) was expressly authorized by Congress to enable the continued examination of claims without a requiring the filing a continuing application.

(b) Patent Owner Properly Advanced Arguments Intended to Gain Allowance the '471 Patent Claims

Examiners appear to take issue with Patent Owner's efforts to seek allowance of certain rejected claims following the Examiners' determination that certain other claims were in condition for allowance. As a threshold matter, Examiners' argument is facially unjustified because the *very purpose* of prosecution is to afford the applicant an opportunity to present good-faith arguments to obtain the patent rights to which the invention is entitled, even if the arguments presented turn out not to be completely successful (*e.g.*, by resulting in a finding of certain but not all of the claims allowable).

Here the reasonableness of Patent Owner's efforts is demonstrated by the degree of success eventually achieved in overcoming the rejections applied during the prosecution of the '093 Application. A brief summary of the prosecution of the '093 Application illustrates this point.

On December 22, 1995, Patent Owner submitted amendments "as suggested by the Examiner." SOF ¶ F33. Nevertheless, in the next action, the Office rejected these claims. *Id.* ¶ F34. Rather than pursue an appeal, Patent Owner chose to use the procedure authorized by 37 C.F.R. § 1.129(a) to seek reconsideration of the rejected claims. *Id.* ¶¶ F34-F35.

The Office responded on August 5, 1997 with another final rejection of all pending claims, but later withdrew the finality of the rejection after Patent Owner pointed out it was improper to make the rejection final. *Id.* ¶¶ F36-F38.

Patent Owner then submitted claim amendments and arguments in favor of patentability on December 8, 1997. *Id.* ¶ F39. The Office indicated on March 3, 1998 that some of the pending claims (*i.e.*, claims 31, 133, and 136-139) were allowable, but maintained rejections of all other pending claims. *Id.* ¶ F40.

After an interview and further claim amendments submitted August 3, 1998, the Office indicated on September 29, 1998 that it would not enter the August 3 amendments but observed that claims 134-135 were now also allowable, and rejected the remaining pending claims. *Id.* ¶¶ F40-F44. Patent Owner then properly requested, on March 2, 1999, that the August 3 amendments be entered by invoking the Section 129(a) authority. *Id.* ¶ F45.

On July 6, 1999, in response to arguments presented with Patent Owner's Section 129(a) authorized response and amendment, the Office indicated, in addition to the claims previously indicated as allowable, that claims 146-147 were also now allowable, and issued a non-final rejection of the remaining pending claims. *Id.* ¶ F46. Patent Owner submitted additional amendments and arguments on January 6, 2000. *Id.* ¶ F47.

After the Office issued a final rejection on March 28, 2000, Patent Owner conducted another interview with the Office on August 23, 2000 and followed up by submitting remarks with accompanying references to overcome the final rejection on September 29, 2000. *Id.* ¶¶ F48-F49. Although Patent Owner indicated that the interview and subsequent submission had significantly advanced prosecution, the Office did not reply as expected. *Id.* ¶ F50. Thus, "to expedite issuance of the case," Patent Owner cancelled all then-rejected claims on December 1, 2000, leading to issuance of the '471 Patent on September 4, 2001. *Id.* ¶¶ F50-F54.

This record of examination reflects that the Patent Owner complied with routine prosecution procedure, and did not take any actions that controlled the rate of prosecution of the '471 Patent claims to thereby delay their issuance. The mere fact that Patent Owner's final round of arguments did not prevail cannot constitute an action that "controlled the rate of prosecution" under relevant law. Indeed, under the Examiners' standard, any effort by a patent applicant to dispute a rejection would disqualify a patent from being considered under the two-way test. Under the law, Patent Owner was entitled to request reversal of rejections previously imposed, and had prevailed several other times in doing so. By no stretch of the imagination may this conventional examination activity be considered equivalent to the type of conduct the Federal Circuit found inappropriate under *Berg*. *See Berg*, 140 F.3d at 1434 ("PTO actions did not *dictate the rate of prosecution*" where "applicant chose to file a continuation and seek early issuance of the narrow species of claim.") (quoting *In re Goodman*, 11F.3d 1046, 1049, 29 USPQ2d 2010, 2013 (Fed. Cir. 1993)) (emphasis in original). Thus, Patent Owner's efforts to prosecute both allowable and rejected claims in the same application cannot weigh against Patent Owner or otherwise disqualify the '471 Patent claims from being considered under the two-way obviousness test for obviousness-type double patenting. Accordingly, the Board should apply the two-way obviousness test to evaluate the '471 Patent claims relative to the claims in the Reference Patents.

3. The Claims of the '471 Patent Do Not Render the Claims of the Reference Patents Obvious

The Examiners take the position that because the two-way test is not appropriate, Patent Owner's arguments for the patentability of the claims, supported by the declarations of Dr. Sander van Deventer and Dr. John Ghrayeb, "are not persuasive." Final Action at 25. Based on that mistaken belief, at no point during this reexamination of the '471 Patent did the Examiners engage in a substantive analysis of Patent Owner's arguments or evidence. *Id.* By declining to do so, the Examiners tacitly acknowledge that under the two-way test, Patent Owner's evidence establishes that claims 1 to 7 of the '471 Patent are not unpatentable over the claims of the '195 and '272 Reference Patents for reasons of obviousness-type double patenting.

(a) The Patent Owner Provided Substantial Evidence of Non-Obviousness Under the Two-Way Test

Under a two-way test for non-statutory double patenting, the Office must establish that, in March of 1991, a person of ordinary skill in the art, considering the claims of the '471 Patent, would have found the methods claimed in the '272 Reference Patent or in the '195 Reference Patent to have been obvious. More specifically, the Office must establish that the existence of a particular antibody specific to TNFα (*e.g.*, the chimeric antibodies claimed by the '471 Patent) would have made obvious the treatment of rheumatoid arthritis ("RA") per the method claims of the '195 Reference Patent, or the treatment of Crohn's disease, per the method claims of the '272 Reference Patent, by administering to a human a therapeutically effective amount of a particular anti-TNFα chimeric antibody. Since a person of ordinary skill in the art would have considered neither of these methods to have been suggested by the prior art or feasible to achieve in March of 1991, neither of these treatment methods would have been considered obvious by the person of ordinary skill in the art in March of 1991.

To support its arguments, Patent Owner submitted on December 19, 2013 declarations under 37 C.F.R. § 1.132 from two experts in the field of the '471 Patent.

- The first declaration is from Dr. Sander van Deventer (cited as "VD ¶ __"). Dr. van Deventer is a noted expert in the field of rheumatoid arthritis and Crohn's disease. Dr. van Deventer also has direct experience from working in the field in the 1990-1991 timeframe, and participated in a number of the clinical trials for

treatment of RA and Crohn's disease, both with respect to the chimeric anti-TNFα antibody infliximab (cA2) and other agents.

- The second declaration is from Dr. John Ghrayeb (cited as "JG ¶ _"), one of the named inventors of the '471, '272 and '195 Reference Patents. Dr. Ghrayeb has personal experience in the development of infliximab to treat RA and Crohn's disease, as well as experience with other efforts to develop both infliximab and other agents for treating RA and other diseases. These experiences include efforts to develop treatments for treatment of sepsis using TNFα targeting antibodies, as well as efforts to develop agents to treat RA. Dr. Ghrayeb's declaration provides insights into the challenges of successfully developing human therapeutic agents based on experiments conducted in animals or in cell-based assays.

As explained below, the testimony of these two experts shows that, in the March 1991 timeframe, a person of ordinary skill in the art would not have not considered it to be routine, predictable, or assured that any antibody product would provide a safe and effective method of treating any human disease, let alone that an anti-TNFα antibody like cA2 would provide a safe and effective method of treating complex, chronic diseases like RA and Crohn's disease. VD ¶¶ 15-17, 23-35, 40-53; JG ¶¶ 18-27; Trentham[38] at 371.

i. The '471 Patent Claims Would Not Have Rendered Obvious Methods of Treating Rheumatoid Arthritis Claimed in the '195 Reference Patent

In March of 1991, a person of ordinary skill in the art would not have had a reason to believe that targeting TNFα would provide any benefits in treating a patient suffering from RA. JG ¶ 33; VD ¶¶ 12, 27, 31-32, 37-39; Kingsley[39] at 177; Trentham at 370-71. Indeed, to the extent that one might have considered targeting an agent present in elevated levels in an RA patient, the logical choice would have been to focus on other agents, particularly interleukins (*e.g.*, IL-1, IL-2, IL-6, IL-8), rather than TNFα, all of which were known to be present in RA patients in higher amounts. VD ¶¶ 58-59. A person of ordinary skill in the art would not have

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[38] David E. Trentham in "Immunotherapy and other novel therapies," *Current Opinion in Rheumatology* 3:369-372 (Jun. 1991), was submitted as Exhibit E17 on December 19, 2013.

[39] Gabrielle Kingsley *et al.*, in "Immunotherapy of rheumatic diseases - practice and prospects," *Immunology Today* 12:177-179 (1991), was submitted as Exhibit E14 on December 19, 2013.

focused on TNFα in considering possible methods for treating RA patients in the March 1991 timeframe. VD ¶¶ 25-28, 60-62, 69, 71-76. Because of the high level of unpredictability in the field of RA in the March 1991 timeframe, and the lack of understanding of the disease and its progression, a person of ordinary skill in the art would have had no reasonable basis for believing that an anti-TNFα antibody-based treatment would be effective in treating RA in a human. JG ¶¶ 28-44; VD ¶ 65.

ii. The '471 Patent Claims Would Not Have Rendered Obvious Methods of Treating Crohn's Disease Claimed in the '272 Reference Patent

In 1990 and 1991, the causes of Crohn's disease were not well understood, and effective treatment options remained elusive. VD ¶ 13. As was the case with RA, elevated TNFα levels were found to be present in Crohn's disease patients, but the significance of this fact was not known. Indeed, even after March of 1991, there was no agreement in the field about the role, if any, that TNFα played in Crohn's disease. *See, e.g.*, VD ¶¶ 66-68, 71-80. Thus, as was the case for RA, the role of TNFα in Crohn's disease, if any, remained unclear and disputed.

Consequently, on the basis of knowledge in the field of Crohn's disease before March of 1991, a person of ordinary skill would not have considered treating human patients suffering from Crohn's disease with anti-TNFα antibodies, and would not have had a reasonable basis for expecting such treatments to provide any therapeutic benefits for those patients. VD ¶ 90. Thus, one of ordinary skill in the art would not have expected that an anti-TNFα antibody would be a safe and effective treatment for Crohn's disease.

(b) The Office Has Never Contended the Claims of the '471 Patent Are Obvious Under the Two-Way Test

The Examiners have never contested the substance of Patent Owner's evidence of non-obviousness. In response to this substantial evidence, the Examiners have stated only that the evidence need not be considered. Final Action at 25.[40] In so doing, the Examiners did not dispute the merits of the opinions expressed by these two experts, and did not suggest their

[40] Aside from a single change in verb tense, the same paragraph appeared in the proceeding Office Action. *See* '851 Reexamination, Final Action dated Aug. 26, 2014 at 23. The Examiner has not otherwise addressed the substance of the van Deventer and Ghrayeb declarations.

insights are not probative of the question of obviousness of the methods claimed in the '272 and '195 Reference Patents relative to the claims in the '471 Patent.

Because the two-way test is the proper test to use to evaluate the '471 Patent claims, and in view of the absence of any dispute about the expert testimony of Drs. van Deventer and Ghrayeb, the record overwhelmingly supports finding the claims of the '272 and '195 Reference Patents not obvious over the antibody claims of the '471 Patent.

(c) Strong Secondary Indicia of Non-Obviousness Provides Further Validation that the Claims of the Reference Patents and '471 Patent Are Patentably Distinct from Each Other

Secondary indicia of non-obviousness provides further validation of the conclusion that the claims of the Reference Patents and the '471 Patent are patentably distinct from each other. The claims are directed to a particular antibody, the cA2 antibody, which is marketed commercially as Remicade® (infliximab). Remicade® has been demonstrated to be safe and effective in the treatment of human patients afflicted with rheumatoid arthritis or with Crohn's disease. *See* "Prescribing Information," Remicade §§ 1.1, 1.2, 1.5 (submitted as Exhibit E81 on Dec. 19, 2013). Use of Remicade (infliximab) (*i.e.*, the cA2 antibody) to treat either RA or Crohn's disease is encompassed in the claimed inventions of the '272 and '195 Reference Patents, respectively. The claims of the '272 and '195 Reference Patents, thus, have a direct and clear nexus to several types of secondary indicia of non-obviousness that are linked directly to the use of infliximab to treat human patients afflicted with Crohn's disease or RA, respectively.

In both RA and Crohn's disease, there existed before March of 1991, a long-felt but unmet medical need for safe and effective treatment of each disease. VD ¶¶ 71-79; Elliott 1995.[41] The administration of Remicade (infliximab) to human patients afflicted with RA and Crohn's disease to treat those disorders, claimed in the '272 and '195 Reference Patents, has been proven through clinical trials to be safe and effective. VD ¶ 89; GD ¶¶ 15, 17; "Prescribing Information," Remicade §§ 1.1, 1.2, 1.5. The use of infliximab in this manner addresses the long-felt need. The use of Remicade (infliximab) to treat RA and Crohn's disease was met with a great deal of skepticism, which ultimately was shown to be unwarranted based on the

[41] M.J. Elliott, *et al.*, "TNFα Blockade in Rheumatoid Arthritis: Rationale, Clinical Outcomes and Mechanisms of Action," *Int'l J. Immunopharmacology* 17:141-145 (Feb. 1995), was submitted as Exhibit E72 on December 19, 2013.

surprising efficacy of Remicade (infliximab) in altering the course of disease progression in each type of disease. VD ¶¶ 69, 76, 81-92; Elliott 1993[42]; Breese.[43] Administration of Remicade (infliximab) to treat RA and Crohn's disease has been approved by the FDA, has enjoyed significant commercial success, and has been a significant contributor to the economic success of the Remicade product. JG ¶ 9, 14-17; VD ¶ 89; Exhibit E101.[44]

Since its first approval in 1998, the use of Remicade to treat Crohn's disease and to treat RA has been the subject of substantial praise. JG ¶ 16. The evidence of long-felt need for, skepticism about, considerable commercial success of, and praise for the use of Remicade (infliximab) to treat human patients afflicted with RA or Crohn's disease further supports the non-obviousness of the method claims in each of the '272 and '195 Reference Patents. *E.g.*, VD ¶¶ 23-35, 40-53, 69, 71-79, 81-92; JG ¶¶ 9, 14-17, 18-27

F. Conclusions

Claims 1 to 7 of the '471 Patent are not unpatentable for obviousness-type double patenting over the claims of the '272 and '195 Reference Patents, alone or in view of additional prior art, for the reasons presented above. Specifically:

- The safe harbor of Section 121 precludes the use of the claims of the Reference Patents in support of any obviousness-type double patenting rejections of the claims of the '471 Patent; and
- The claims of the References Patents and '471 Patent are, in any event, patentably distinct from each other as determined using the proper "two-way" test for obviousness-type double patenting.

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[42] Michael Elliott *et al.*, "Treatment of Rheumatoid Arthritis with chimeric monoclonal antibodies to tumour necrosis factor α," *Arthritis & Rheumatism*, 36:1681-1690 (Dec. 1993), was submitted as Exhibit E73 on December 19, 2013.

[43] Emma J. Breese *et al.*, "Tumor necrosis factor α-producing cells in the intestinal mucosa of children with inflammatory bowel disease," *Gastroenterology* 106:1455-1466 (Jun. 1994), was submitted as Exhibit E75 on December 19, 2013.

[44] The Johnson & Johnson 2003 annual report was submitted as Exhibit E101 on December 19, 2013.

Accordingly, Patent Owner respectfully requests that the rejections of claims 1 to 7 of the '471 Patent be withdrawn. Specifically, Patent Owner respectfully requests that the Board reverse:

- the rejection of claims 1, 3 and 5-7 of the '471 Patent over claims 1 to 16 of the '195 Reference Patent;
- the rejection of claims 1, 3 and 5-7 of the '471 Patent over claims 1-7 of the '272 Reference Patent; and
- the rejection of claims 2 and 4 of the '471 Patent over either claims 1-16 of the '195 Reference Patent or claims 1-7 of the '272 Reference Patent, in view of Fendly *et al.*, or Bringman *et al.*

V. RELIEF REQUESTED

For the reasons set forth above, claims 1 to 7 of the '471 Patent are thus patentable, and the Board is requested to reverse the Office's contrary determination and direct the Examiners to issue a certificate confirming the patentability of claims 1 to 7 of the '471 Patent.

Please charge Deposit Account No. 08-0380 for any fees that may be due in this matter.

Respectfully submitted,

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APPENDIX A:

Appendix of Claims [37 C.F.R. § 41.37(c)(1)(v)]

1. A chimeric antibody comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

2. An immunoassay method for detecting human TNF in a sample, comprising:

(a) contacting said sample with an antibody according to claim 1, or a TNF binding fragment thereof, in detectably labeled form; and

(b) detecting the binding of the antibody to said TNF.

3. A chimeric antibody comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

4. An immunoassay method for detecting human TNF in a sample, comprising:

(a) contacting said sample with an antibody according to claim 3, or a TNF binding fragment thereof, in detectably labeled form; and

(b) detecting the binding of the antibody to said TNF.

5. A chimeric antibody, comprising two light chains and two heavy chains, each of said chains comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said variable region capable of binding an epitope of human tumor necrosis factor hTNFα, wherein said light chains comprise variable regions comprising SEQ ID NO: 3 and said heavy chains comprise variable regions comprising SEQ ID NO: 5.

6. A chimeric antibody according to claim 5, wherein the human immunoglobulin constant region is an IgG1.

7. A chimeric antibody comprising at least part of a human IgG1 constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an

epitope specific for human TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

APPENDIX B:

Patent Owner's Listing of Undisputed or Admitted Facts

A. The Examiner Required Restriction in the Parent Application

F1. On September 27, 1993, the Parent Application was subjected to a telephone restriction requirement (the "Sept. 27 Restriction Requirement"), later documented in a non-final Office Action dated October 27, 1993 (the "Oct. 27 Office Action"). *See* U.S. Application No. 08/013,413 File Wrapper ("Parent Application File Wrapper"), Paper No. 8, Non-Final Action dated Oct. 27, 1993 at 6-7.

F2. The September 27, 1993 restriction requirement set forth five groups, which the Examiner determined represented distinct inventions. As the Examiner stated:

> Restriction to one of the following inventions is required under 35 U.S.C. § 121:
>
> I. Claims 1-21, 24, 38, 39 and 48, drawn to monoclonal antibodies, detectably labelled monoclonal antibodies, *chimeric antibodies*, pharmaceutical compositions, and assay methods, classified for example, in Classes 530, 424 and 435, subclasses (387.3, 388.23, 391.3), 85.8 and 7.2, respectively.
>
> II. Claims 22 and 23, drawn to *TNF polypeptides*, classified in Class 530, subclass 350.
>
> III. Claims 25-31 and 49, drawn to *polynucleotides* encoding antibodies, transformed hosts, transfected hosts, and processes for preparing antibodies by culturing transformed/transfected hosts, classified for example in Classes 536 and 435, subclasses 23.53 and (70.21, 240.2 and 252.3), respectively.
>
> IV. Claims 32, 33, 40-47 and 50, 51 and 54-57, drawn to *methods for treating* an animal by administering a pharmaceutical composition containing an antibody, classified in Class 424, subclass 85.8.
>
> V. Claims 34-37, 52 and 53, drawn to *methods for removing TNF-alpha* from a sample and treatment methods involving removal of TNF-alpha from a body fluid and returning said

> body fluid to an animal, classified for example, in Classes 530 and 424, subclasses 413 and 85.8.

Id. at 2 (emphases added).

F3. The Examiner set forth the bases for concluding that the inventions were distinct at pages 2 to 4 of the October 27 Office Action. As the Examiner explained:

> Inventions I and (IV and V) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products as claimed can be used in other and materially different methods of use as evidenced by the separate and distinct methods of use claimed in Groups I, IV and V.

Id. at 3-4.

F4. The Examiner also indicated that an election of species would be required if Patent Owner elected the Group IV invention for examination. As the Examiner explained:

> 16. Upon the election of Group IV above, a further election of species is required as follows:
>
> Claims 41 and 43 are generic to a plurality of disclosed patentably distinct species comprising methods of treating an animal having a pathology mediated by TNF wherein the pathology is selected from I) alcohol-induced hepatitis; II) chronic inflammatory pathology; III) a neurodegenerative disease; IV) a vascular inflammatory disease; V) a graft-versus-host pathology; VI) Kaisaki's pathology and VII) a malignant pathology. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed. The above species are distinct in that they relate to methods of use of anti-TNF monoclonal antibodies for treatment of distinct diseases which differ in the disease pathology and disease mechanisms.

Id. at 4-5.

F5. During the September 27, 1993 telephone conference, Patent Owner provisionally elected the Group IV invention (*i.e.*, methods of treatment using antibodies) for examination. With respect to the species election the Examiner conditionally imposed for Group IV,

Patent Owner elected the second species, *i.e.*, claims related to "chronic inflammatory pathology." *See id.* at 6-7.

F6. During the September 27, 1993 telephone conference, and in the subsequently mailed Office Action, the Examiner indicated that claims directed to non-elected subject matter (*i.e.*, the claims directed to inventions in Groups I, II, III and V) were withdrawn from consideration. *Id.* As the Examiner stated:

> During a telephone conversation with Mr. Townsend on 9/27/93 a *provisional election was made* with traverse to prosecute the invention of *Group IV*, claims 32, 33, 40-47, 50, 51 and 54-57. In response to the election of species requirement set forth in paragraph 16, above, Applicant *further elected species II.* Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-31, 34-39, 44-48, 49, 52, 53 are *withdrawn from further consideration* by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to *non-elected inventions*.

Id. at 6-7 (emphasis added).

F7. In an Office Action dated October 27, 1993, the Examiner rejected the claims in Group IV that had been elected for examination (*i.e.*, claims 32, 33, 40-47, 50, 51 and 54-57), and did not further consider the claims falling within the other four non-elected groups of the restriction requirement. *Id.* at 9-30.

F8. The Office never withdrew the restriction requirement applied in the Parent Application. *See* U.S. Application No. 08/192,093 File Wrapper ("'093 Application File Wrapper"), Non-Final Action dated Apr. 7, 1995; Non-Final Action dated Aug. 23, 1995; Final Rejection dated May 1, 1996; Final Rejection dated Aug. 5, 1997; Withdrawal of Finality of Rejection dated Nov. 12, 1997; Non-Final Action dated Mar. 3, 1998; Advisory Action dated Sept. 29, 1998; Non-Final Action dated July 6, 1999; Final Rejections dated Mar. 28, 2000.

B. The Reference Patents Claim the Group IV Invention

F9. In response to the non-final action mailed on October 27, 1993 in the Parent Application, Patent Owner filed several continuing applications in which claims within the Group IV

invention that had been elected in the Parent Application were presented for continued examination.[45]

F10. Among the applications filed to continue examination of the Group IV invention were:

1) U.S. Application Serial No. 08/192,102 ("the '102 Application"), filed on February 4, 1994, which issued as the '272 Reference Patent, and

2) U.S. Application Serial No. 08/324,799 ("the '799 Application"), filed on October 18, 1994, which issued as the '195 Reference Patent.

1. The '272 Reference Patent Claims Are Consonant with the Restriction Imposed in the Parent Application

F11. On December 23, 1994, before substantive examination began, Patent Owner presented a preliminary amendment in the '102 Application that cancelled all pending claims (*i.e.*, claims 1-70) in favor of new claims limited to the non-elected Group III invention of the September 27 Restriction (*i.e.*, new claims 71-90). *See* U.S. Application No. 08/192,102 File Wrapper ("'102 Application File Wrapper"), Preliminary Amendment dated Dec. 23, 1994 at 1-4. Patent Owner stated in this preliminary amendment that "[t]he Amendment present[ed] claims drawn to Group III of the restriction requirement set forth in parent application Serial No. 08/013,413 (Paper No. 8)." *Id.* at 4.

F12. On December 1, 1995, Patent Owner's representative conducted a telephone interview with the Examiner. In the interview, the Examiner provided guidance to Patent Owner as to how to pursue the elected and non-elected inventions from the restricted Parent Application in different continuing applications pending before the Office. *See* '102 Application File Wrapper, Preliminary Amendment dated Dec. 5, 1995 at 3 (referring to actions being taken "pursuant to the telephone conversation between Examiner Nisbet

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[45] Patent Owner petitioned for a one-month extension of time in the Parent Application to extend the deadline for responding to the October 27, 1993 Office Action to maintain the pendency of the Parent Application until after the date three of the subsequent applications were filed. *See* Parent Application File Wrapper, Paper 10, Response in Parent Case in Support of Petition and Fee for Extension of Time When Filing New Application Claiming Benefit of a Prior Filing dated Feb. 4, 1994.

and the undersigned on December 1, 1995" and was "made to reduce issues on examination [to] expedite prosecution."). *See also* '093 Application File Wrapper, Preliminary Amendment dated Dec. 22, 1995 at 3 (stating that claims were being "amended as suggested by the Examiner."); U.S. Application No. 08/192,861 ("the '861 Application") File Wrapper, Examiner's Interview Summary dated Dec. 1, 1995 ("Examiner suggested applicants file a supplemental preliminary amendment . . . .").

F13. On December 5, 1995, pursuant to the Examiner's guidance in the December 1, 1995 telephonic interview, and before substantive examination began in the '102 Application, Patent Owner filed another preliminary amendment, cancelling claims 71-90, and presenting new claims 91-97 directed to methods of treating Crohn's disease by administering a particular chimeric antibody, which fall within Group IV of the September 27 Restriction Requirement. '102 Application File Wrapper, Preliminary Amendment dated Dec. 5, 1995 at 1-3.

F14. On September 18, 1996, the Office issued a notice of allowance, and the '272 Reference Patent issued on August 12, 1997.

F15. The claims issued in the '272 Reference Patent are consonant with the restriction requirement imposed in the Parent Application, as each issued claim defines a method of treatment of Crohn's disease using antibodies to TNF that falls within the Group IV invention of the restriction requirement imposed in the Parent Application.

F16. In the present reexamination, the Examiners have acknowledged that the methods defined by the claims of the '272 Reference Patent are within the Group IV invention defined in the restriction requirement applied in the Parent Application. *See* '851 Reexamination, Final Action dated Feb. 12, 2015 ("Final Action") at 11 ("The '272 Reference Patent claims are drawn to a method of treating TNFα mediated Crohn's disease in a human by administering anti-TNF chimeric antibody.").

F17. In the present reexamination, the Examiners have acknowledged that the '102 Application that led to the '272 Reference Patent was used to continue examination of the same invention elected for examination in the Parent Application. *See id.* at 20 (". . . the '102

and '799 applications continue examination of the 'same invention' (Group IV) as in the parent '413 [Parent] application . . . .").

F18. In the Final Action in the present reexamination, the Examiners have described the relationship of claims 91-97 added to the '102 Application that issued in the '272 Reference Patent as follows:

> New claims 91-97 recite *a* method of treating Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of *an anti-TNF* chimeric antibody. Thus, the claims of the '102 Application covered the same subject matter elected (group IV) and examined in the parent '413 application.

Id. at 18.

2. The '195 Reference Patent Claims Are Consonant with the Restriction Imposed in the Parent Application

F19. On January 17, 1996, Patent Owner filed a preliminary amendment in the '799 Application cancelling all claims filed with the application, and presenting new claims limited to methods of treating rheumatoid arthritis in a human, one of the species of the Group IV invention defined in the Parent Application restriction. U.S. Application No. 08/324,799 File Wrapper ("'799 Application File Wrapper"), Preliminary Amendment dated Jan. 17, 1996 at 1-3.

F20. The Office issued a notice of allowance on May 28, 1997, and the '195 Reference Patent issued on December 16, 1997.

F21. All of the claims issued in the '195 Reference Patent are consonant with the restriction requirement imposed in the Parent Application, as each defines "[a] method of treating rheumatoid arthritis" using anti-TNF chimeric antibodies that falls within the Group IV invention of the restriction requirement applied in the Parent Application.

F22. In the present reexamination, the Examiners have acknowledged that the methods defined by the claims of the '195 Reference Patent are within the Group IV invention of the restriction requirement applied in the Parent Application. *See* '851 Reexamination, Final Action dated Feb. 12, 2015 at 9 ("The '195 [Reference Patent] claims are drawn to a

method of treating rheumatoid arthritis in a human by administering anti-TNF chimeric antibody.").

F23. In the present reexamination, the Examiners have acknowledged that the '799 Application that led to the '195 Reference Patent was used to continue examination of the same invention elected for examination in the Parent Application. *See id.* at 20 (". . . the '102 and '799 applications *continue examination of the "same invention" (Group IV) as in the parent '413 [Parent] application* . . . .") (emphasis added).

C. The '471 Patent Claims the Group I Invention

F24. On February 4, 1994, Patent Owner filed the '093 Application that issued as the '471 Patent.

F25. On December 23, 1994, Patent Owner filed a preliminary amendment that limited the claims presented for examination to "chimeric antibody" claims within the Group I invention of the restriction requirement applied in the Parent Application. *See* '093 Application File Wrapper, Preliminary Amendment dated Dec. 23, 1994 at 5.

F26. In the December 23, 1994 preliminary amendment, Patent Owner expressly stated it was presenting claims to the non-elected Group I invention that had been withdrawn from consideration in the Parent Application pursuant to the restriction in that application. *Id.* at 5 ("The above Preliminary Amendment cancels subject matter which is drawn to a non-elected invention pursuant to the restriction requirement set forth in parent application Serial No. 08/013,413 (Paper No. 8).").

F27. The '093 Application, as filed, was initially denominated a "continuation-in-part" application. This reflected the fact that the '093 Application's written description initially included information not found solely within the Parent Application to which the '093 Application claimed benefit, and which the '093 Application incorporated by reference.[46] The additional information derived, *inter alia*, from the disclosure of U.S. Application No. 08/010,406 ("the '406 Application").

[46] The '102 and '799 Applications are also designated continuation-in-part applications which claim the benefit of both the Parent Application and the '406 Application.

F28. The additional information originally in the '093 Application is unnecessary to support any of the Group I invention claims that were examined in the '093 Application and is unnecessary to support the claims that issued in the '471 Patent. The Examiner does not dispute these facts. *See, e.g.*, '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2 (withdrawing objections under § 112).

F29. On April 7, 1995, the Examiner issued a first Office Action that, *inter alia*, required an election of species between "I. [c]himeric antibodies, monoclonal antibodies, and immunoassay using an antibody and immunoreceptors which comprise the epitope binding region of an antibody," and "II. [i]mmunoreceptor molecules comprising TNF receptor fragments and anti-TNF peptides which are fragments of TNF receptors." '093 Application File Wrapper, Paper 18, Non-Final Action dated Apr. 7, 1995 at 2. The Examiner stated that if species II were to be elected, a further election between "[i]mmunoreceptor molecules comprising" fragments "of the TNF receptor p55" and "p75" would have to be made. *Id.* at 3-4.

F30. On May 1, 1995, Patent Owner responded to the election of species requirement, and elected species I for examination. '093 Application File Wrapper, Paper 19, Response to Restriction Requirement dated May 1, 1995 at 1-2.

F31. On August 23, 1995, the Examiner issued a non-final rejection. In this action, the Examiner confirmed the prior Office Action had "set forth an election of species requirement" rather than a restriction requirement. '093 Application File Wrapper, Paper 20, Non-Final Action dated Aug. 23, 1995 at 2.

F32. The Examiner did not substantively examine any of the claims in the '093 Application that were directed to subject matter derived from the '406 Application. *Id.*

F33. On December 22, 1995, Patent Owner timely responded to the non-final rejection with an amendment.[47] '093 Application File Wrapper, Amendment dated December 22, 1995 at 1. Patent Owner indicated that claims were being "amended as suggested by the

[47] The response was timely filed as it was filed in compliance with 35 U.S.C. §§ 41(a)(8) and 132.

Examiner." *Id.* at 3. Patent Owner stated that it was "actively prosecuting the non-elected subject matter in the file wrapper continuation of parent application Serial No. 08/010,406." *Id.*

F34. On May 1, 1996, the Examiner issued a final rejection of all pending claims. '093 Application File Wrapper, Paper 25, Final Rejection dated May 1, 1996 at 1. Patent Owner responded by timely filing a notice of appeal of the final rejection on October 31, 1996. '093 Application File Wrapper, Notice of Appeal dated Oct. 31, 1996.

F35. On May 5, 1997, Patent Owner timely filed a statutorily authorized submission under 37 C.F.R. § 1.129(a) to withdraw the finality of the May 1, 1996 Office Action, and to reopen prosecution. '093 Application File Wrapper, Amendment Under 37 CFR 1.129(a) dated May 5, 1997 at 1-2.

F36. On August 5, 1997, the Examiner issued a final rejection of all pending claims, but indicated that claims 136 to 139 would be allowable if rewritten in independent form. '093 Application File Wrapper, Paper 32, Final Rejection dated Aug. 5, 1997 at 1-3.

F37. On October 6, 1997, Patent Owner requested withdrawal of the finality of the rejection, pointing out that the Office had improperly imposed a new ground of rejection in the August 5, 1997 final Office Action. '093 Application File Wrapper, Request for Withdrawal of Finality of Rejection dated Oct. 6, 1997 at 1-2.

F38. On November 12, 1997, the Office mailed an action which withdrew the finality of the August 5, 1997 Office Action, stating "Upon consideration of applicant's request, the finality of the previous Office action, paper No. 32 is withdrawn." '093 Application File Wrapper, Paper 34, Office Communication dated Nov. 12, 1997 at 2.

F39. On December 8, 1997, Patent Owner timely responded with claim amendments and argument in favor of patentability. '093 Application File Wrapper, Amendment dated Dec. 8, 1997.

F40. On March 3, 1998, the Examiner issued a final rejection. '093 Application File Wrapper, Paper 38, Final Action dated Mar. 3, 1998 at 1. In that action, the Examiner indicated

that pending claims 31, 133, and 136-139 were allowed, but the Examiner continued to reject, *inter alia*, claims 134-135. *See id.* at 2, 4.

F41. On June 9, 1998, Patent Owner conducted an interview with the Examiner. '093 Application File Wrapper, Paper 40, Interview Summary dated Jun. 9, 1998.

F42. On August 3, 1998, Patent Owner timely filed an amendment after final. '093 Application File Wrapper, Amendment After Final Rejection dated Aug. 3, 1998.

F43. On September 1, 1998, Patent Owner filed a notice of appeal. '093 Application File Wrapper, Notice of Appeal from the Primary Examiner to the Board of Appeals dated Sept. 1, 1998.

F44. On September 29, 1998, the Examiner mailed an advisory action. '093 Application File Wrapper, Paper 44, Advisory Action dated Sept. 29, 1998. The advisory action indicated that the Examiner refused to enter the August 3, 1998 amendment and response, but indicated that claims 134 and 135 were now being allowed. *Id.* at 1.

F45. On March 2, 1999, Patent Owner filed a second request under 37 C.F.R. § 1.129(a) to withdraw the finality of the March 3, 1998 Office Action, and to treat the amendment and response filed by Patent Owner on August 3, 1998 as a § 129(a) submission. '093 Application File Wrapper, Submission Under 37 CFR 1.129(a) dated Mar. 2, 1999.

F46. On July 6, 1999, the Examiner issued a non-final rejection. '093 Application File Wrapper, Non-Final Action dated Jul. 6, 1999. In this action, the Office also indicated that claims 146-147 were allowed. *Id.* at 1, 3.

F47. On January 6, 2000, Patent Owner timely responded to the non-final rejection with an amendment. '093 Application File Wrapper, Amendment dated Jan. 6, 2000 at 1.

F48. On August 23, 2000, Patent Owner conducted another interview with the Examiner. *See* '093 Application File Wrapper, Remarks dated Sept. 29, 2000 at 1.

F49. On September 29, 2000, pursuant to the August 23, 2000 interview, Patent Owner timely submitted Remarks with accompanying references to overcome the final rejection. *Id.*

Patent Owner also filed a notice of appeal. '093 Application File Wrapper, Notice of Appeal from the Primary Examiner to the Board of Appeals dated Sept. 27, 2000.

F50. On October 12, 2000 and again on November 2, 2000, Patent Owner attempted to contact the Examiner to ascertain the status of the Remarks it had filed and of the application. *See* '093 Application File Wrapper, Amendment After Final Rejection Under 37 C.F.R. 1.116 dated Dec. 1, 2000 at 2.

F51. On December 1, 2000, Patent Owner submitted an amendment. *Id.* In the amendment, Patent Owner stated that it had understood "that the Examiner would reconsider the rejections in light of the discussion of the claims during the interview, the Remarks and accompanying references establishing the advantages of IgG1 in the context of the invention and contact the Applicants as to those claims which would be allowable," but in light of the lack of any response from the Office, it was now cancelling all rejected claims pending in the application "to expedite issuance of the case." *Id.*

F52. On March 20, 2001, the Examiner entered the December 1, 2000, amendment. '093 Application File Wrapper, Examiner's Amendment dated Mar. 20, 2001 at 2. On that date, the Examiner also entered an Examiner's amendment based on a telephone interview that occurred on March 15, 2001. *Id.*

F53. The Examiner mailed a notice of allowance on April 4, 2001, allowing claims "31, 133-136, 138, 139, 146 and 147" and stating that they would be "renumbered as 2, 4, 5, 6, 1, 3, 7, 8 and 9 respectively." '093 Application File Wrapper, Notice of Allowance and Issue Fee Due dated Apr. 4, 2001.

F54. On July 6, 2001, the Office noted payment of the issue fee, and the '471 Patent issued on September 4, 2001.

F55. All issued claims in the '471 Patent are consonant with the restriction requirement imposed in the Parent Application, as each defines antibodies or immunoassays within Group I ("monoclonal antibodies, detectably labelled monoclonal antibodies, chimeric antibodies, pharmaceutical compositions, and assay methods") of that restriction requirement:

1) Claims 1, 3, 5, 6, and 7 are claims that recite "[a] chimeric antibody."

2) Claims 2 and 4 are dependent claims which recite "[a]n immunoassay method" using the antibody of claim 1 or 3, respectively.

3) Claims 8 and 9 (subsequently cancelled in this reexamination) recite "[a] polypeptide comprising" either "the amino acid sequence of SEQ ID NO: 3" or "SEQ ID NO: 5" which "bind[] to hTNFα and competitively inhibit[] the binding of monoclonal antibody cA2 to hTNFα." Such polypeptides necessarily comprise the functional portions of chimeric antibodies because the recited sequences are the light chain and heavy chain variable regions of the chimeric antibody cA2 disclosed in the specification of the '471 Patent.

See '471 Patent at 7:19-25.

F56. The Examiners have not contested that claims 1 to 9 of the '471 Patent are within Group I of the September 27 Restriction.

D. The Present Reexamination Proceeding

F57. On April 29, 2013, a third-party requester filed a request for reexamination of the '471 Patent. '851 Reexamination, Request for Ex Parte Reexamination of United States Patent No. 6,284,471 (Le et al.). The request sought reexamination of '471 Patent claims 1-9 based on three grounds:

1) claims of the '195 Reference Patent render all claims of the '471 Patent unpatentable for obviousness-type double patenting;

2) claims of the '272 Reference Patent render all claims of the '471 Patent unpatentable for obviousness-type double patenting; and

3) claims of U.S. Patent No. 6,277,969 ("the '969 Patent") render all claims of the '471 Patent unpatentable for obviousness-type double patenting.

Id. at 4.

F58. On June 16, 2013, the Office determined that the request for reexamination raised a substantial new question of patentability for claims 1-9 of the '471 Patent. '851

Reexamination, Order Granting Ex Parte Reexamination at 2. The Office then commenced reexamination of the '471 Patent based on the requester's allegations of obviousness-type double patenting over the '195 Reference Patent, the '272 Reference Patent, and the '969 Patent. *Id.*

F59. In an Office Action dated September 6, 2013, the Examiners rejected the '471 Patent claims on the following grounds:

1) Claims 1, 3 and 5-9 were rejected for non-statutory double patenting based on claims 1-16 of the '195 Reference Patent. '851 Reexamination, Non-Final Action dated September 6, 2013 at 5-6.

2) Claims 1, 3 and 5-9 were rejected for non-statutory double patenting based on claims 1-7 of the '272 Reference Patent. *Id.* at 6-7.

3) Claims 8 and 9 were rejected for non-statutory double patenting based on claims 1-4 of the '969 Patent. *Id.* at 7-8.

4) Dependent claims 2 and 4 were rejected for non-statutory double patenting based on the claims in the '195 Reference Patent and claims in the '272 Reference Patent, in view of two other references. *Id.* at 8-9.

F60. Patent Owner conducted interviews with representatives of the Office on October 2, 2013 and October 30, 2013 to discuss the rejections set forth in the September 6, 2013 Office Action. '851 Reexamination, Summary of Interviews dated Nov. 1, 2013 at 1. During the interviews, Patent Owner expressed its intention to amend the specification of the '471 Patent to reflect the '471 Patent's status as a divisional of the Parent Application. *Id.* at 2-5. Patent Owner also expressed its intention to cancel claims 8 and 9, thereby rendering moot the rejection of those claims over the claims of the '969 Patent. *Id.* at 5.

F61. On December 19, 2013, Patent Owner filed a response to the September 6, 2013 Office Action. In the response, Patent Owner observed that the rejections were inconsistent with the prior restriction requirement as a matter of both law and science. '851 Reexamination, Amendment dated Dec. 19, 2013 at 26-56. Patent Owner also cancelled

claims 8 and 9 of the '471 Patent. *Id.* at 5, 10, 26. Patent Owner also submitted evidence demonstrating that the '195 or '272 Reference Patent claims would not have been obvious over the '471 Patent claims. *Id.* at 53-79.

F62. In the December 19, 2013 response, Patent Owner also presented an amendment to the specification of the '471 Patent to conform it to the disclosure of the Parent Application and to designate the '093 Application a divisional of the Parent Application. *Id.* at 19. In particular, Patent Owner proposed to amend the specification to remove unclaimed subject matter concerning immunoreceptor molecules from the specification. *See id.* at 13 ("The amendments to the specification of the '471 patent do not introduce new matter as a consequence of removing subject matter not found within the specification of the '413 application. Certain of the subject matter being removed by this amendment is the subject matter found solely in the '406 application that concerns 'immunoreceptor molecules.' *See, e.g.*, Examples XXIV-XXVI of the '471 patent.") (footnotes omitted).

F63. Patent Owner established that claims 1 to 7 of the '471 patent are fully supported by the disclosure of the Parent Application, which is now the same as the disclosure of the '471 Patent. *See* '851 Reexamination, Amendment dated Dec. 19, 2013 at 11-16; *see also* '851 Reexamination, Amendment After Final Rejection dated Oct. 10, 2014 at 116-117; '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2 (withdrawing objections under § 112).

F64. Claims 8 and 9, which were cancelled in the December 19, 2013 amendment, were directed to a polypeptide comprising the light or heavy chain sequence, respectively, of the cA2 chimeric antibody. The polypeptide also was required to inhibit the binding of the cA2 antibody to human TNF alpha. Claims 8 and 9 are fully supported under 35 U.S.C. § 112 by the disclosure of the Parent Application alone, and do not depend on any information found in either the '406 Application or in the original disclosure of the '093 application. Parent Application File Wrapper, Specification at 6 ("anti-TNF antibodies of the present invention competitively inhibit the binding of A2 antibodies to TNF"), 9 ("a chimeric antibody is provided which binds epitopes of the antibody designated chimeric

A2 (cA2), or a chimeric human-mouse anti-TNF mAb that competitively inhibits the binding of cA2 to TNFα").

F65. On August 26, 2014, a final Office Action was mailed that maintained the rejections set forth in the September 6, 2013 Office Action. '851 Reexamination, Final Action dated Aug. 26, 2014. In the Final Office Action, the Examiners refused to enter the amendments that Patent Owner presented in its December 20, 2013 response. *Id.* at 2.

F66. On September 17, 2014, Patent Owner conducted another interview with representatives of the Office, this time discussing the amendments to the specification, the entitlement of the patent to evaluation under the "two-way" test for obviousness-type double patenting, and reconsideration of the basis of the obviousness-type double patenting rejections. '851 Reexamination, Examiner Interview Summary dated Oct. 1, 2014.

F67. On October 10, 2014, Patent Owner submitted a response to the final rejection. In the response, Patent Owner explained that entry of the amendments was proper and justified and responded to the Examiners' rejections. '851 Reexamination, Amendment After Final Rejection Under 37 C.F.R. § 1.116 dated Oct. 10, 2014.

F68. On October 26, 2014, Patent Owner petitioned pursuant to 37 C.F.R. § 1.181 to direct entry of the amendments presented with Patent Owner's October 10, 2014 response. '851 Reexamination, Petition Under 37 C.F.R. § 1.181 to Direct Entry of Amendments dated Oct. 26, 2014.

F69. On October 27, 2014, Patent Owner petitioned pursuant to 37 C.F.R. § 1.181 requesting that the Office act consistently in this proceeding with its prior determination in the restriction applied in the Parent Application that the inventions defined by the claims of the '471 Patent and the '272 and '195 Reference Patents are patentably distinct. '851 Reexamination, Petition Under 37 C.F.R. § 1.181 to Require Consistent Determinations dated Oct. 27, 2014.

F70. On October 31, 2014, the Examiners mailed an Advisory Action in which they declined to enter the October 10, 2014 amendments to the specification and maintained the

obviousness-type double patenting rejections. '851 Reexamination, Advisory Action dated Oct. 31, 2014.

F71. On November 25, 2014, the Director of the Central Reexamination Unit granted Patent Owner's October 26, 2014 Petition, entered the amendments presented in Patent Owner's October 10, 2014 response, and returned the proceeding to the Examiners. '851 Reexamination, Decision on Petition dated Nov. 25, 2014.

F72. On December 22, 2014, the Supervisory Patent Reexamination Specialist of the Central Reexamination Unit dismissed the Petition to Require Consistent Determinations as "moot since the ultimate relief which is requested by petition was already granted in the Petition Decision dated November 25, 2014, which reopened prosecution and returned the proceeding back to the Examiner for issuance of a new Office Action." '851 Reexamination, Decision on Petition dated December 22, 2014.

F73. In an Office action dated February 12, 2015, the Examiners acknowledged the effectiveness of the amendments to the disclosure of the '471 Patent designating the '093 Application a division of the Parent Application, but nonetheless issued another final Office Action maintaining rejections of the '471 Patent claims over claims of the '272 and '195 Reference Patents. '851 Reexamination, Final Action dated February 12, 2015 ("Final Action") at 3, 9, 11.

F74. In the February 12, 2015 Final Action, the Examiners reapplied the previous double patenting rejections, and responded to Patent Owner's safe harbor arguments, *inter alia*, by alleging (a) that the applications that issued as the Reference Patents were not filed "as divisional applications as a result of restriction requirement in the parent '413 application" or divisionals of the '093 Application, and (b) the '093 Application which issued as the '471 Patent was not, on the date it was filed, designated a "divisional" application but instead was designated a "continuation-in-part" application. The Examiners concluded, "[t]herefore the 35 USC 121 safe harbor provision does not apply to the '471 patent (see MPEP 804.01)." Final Action at 13 (parenthetical cross-reference omitted), 19-20.

F75. In the February 12, 2015 Final Action, the Examiners acknowledged that Patent Owner elected claims drawn to Group I during prosecution of the '093 Application. *See* Final Action at 16.

F76. In the February 12, 2015 Final Action, the Examiners maintained that the '471 Patent claims are not entitled to be evaluated for ODP purposes based on the two-way test for two reasons: (i) because the '471 Patent and '272 Reference Patent were filed on the same day, and (ii) because, in view of the amendments and extensions involved in prosecuting the '471 Patent, "applicant's [sic] exercised significant control over the rate of prosecution of the application at issue." Final Action at 25.[48]

F77. At footnote 5 of the final Office Action of February 12, 2015, in reference to the introduction of certain polypeptide claims (claims 140-159) into the '093 Application, the Examiners contended that the "line of demarcation between the independent inventions as set forth in the restriction of the parent '413 application" had been crossed by "bringing polypeptide claims into the present application ('093 application)." *Id.* at 17. The Examiners further contended that the "Examiner in the 08/570,674 application restricted the chimeric antibodies and polypeptides into distinct groups (9/18/96)." *Id.*

F78. On March 31, 2015, Patent Owner conducted another interview with the Examiner, this time to discuss a number of issues raised in the Final Action, including why assertions in footnote 5 suffered from factual errors or inaccuracies. '851 Reexamination, Interview Agenda dated Mar. 30, 2015.

F79. On April 13, 2015, Patent Owner filed a response after final in which it requested withdrawal of the rejections. In the response, Patent Owner explained, *inter alia*, that entry of the Patent Owner's October 10, 2014 amendments confirms that the '093 Application is a "divisional," and that the '471 Patent claims are within the safe harbor of

[48] Although in the Final Action the Examiner also rejected claims 1-7 as not complying with the written description and enablement requirements, Final Action at 5-9, the Examiner later withdrew the written description and enablement objections. '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2.

35 U.S.C. § 121. '851 Reexamination, Amendment After Final Rejection Under 37 C.F.R. § 1.116 dated Apr. 13, 2015.

F80. In the April 13, 2015 response, Patent Owner also made of record the substance of the March 31 interview, in particular pointing out that Patent Owner's representative explained that the characterization of claims 140-159 added during examination of the '093 Application which appears in footnote 5 of the Final Action was not accurate, as these claims defined antibody polypeptides rather than TNF polypeptides that were the subject of Group II of the '413 restriction requirement. *Id.* at 12-14. Patent Owner's representative also explained at the interview that the restriction imposed in U.S. Application 08/570,674 was consistent with the restriction imposed in the Parent Application, and noted that the claims presented in the '674 Application did not correspond to the range of claims presented in the Parent Application, which explained why certain of the groups of the original restriction were not reiterated in the '674 Application. *Id.*

F81. Patent Owner also made of record that "Representatives of the Office acknowledged the clarifications made by Patent Owner's representative." *Id.*

F82. Also on April 13, 2015, Patent Owner petitioned to have the Examiners apply consistent determinations between the September 27, 1993 restriction requirement and the present reexamination proceeding by finding the '471 Patent claims patentably distinct from the claims of the '272 and '195 Reference Patents. '851 Reexamination, Petition Under 37 C.F.R. § 1.181 to Adhere to Prior Restriction Requirement dated April 13, 2015.

F83. On April 29, 2015, the Examiners mailed an Advisory Action maintaining the position that 35 U.S.C. § 121 is not applicable despite entry of the amendment designating the '093 Application a divisional application of the Parent Application. '851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2. In that Advisory Action, the Examiners stated:

> The '195 and the '272 patent applications were filed as Continuation-in-part of applications of the parent '413 application.

> The specification of the '195 and '272 patent applications were different from the parent '413 application; the original claims which were subjected to the resriction [sic] requirement in the parent application were not present (at the time of the filing of the application) in these applications. Since the '195 and '272 patent applications were filed as CIP applications and include different specification (new matter as compared to the parent '413 application) and claim priority to more than one prior application, the safe harbor provision of 37 CFR 121 does not apply.
>
> Further, the present '471 patent application was originally (2/4/94) filed as continuation-in-part application of parent '413 application (with a different specification as compared to the parent), thus the present '471 patent application was not filed "as divisional application as a result of restriction requirement." The 10/10/14 amendment corrected the relationship of the '471 patent to the '413 application as "Divisional", which would not read on the third sentence of the 37 CFR 121, which refers to a "patent issuing on an application filed as a result of restriction requirement." The '471 patent application was not filed (2/4/94) as divisional as a result of restriction requirement. Thus, for the reasons of record the safe harbor provisions of 37 CFR 121 are not applicable for the present '471 patent and for the reasons of record set forth in the final office action, the ODP rejections are maintained.

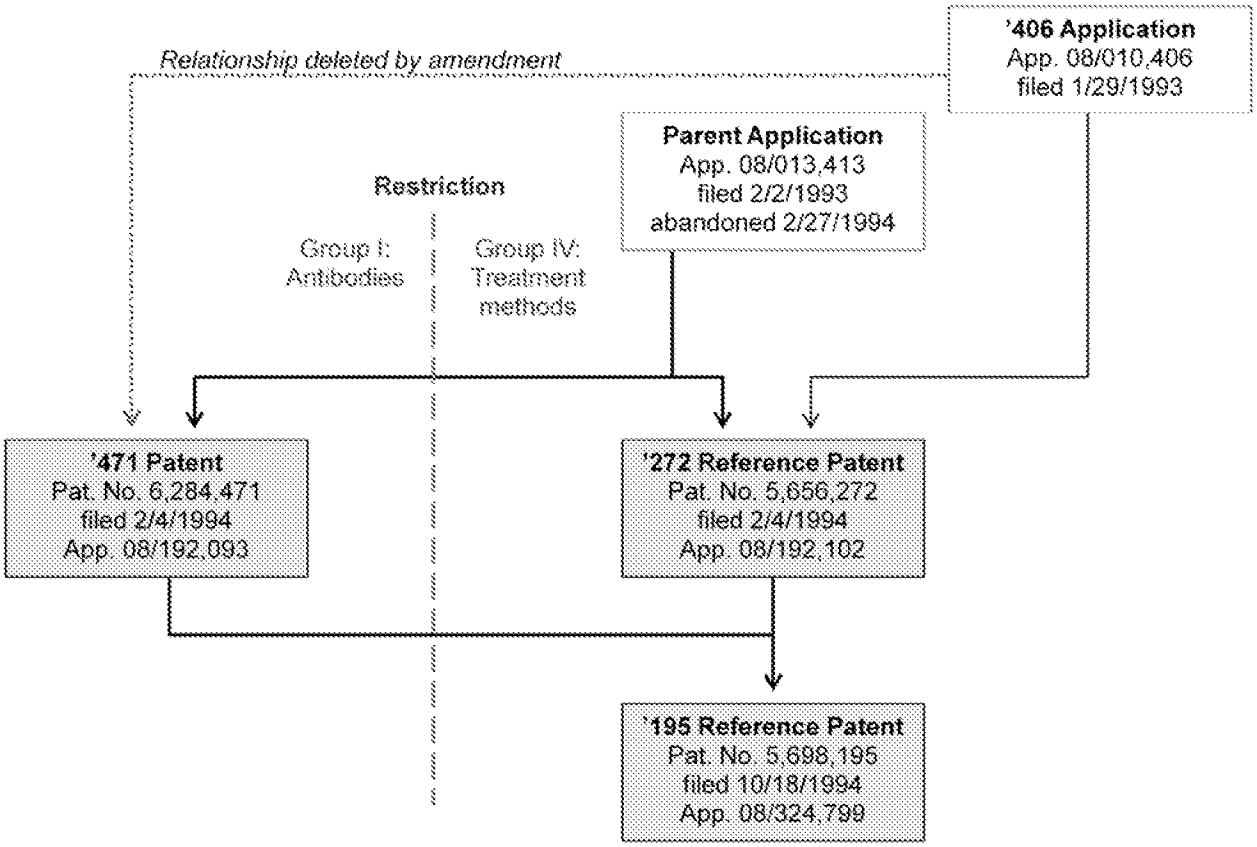
'851 Reexamination, Advisory Action dated Apr. 29, 2015 at 2.

F84. On May 21, 2015, the Director of the Central Reexamination Unit dismissed the petition for consistent determinations between the September 27, 1993 restriction requirement and the present reexamination proceeding as "moot." '851 Reexamination, Petition Decision dated May 21, 2015 at 4. The Director of the Central Reexamination Unit reasoned that "the relief requested by Patent Owner" was available via appeal to the Board, and thus could not be obtained via petition. *Id.*

F85. On May 27, 2015, Patent Owner timely filed a notice of appeal. '851 Reexamination, Notice of Appeal dated May 27, 2015.

APPENDIX C:

Diagram of '471 Patent Family History



* Other applications claiming benefit of the Parent Application and the '406 Application are not depicted. For simplicity, types of relationships between patents and applications are not indicated.

APPENDIX D:

Table Comparing Patent Claims to '413 Restriction Groups

Group I of the '413 Restriction Requirement	**Group IV of the '413 Restriction requirement**	
I. Claims 1-21, 24, 38, 39 and 48, drawn to monoclonal antibodies, detectably labelled monoclonal antibodies, ***chimeric antibodies****, pharmaceutical compositions, and* ***assay methods****, classified for example, in Classes 530, 424 and 435, subclasses (387.3, 388.23, 391.3), 85.8 and 7.2, respectively.*	*IV. Claims 32, 33, 40-47 and 50, 51 and 54-57, drawn to methods for* ***treating an animal*** *by* ***administering a pharmaceutical composition containing an antibody****, classified in Class 424, subclass 85.8.*	
'471 Patent Claims	**'195 Patent Claims**	**'272 Patent Claims**
1. A **chimeric antibody** comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.	1. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody comprises a non-human variable region or a TNF antigen-binding portion thereof and a human constant region. 2. The method of **claim 1** wherein the non- human variable region is of murine origin. 3. The method of **claim 1** wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO.: 1 of hTNF. 13. The method of **claim 1** wherein the non- human variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO.: 3 and	1. A method of **treating TNFα-mediated Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody comprises a non-human variable region or a TNF-binding portion thereof and a human constant region. 2. The method of **claim 1** wherein the non- human variable region is of murine origin. 3. The method of **claim 1** wherein said anti- TNF chimeric antibody competitively inhibits binding of TNF to the monoclonal antibody cA2. 4. The method of **claim 1** wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57, or 155-157 of SEQ ID NO.: 1 of hTNF.

	SEQ ID NO.: 5. 14. The method of **claim 1** wherein the non- human variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO.: 3 and SEQ ID NO.: 5. 15. The method of **claim 1** wherein the non- human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO.: 2 and SEQ ID NO.: 4.	
2. An **immunoassay** method for detecting human TNF in a sample, comprising: (a) contacting said sample with an antibody according to claim 1, or a TNF binding fragment thereof, in detectably labeled form; and (b) detecting the binding of the antibody to said TNF.	4. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2.	5. A **method of treating TNFα-mediated Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to the monoclonal antibody cA2.
3. A **chimeric antibody** comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.	5. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO.:1 of hTNF.	6. A **method of treating TNFα-mediated Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody binds to one or more epitopes included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO.:1 of hTNF.

4. An **immunoassay** method for detecting human TNF in a sample, comprising: (a) contacting said sample with an antibody according to claim 3, or a TNF binding fragment thereof, in detectably labeled form; and (b) detecting the binding of the antibody to said TNF.	6. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of chimeric anti-TNF antidody** [sic] **cA2**.	7. A **method of treating TNFα-mediated Crohn's disease in a human comprising administering to the human an effective TNF-inhibiting amount of chimeric anti-TNF antibody cA2**.
5. A **chimeric antibody**, comprising two light chains and two heavy chains, each of said chains comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said variable region capable of binding an epitope of human tumor necrosis factor hTNFα, wherein said light chains comprise variable regions comprising SEQ ID NO: 3 and said heavy chains comprise variable regions comprising SEQ ID NO: 5. 6. A **chimeric antibody** according to claim 5, wherein the human immunoglobulin constant region is an IgG1.	7. A method of **treating rheumatoid arthritis, in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody comprises a non-human variable region or a TNF antigen-binding portion thereof and an IgG1 human constant region. 8. The method of **claim 7** wherein the non- human variable region is of murine origin. 9. The method of **claim 7** wherein said anti- TNF chimeric antibody competitively inhibits binding of TNF to monoclonal antibody cA2. 10. The method of **claim 7** wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO.: 1 of hTNF. 16. The method of **claim 7** wherein the non- human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO.: 2 and SEQ ID NO.: 4.	

7. A **chimeric antibody** comprising at least part of a human IgG1 constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.	11. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.	
8. A polypeptide comprising the **amino acid sequence of SEQ ID NO: 3**[49], wherein said polypeptide binds to h TNFα and competitively inhibits the binding of monoclonal antibody cA2 to hTNFα. [*cancelled*]	12. A method of **treating rheumatoid arthritis in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody**, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO.:1 of hTNF.	
9. A polypeptide comprising the **amino acid sequence of SEQ ID NO: 5**, wherein said polypeptide binds to h TNFα and competitively inhibits the binding of monoclonal antibody cA2 to hTNFα. [*cancelled*]		

[49] The amino acid sequences defined in SEQ ID NO: 3 and in SEQ ID NO: 5 constitute a chimeric immunoglobulin polypeptide sequence having murine variable region sequences and human constant region sequences.