Celgene Patent Review - Revlimid®

Revlimid® and its patent families do not appear to meet the criteria for legitimate patent protection

M·CAM

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Executive Summary

On May 7, 2015, the European Patent Office (EPO) revoked one of Celgene's (NASDAQ: CELG) patents on Revlimid®. Revlimid® reportedly accounts for almost $5 billion of Celgene's nearly $7.5 billion in annual revenueand is approved by the U.S. Food and Drug Administration (FDA) for the treatment of cancer and other autoimmune diseases.A systematic and rigorous review of the available precedent information provides a sound basis for the invalidation of many other Revlimid® patents, including those currently listed in the FDA's Orange Book, on the grounds that they are based on an older drug and that the use of the drug in the treatment of cancer was obvious. If the invalidation of the entire Revlimid® portfolio were systematically pursued by a third party, it could materially and adversely impact Celgene.

Simply put, the core Revlimid® compound patent, U.S. Pat. No. 5,635,517 ('517), is and has always been based on an old drug (thalidomide) and the "innovations" on which Revlimid is based, going back to its priority date in 1996, are obvious in light of precedent innovation. As a result, the '517 patent should not be entitled to patent protection in the United States or any of the nearly 70 countries where Revlimid® is approved. Since this base patent of the Revlimid® families of patents is not valid, then many of the Revlimid® patents are subject to validity or commercial relevance challenges.

Thalidomide, the drug on which Revlimid is based, was first on the market in 1957 and used as a sedative. It was found to be immunotherapeutic in the 1960s, which means it could treat diseases "by inducing, enhancing, or suppressing an immune response".Beginning with the seminal works of Sheskin and Hellmann in 1964 and 1965, extensive non-patent literature establishes the immunomodulatory properties of thalidomide and its derivatives, including lenalidomide, the active ingredient in Revlimid®. For example, a 1970 scientific study by Coulson et al. found thalidomide derivatives to have the same immunomodulatory properties as thalidomide. Then, in 1991, Sampaio et al. established the clinical action of thalidomide in inhibiting tumor necrosis factor α (TNFα) (See references in the Appendix). In light of these precedents, examiners of Celgene's '517 patent should have found it obvious that a closely-related chemical analog like lenalidomide would reasonably exhibit similar properties and therefore should not have issued this core Revlimid® patent upon which all of the Revlimid® patents are based. There has been nothing unexpected or unanticipated about the effects or uses of the pharmaceutical compounds claimed by Celgene over the precedent scientific literature.

Wall Street has been focused for weeks on a European Patent Office (EPO) opposition proceeding of Celgene Corporation's European Pat. No. 1,667,682 ('682), which purportedly covers polymorphic forms of Celgene's drug Revlimid® (lenalidomide). On May 7, 2015, attorneys from Celgene, Teva Pharmaceutical Industries Ltd. (TEVA), and Mylan N.V. (MYL) argued the novelty and obviousness of the '682 patent and the patent was revoked. This result was largely anticipated as polymorphs, also known as solvates or crystalline forms, of a previously-patented compound are routinely developed as "a standard practice in the industry"[1]and are not generally believed to be separately patentable.

Some commentators have expressed opinions as to whether the elimination of the '682 patent in the EPO proceeding will invite additional scrutiny of Celgene's U.S. polymorph patents. The polymorph patents are not, however, the most significant hole in Celgene's protection around Revlimid®. We see much more comprehensive challenges to Revlimid® that strike at the *entire suite of patents* given exclusivity in the Orange Book.

[1]During the examination of U.S. Patent 7,968,569, U.S. patent examiner Michelle Graffeo rejected the novelty of a Revlimid® patent application stating: "***Methods of preparing and use of salts and solvates of pharmaceuticals is a standard practice in the industry. Thus one skilled in the art would understand that the present invention can be practiced with a salt or solvate of the enantiomeric compound***." This objection reportedly was overcome in a telephonic interview the substance of which is not in the public record. *United States Patent and Trademark Office. Office action: Non-final rejection. 30 June, 2005. p. 3.*

While the market has been primarily focused on the EPO opposition proceeding (and whether the result will "read across" to the U.S. polymorph patents), Celgene's case against Natco Pharma, and Hayman Capital's filing of *inter partes* review (IPR) petitions, the focus should be much more broadly applied. With the exception of Hayman Capital's recent IPR petitions, which are aimed at the core Revlimid® compound patent and Revlimid® patents on methods of drug distribution, the other events that have gained market attention are largely related to patents that do not address the formulation of the drug itself, but rather for testing for contraindications. Any invalidation or limitation of this group of patents would do little to limit Celgene's ability to enforce exclusivity of various forms of lenalidomide (Revlimid®).

These events may likely prove to be peripheral as the market shifts its focus to the fundamental flaws in the Revlimid® compound patents, the invalidation of which would take away Celgene's market exclusivity for the drug.

Revlimid Patents Under Review in This Report

Family	Revlimid Patents Under Review	International Coverage	Priority Date
Elasayed	US6045501, US6561976	----	08/28/1998
Williams	US8315886, US6315720, US6561977, US6755784	Japan, Canada, Australia	10/23/2000
Muller	US5635517	Russia	07/24/1996
Zeldis-2	US8404717, US7189740	South Korea, Australia, Canada, Japan	10/15/2002
Zeldis-1	US7968569	Taiwan, South Korea, Japan, Canada, Australia	05/17/2002
Jaworsky	US8431598, US8193219, US7977357, US7465800, EP1667682	South Africa, Japan, Europe, China, Canada, Australia, South Korea, African Intellectual Property Organization	09/04/2003

Appendices

Celgene Patent on Reduction of TNFα

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Muller et al	07/24/1996 07/24/1996 10/04/2019

Commentary

Celgene's '517 patent claims a method of inhibiting Tumor Necrosis Factor α (TNFα) via various analogues of the compound thalidomide. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '517 patent's claimed mechanism of TNFα inhibition was well known before the patent's 1996 priority date. A person skilled in the art would reasonably expect that lenalidomide, being an analogue of thalidomide, would exhibit the same mechanisms of action on immunomodulatory systems and that derivatives such as lenalidomide would be produced in a laboratory. The U.S. Patent and Trademark Office's (USPTO) Manual of Patent Examining Procedure (MPEP) Section 2144 cites a precedent set in the Federal Circuit in which it was established that "obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. See, e.g., In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)."

The immunomodulatory effects of thalidomide became known in the 1960s. Hellmann (1965) describes this property as seen in the lab: "Thalidomide prolongs skin homografts in mice at non-toxic doses. The best results were obtained when the donor graft was treated with thalidomide either in vivo or in vitro in addition to the recipient. These findings are discussed and lend some support to the idea that thalidomide may have an immunosuppressive action."

Coulson (1970) established that several thalidomide derivatives are also effective in immunosuppression: "The experiments reported here were undertaken to investigate the possible immunosuppressive action of thalidomide by the examination in vitro of the effects of the soluble thalidomide derivatives CG601 and its isomer CG603, on the mixed lymphocyte reaction and on the response to PHA. […] The main finding was that in the presence of drugs 601 and 603 the production of transformed cells in the mixed cultures was markedly reduced ($P < 0.001$)." Hayman's IPR filing cites the later Piper (1981) and Agrawal (1981) as teaching the effects on immunosuppression by thalidomide and its amino-substituted analogues.

Hendler (1983) also notes that thalidomide is effective in the treatment of autoimmune diseases: "Thalidomide has unquestioned value in the treatment of erythema nodosumleprosum, which appears to be an immune-complex disease. The recent anecdotal reports of possible activity in autoimmune disorders such as ulcerative colitis, discoid LE, apthous stomatitis, Weber-Christian disease, and actinic prurigo, cannot help but reinforce the suspicion that thalidomide may have a more general utility in the treatment of autoimmune disease. In particular, it appears that thalidomide may alleviate neutrophil-mediated cytoxicity and inflammation in immune complex disease."

Sampaio et al (1991) establishes that TNFα production is inhibited by thalidomide: "These experiments demonstrate that thalidomide inhibits TNFα production by human blood monocytes, without influencing either general protein synthesis or the expression of three other monocyte-derived cytokines."Hayman's IPR filing cites Sampaio and Kaplan's U.S. Pat. No. 5,385,901 as teaching TNFα inhibition.

D'Amato (1994) establishes that thalidomide is an angiogenesis inhibitor which also aids in the treatment of multiple myeloma: "In conclusion, thalidomide is a potent angiogenesis inhibitor in vivo. In this model of corneal angiogenesis, we have tested many putative angiogenesis inhibitors (including antimitotic agents, cis-retinoic acid, tamoxifen, and others). Thalidomide was the only agent capable of inhibiting angiogenesis after oral administration." Hayman's IPR filing also cites D'Amato (WO 94/20085) as teaching angiogenesis inhibition.

A person skilled in the art will observe that thalidomide and its derivatives were known to be immunomodulatory in the 1960s and 1970s. Since 1991, it has been known that thalidomide inhibits TNFα. Under section 2144, one would have the reasonable expectation that a derivative such as lenalidomide would have the same effect.

Based on this information, it seems clear that the method claimed by Celgene's '517 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Argawal, K. C., et al. "Structure activity relationship studies of thalidomide analogs as anti-inflammatory and immunosuppressive agents."*Sixteenth Joint Leprosy Conference* 49.4 (1981):512.
2. Coulson, A. S., et al. "The effect of two soluble thalidomide derivatives on lymphocyte stimulation." *Clinical and experimental immunology* 7.2 (1970): 241.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." *Proceedings of the National Academy of Sciences* 91.9 (1994): 4082-4085.
4. Hellmann, K., D. I. Duke, and D. F. Tucker. "Prolongation of skin homograft survival by thalidomide." *BMJ* 2.5463 (1965): 687-689.
5. Hendler, Sheldon S., and Mark F. McCarty. "Thalidomide for autoimmune disease." *Medical hypotheses* 10.4 (1983): 437-443.
6. Piper, L. M., et al. "Anti-inflammatory immunosuppressive thalidomide analogs" *Sixteenth Joint Leprosy Conference* 49.4 (1981):511-512.
7. Sampaio, Elizabeth P., et al. "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes." *The Journal of experimental medicine* 173.3 (1991): 699-703.

Patent No.	Title	Assignee	Priority Date File Date
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955
WO1994020085	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 02/24/1994

Celgene Patent on Treatment of Myelodysplastic Syndromes

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US8404717	Methods of treating myelodysplastic syndromes using lenalidomide	Zeldis	10/15/2002 03/24/2011 04/11/2023

Commentary

Celgene's '717 patent claims methods for the treatment of myelodysplastic syndromes. The claims include a method of treating a patient having transfusion-dependent anemia due to low to intermediate-1-risk myelodysplastic syndrome with genetic deletion 5q and provides dosing regimens.After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '717 patent had initial rejections as being unpatentable under 35 U.S.C. 103 for obviousness over Musto's article (2002) "Thalidomide Abolishes Transfusion-Dependence In Selected Patients With Myelodysplastic Syndromes" in view of Celgene's '517 patent. Musto teaches a method of treating transfusion-dependent patients with myelodysplastic syndrome (MDS) by administering Thalidomide.

The examiner notes that Celgene inventor Muller "discloses a method of administering thalidomide analogs for reducing undesirable levels of TNFα in a mammal. The examiner also states that "It would have been obvious to one of ordinary skill in the art at the time the invention was to incorporate 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione into [Musto's] composition." The claims were also rejected on the grounds of obvious double patenting over claims in another Celgene patent, U.S. 7,189,740 (see analysis below) in view of Musto.

The '717 patent suffers from the fact that inventor Jerome Zeldis coauthored "Antitumor Activity of Thalidomide in Refractory Multiple Myeloma" in 1999, which discloses findings on the effects of Thalidomide in the treatment of myeloma. Zeldis also coauthored a study titled "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2" in 2001 which demonstrated that structural analogues inhibited cancerous growth targets.

Despite claiming treatment of multiple myeloma, this mechanism was well known before the priority date of the patent. Lenalidomide, being an analogue of thalidomide, has the same mechanisms of action on immunomodulatory systems. Sampaio et al (1991) establishes that TNFα production is inhibited by thalidomide: "These experiments demonstrate that thalidomide inhibits TNFα production by human blood monocytes, without influencing either general protein synthesis or the expression of three other monocyte-derived cytokines."

D'Amato (1994) establishes that thalidomide is an angiogenesis inhibitor which also aids in the treatment of multiple myeloma: "In conclusion, thalidomide is a potent angiogenesis inhibitor in vivo. In this model of corneal angiogenesis, we have tested many putative angiogenesis inhibitors (including antimitotic agents, cis-retinoic acid, tamoxifen, and others). Thalidomide was the only agent capable of inhibiting angiogenesis after oral administration."

Singhal (1999), co-authored by Zeldis, also describes anti-tumor activity regulated by thalidomide: "We found that thalidomide had substantial antitumor activity in patients with advanced myeloma. Ten percent of patients had complete or nearly complete remission, and 32 percent had a reduction in serum or urine paraprotein levels of at least 25 percent."

Corral (1999), also a Celgene inventor, describes the same inhibition by thalidomide and its analogues: "Thalidomide inhibits TNFα production in different diseases without causing the immunosuppression often associated with standard agents such as glucocorticoids and cyclosporin A. Our results indicate that the immunomodulating effects of thalidomide may occur via the inhibition of TNFα production and/or the stimulation of T cell responses, without the suppression of host immunity."

Muller (1999), another Celgene inventor, establishes the same, finding that analogues of thalidomide exercise the same action: "The clinical activity of thalidomide and the importance of TNFα inhibition led us to initiate a program to improve the TNFα inhibitory activity of thalidomide by structural modification. […] Only the 4-amino analog 8a potently inhibited TNFα production (IC_{50} less than 100 uM). Compound 8a was found to have an IC_{50} of 100 nM (Table 1)."

Davies and Muller (2001) further establish that IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment in multiple myeloma before the '717 patent's 2002 priority date: "In this study, we describe a novel immunomodulatory mechanism of action of Thal and IMiDs®. These drugs induced NK-cell–mediated lysis of MM cell lines and patient cells. […] Specifically, our results suggest that Thal and new analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity."

Clearly, the action and treatment using analogues or derivatives of thalidomide, such as lenalidomide, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the methods claimed by Celgene's '717 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
4. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
5. Fujita, Junya, et al. "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2." Clinical Cancer Research 7.11 (2001): 3349 3355.
6. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625- 1630.
7. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 1996): 3238-3240.
8. Musto, Pellegrino, et al. "Thalidomide abolishes transfusion-dependence in selected patients with myelodysplastic syndromes." *haematologica* 87.8 (2002): 884-886.
9. Sampaio, Elizabeth P., et al. "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes." The Journal of experimental medicine 173.3 (1991): 699-703.
10. Singhal, Seema, et al. "Antitumor activity of thalidomide in refractory multiple myeloma." New England Journal of Medicine 341.21 (1999): 1565-1571.

Patent No.	Title	Assignee	Priority Date File Date
US7189740	Methods of using 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for the treatment and management of myelodysplastic syndromes	Celgene Corporation	10/15/2002 04/11/2003
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997

Patent No.	Title	Assignee	Priority Date File Date
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patent on Treatment of Myelodysplastic Syndromes

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US7189740	Methods of using 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for the treatment and management of myelodysplastic syndromes	Zeldis	10/15/2002 04/11/2003 04/11/2023

Commentary

Celgene's '740 patent claims a method of treating myelodysplastic syndromes using various forms of lenalidomide. The claims include variations of the compound and dosing regimens. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '740 patent had two non-final rejections and one final rejection in the USPTO. The first non-final rejection was for novelty (35 U.S.C. 102) anticipated by Hariri (U.S. published App. 2003/0235909) and Stein (U.S. published App. 2004/0067953). Hariri teaches use of an immunomodulatory compound such as amino-substituted isoindolines for treating myelodysplasia. Stein teaches methods and compounds for the treatment of cancers and discloses a patented composition of Actimid® (pomalidomide) or Revimid® (Celgene's initial, now abandoned, brand name for lenalidomide) in combination with a JNK inhibitor.

The '740 patent was also rejected for being anticipated by its inventor Zeldis' own WO 01/87307 (U.S. Pat. No. 7,435,726) with a priority date of 2000, which teaches a treatment of cancer using a composition comprising of thalidomide or derivatives thereof (EM12) and anticancer drugs. The '740 patent was additionally rejected for double patenting over claims 1-12 of the co-pending application 10/438213 (U.S. Pat. No. 7,968,569), from which the '740 patent was not "patentably distinct."

The second non-final rejection under 35 U.S.C. 103 for obviousness was over Raza's "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes" in view of Zeldis (WO 01/87307) or Hariri (U.S. published App.2003/0235909). In this rejection, the patent examiner stated that "Raza teaches treatment of myelodysplastic syndromes using thalidomide...it should have been obvious to one of ordinary skill in the art at that time the invention was made to substitute thalidomide (Raza's) with amino thalidomide analogues (Actimid® or Revimid®) because secondary references remedy deficiency found in Raza's teaching."

The earlier Zeldis prior art (WO 01/87307) teaches a treatment of cancers with a composition containing thalidomide or analogues, especially amino-analogues. Hariri teaches the use of immunomodulatory compounds such as thalidomide or amino-substituted isoindolines (Actimid® or Revlimid®) in the treatment of various diseases. Hariri teaches that the compound used in the patent includes racemic, stereomerically enriched, pure, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, and prodrugs.

The second non-final rejection of the '740 patent cites 35 U.S.C. 112, the first and second paragraph, and rejects the claims as being indefinite for failing to particularly point out and distinctly claim the subject matter, thus failing to enable the invention.

In the final rejection of the '740 patent, the examiner points out that Raza teaches the use of thalidomide or its analogues when taken in view of the earlier Zeldis prior art (WO 01/87307).

The '740 suffers from the fact that the inventor Zeldis coauthored "Antitumor Activity of Thalidomide in Refractory Multiple Myeloma" in 1999, which discloses findings on the effects of thalidomide in the treatment of myeloma. Zeldis also coauthored a study titled "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2" in 2001 which demonstrated that structural analogues inhibited cancerous growth targets.

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Davies and Muller (2001) further establish that IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment in multiple myeloma before the '740 patent's 2002 priority date: "In this study, we describe a novel immunomodulatory mechanism of action of Thal and IMiDs®. These drugs induced NK-cell–mediated lysis of MM cell lines and patient cells. […] Specifically, our results suggest that Thal and new analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity."

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2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
4. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
5. Fujita, Junya, et al. "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2." Clinical Cancer Research 7.11 (2001): 3349-3355.
6. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.
7. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of

medicinal chemistry 39.17 (1996): 3238-3240.

8. Musto, Pellegrino, et al. "Thalidomide abolishes transfusion-dependence in selected patients with myelodysplastic syndromes." *haematologica*87.8 (2002): 884-886.
9. Raza, Azra, et al. "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes." Blood 98.4 (2001): 958-965.
10. Sampaio, Elizabeth P., et al. "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes." The Journal of experimental medicine 173.3 (1991): 699-703.
11. Singhal, Seema, et al. "Antitumor activity of thalidomide in refractory multiple myeloma." New England Journal of Medicine 341.21 (1999): 1565-1571.

Patent No.	Title	Assignee	Priority Date File Date
US7968569	Methods for treatment of multiple myeloma using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione	Celgene Corporation	05/17/2002 05/15/2003
US7435726	Compositions and methods for the treatment of cancer	Celgene Corporation	05/14/2001 05/14/2001
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955
US20040067953	Combination therapy for treating, preventing or managing proliferative disorders and cancers	STEIN BERND M.	03/07/2003 03/07/2003
US20040029832	Methods and compositions using immunomodulatory compounds for treatment and management of cancers and other diseases	ZELDIS JEROME B.	05/15/2003 05/15/2003
US20030235909	Modulation of stem and progenitor cell differentiation, assays, and uses thereof	HARIRI ROBERT J.	04/11/2003 04/11/2003
WO2001087307	COMPOSITIONS AND METHODS FOR THE TREATMENT OF CANCER	CELGENE CORP.	05/15/2000 05/10/2001

Celgene Patent on Treatment of Multiple Myeloma

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US7968569	Methods for treatment of multiple myeloma using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione	Zeldis	05/17/2002 05/15/2003 10/07/2023

Commentary

Celgene's '569 patent claims a method of treating multiple myeloma using lenalidomide. The claims include specific dosing regimens and combinations of other therapeutics. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '569 patent had five non-final rejections and two final rejections in the USPTO. It spent a total of eight years in prosecution involving two different patent examiners. The first non-final rejection of the '569 patent was in 2005 for novelty (35 U.S.C. 102) as anticipated by Treston (U.S. published App. 2004/0147558) and Stein (U.S. published App. 2004/0067953). Treston teaches the use of enantiomerically pure S(-)-3-amino-thalidomide and R(+)-3-amino-thalidomide to treat cancer, melanoma, and multiple myeloma. The '569 patent was also initially rejected for double patenting over claims 1-13 of co-pending application 11/102742 (U.S. Pat. No. 7,468,363), claims of co-pending application 10/704237 (U.S. Pat. No. 7,323,479), claims of the co-pending application 10/534324 (U.S. published App. 2006/0165649), claims of co-pending application 10/515270 (U.S. Pat. No. 8,263,637).

The first final rejection for the '569 patent was in 2006 under the first paragraph of 35 U.S.C. 112. It was also found obvious (35 U.S.C. 103) over U.S. published App. 2004/0147558. The claims were additionally rejected because of double patenting of claims of co-pending applications 10/704237 (U.S. Pat. No. 7,323,479), 10/534234 (U.S. published App.2006/0165649), and 10/515270 (U.S. Pat. No. 8,263,637).

The second non-final rejection was in 2006. The examiner found the claims unpatentable as obvious over Celgene inventor Corral "Immunomodulation by thalidomide and thalidomide analogues." Corral teaches the same mechanism of action relative to LPS-induced inflammation and T-cell activation. One skilled in the art would have a reasonable expectation of success in treating cancer with Revlimid® because of its known effect on TNFα. This rejection included a finding of double patenting over claims of the co-pending applications 10/534324 (U.S. published App.2006/0165649), 10/515270 (U.S. Pat. No. 8,263,637) in view of Corral, and 10/531552 (U.S. Pat. No. 7,842,691) in view of Corral.

The third non-final rejection in 2007 stated that the '569 patent was unpatentable under 35 U.S.C. 103 in view of Kyle et al (2001) "The application of Thalidomide in Multiple Myeloma" and Davies et al (2001) "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." It was also obvious over US2001/0022973 in view of the combination of Kyle and Davies. There was an additional obviousness rejection over the combination of Kyle and Davies in view of Broder "Dideoxycytidine: current clinical experience and future prospects. A summary." There were also rejections for double patenting in view of Kyle and Davies over claims of the co-pending applications 10/534234 (U.S. published App.2006/0165649), 10/515270 (U.S. Pat. No. 8,263,637), and 10/531552 (U.S. Pat. No. 7,842,691).

The examiner, on a quest to explain patent obviousness to the prosecuting attorney, stated in the rejection:
"Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended purpose."

The fourth non-final rejection in 2008 included a rejection under 35 U.S.C. 112, first paragraph. The examiner found that the subject matter was not described in sufficient specificity to convey that the applicant had possession of the claimed invention. There were rejections for obviousness in view of Davies and Kyle over the '517 patent; U.S. Pat. No. 6,555,554; and U.S Pat. No. 6,281,230.More rejections came in

the form of double patenting in view of Davies: the '517 patent; U.S. Pat. No. 6,281,230; U.S. Pat. No. 6,555,554; and U.S. Pat. No. 7,119,106. There were additional rejections for double patenting the claims of U.S. Pat. No. 7,189,740 and U.S. Pat. No. 7,393,862.

The second final rejection in 2009 contained a 35 U.S.C. 112 rejection under the first paragraph for failing to convey possession of specified invention. This included an obviousness rejection over U.S. Pat. No. 5,635,517 in view of Davies and Kyle. The examiner added that the '569 patent was unpatentable in view of the above art, U.S. Pat. No. 6,555,554, and U.S. Pat. No. 6,281,230. The rejection included double patenting over U.S. Pat. No. 6,281,230 in view of the '517 patent and Davies, and another rejection over U.S. Pat. No. 6,555,554, in view of the '517 patent and Davies. There was another obviousness rejection over U.S. Pat. No. 7,119,106 in view of the '517 patent and Davies; over claims 1-34 of U.S. Pat. No.7,189,740 in view of the '517 patent and Davies; and over U.S. Pat. No. 7,393,862in view of the '517 and Davies.

The fifth non-final rejection in 2010 contained an obviousness rejection over Kyle in view of Davies; over a combination of Corral as evidenced by Muller; over U.S. Pat. No. 6,281,230 in view of Kyle, Filella et al (1996), and Corral; and over U.S. Pat. No. 6,555,554 in view of Kyle, Filella, and Corral. It included a double patenting rejection over U.S. Pat. No. 7,393,862 in view of Kyle; over U.S. Pat. No. 6,555,554 in view of Kyle and Filella; and over U.S. Pat. No. 6,281,230 in view of Kyle and Filella.

The '569 suffers from the fact that the inventor Zeldis coauthored "Antitumor Activity of Thalidomide in Refractory Multiple Myeloma" in 1999, which discloses findings on the effects of thalidomide in the treatment of myeloma. Zeldis also coauthored a study titled "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2" in 2001 which demonstrated that structural analogues inhibited cancerous growth targets.

Despite claiming treatment of multiple myeloma, this mechanism was well known before the priority date of the patent. Lenalidomide, being an analogue of thalidomide, has the same mechanisms of action on immunomodulatory systems. Sampaio et al (1991) establishes that TNFα production is inhibited by thalidomide: "These experiments demonstrate that thalidomide inhibits TNFα production by human blood monocytes, without influencing either general protein synthesis or the expression of three other monocyte-derived cytokines."

D'Amato (1994) establishes that thalidomide is an angiogenesis inhibitor which also aids in the treatment of multiple myeloma: "In conclusion, thalidomide is a potent angiogenesis inhibitor in vivo. In this model of corneal angiogenesis, we have tested many putative angiogenesis inhibitors (including antimitotic agents, cis-retinoic acid, tamoxifen, and others). Thalidomide was the only agent capable of inhibiting angiogenesis after oral administration."

Singhal (1999), co-authored by Zeldis, also describes anti-tumor activity regulated by thalidomide: "We found that thalidomide had substantial antitumor activity in patients with advanced myeloma. Ten percent of patients had complete or nearly complete remission, and 32 percent had a reduction in serum or urine paraprotein levels of at least 25 percent."

Corral (1999), also a Celgene inventor, describes the same inhibition by thalidomide and its analogues: "Thalidomide inhibits TNFα production in different diseases without causing the immunosuppression often associated with standard agents such as glucocorticoids and cyclosporin A. Our results indicate that the immunomodulating effects of thalidomide may occur via the inhibition of TNFα production and/or the stimulation of T cell responses, without the suppression of host immunity."

Muller (1999), another Celgene inventor, establishes the same, finding that analogues of thalidomide exercise the same action: "The clinical activity of thalidomide and the importance of TNFα inhibition led us to initiate a program to improve the TNFα inhibitory activity of thalidomide by structural modification. […] Only the 4-amino analog 8a potently inhibited TNFα production (IC_{50} less than 100 uM). Compound 8a was found to have an IC_{50} of 100 nM (Table 1)."

Davies and Muller (2001) further establish that IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment in multiple myeloma before the '569 patent's 2002 priority date: "In this

study, we describe a novel immunomodulatory mechanism of action of Thal and IMiDs®. These drugs induced NK-cell–mediated lysis of MM cell lines and patient cells. […] Specifically, our results suggest that Thal and new analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity."

Clearly, the action and treatment using analogues or derivatives of thalidomide, such as lenalidomide, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the methods claimed by Celgene's '569 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Broder, Samuel, and Robert Yarchoan. "Dideoxycytidine: Current clinical experience and future prospects: A summary." The American journal of medicine 88.5 (1990): S31-S33.
2. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
3. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
4. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
5. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
6. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
7. Filella et al. (CancerDetectPrey. 1996;20(1):52-6).
8. Fujita, Junya, et al. "Thalidomide and its analogues inhibit lipopolysaccharide-mediated induction of cyclooxygenase-2." Clinical Cancer Research 7.11 (2001): 3349-3355.
9. Kyle et al., "The Application of Thalidomide in Multiple Myeloma," Semin. Oncol., 2001, 28(6), 583-587.
10. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.
11. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 (1996): 3238-3240.
12. Raza, Azra, et al. "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes." Blood 98.4 (2001): 958-965.
13. Sampaio, Elizabeth P., et al. "Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes." The Journal of experimental medicine 173.3 (1991): 699-703.
14. Singhal, Seema, et al. "Antitumor activity of thalidomide in refractory multiple myeloma." New England Journal of Medicine 341.21 (1999): 1565-1571.

Patent No.	Title	Assignee	Priority Date File Date
US8263637	Methods for treatment of multiple myeloma using cyclopropane carboxylic acid {2-[(is)-1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 h-isoindol-4-yl}-amide	Celgene Corporation	05/17/2002 05/16/2003
US7842691	Method for the treatment of myelodysplastic syndromes using cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-OXO-2,3-dihydro-1 H-isoindol-4-yl}-amide	Celgene Corporation	04/13/2003 04/13/2003
US7468363	Methods for treatment of cancers using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione	Celgene Corporation	05/17/2002 04/08/2005
US7393862	Method using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for treatment of certain leukemias	Celgene Corporation	05/17/2002 10/04/2005

Patent No.	Title	Assignee	Priority Date File Date
US7323479	Methods for treatment and management of brain cancer using 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline	Celgene Corporation	05/17/2002 11/06/2003
US7189740	Methods of using 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for the treatment and management of myelodysplastic syndromes	Celgene Corporation	10/15/2002 04/11/2003
US7119106	Pharmaceutical compositions of 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline	Celgene Corporation	05/07/1999 01/06/2003
US6555554	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 02/12/2001
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955
US20060165649	Methods of using and compositions comprising selective cytokine inhibitory drugs for the treatment and management of myeloproliferative diseases	ZELDIS JEROME B	11/06/2002 04/13/2003
US20040147558	Synthesis of 3-amino-thalidomide and its enantiomers	TRESTON ANTHONY	03/11/2004 03/11/2004
US20040067953	Combination therapy for treating, preventing or managing proliferative disorders and cancers	STEIN BERND M.	03/07/2003 03/07/2003
US20010022973	Pharmaceutical composition for piperidinoalkanol compounds	ORTYL THOMAS T.	04/30/2001 04/30/2001

Celgene Patent on Polymorphs of Lenalidomide

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
EP1667682	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Jaworsky et al	09/04/2003 09/03/2004 09/04/2023

Commentary

Celgene's EP '682 patent claims crystalline polymorphic forms of lenalidomide. The claims include diffraction patterns and calorimetric melting points, despite the examiner stating that the European Patent Convention allows claims for the "product not the peaks." After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '682 patent failed to meet the requirements of the European Patent Convention on two separate occasions. The examiners referenced U.S. Pat. No.6,316,471 as prior art. They also referenced Muller and Chen (1999) "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production."; Corral et al (1999) "Immunomodulation by thalidomide and thalidomide analogues"; Lentzsch et al (2002) "S-3-Amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice."; and Brittain (2009) "Polymorphism in pharmaceutical solids."

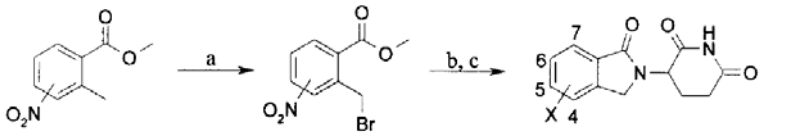
The examiner found that the '682 patent's claims were based on former claims and did not introduce new subject matter. The claims were also regarded as unclear and lacking disclosure. The examiner additionally stated that "a person skilled in the art would learn from D1-D4 (above prior art) the activity of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione against inflammation, inflammatory diseases, autoimmune diseases, cancer, and angiogenesis." The examiner mentions that "the methods to screen for polymorphs are well known in the art…no inventive step would be acknowledged for polymorphs and subject-matter referring to it. Thus the proposed solution is seen as working, albeit obvious and not-inventive one according to Article 56 EPC."

In the current European Patent Office (EPO) proceeding against the '682 patent, the opposition claims that the '682 is obvious in light of the '517. The '682 references the '517, saying: "This compound can be prepared according to the methods described in U.S. Patent Nos. 6,281,230 and 5,635,517." It goes on to list examples of how to prepare the compound by following the prior art. However, in the EPO proceeding, Celgene has argued and produced testimony to the effect that it is not "an inevitable result" for a person skilled in the art to produce lenalidomide by following the steps of Example 1 of the '517, and that therefore the '682 is non-obvious. The opposition's science expert has argued that, if this is true, then the '682 is not reducible to practice and should be invalidated on that ground. If it is, in fact, "inevitable" for a person skilled in the art to produce lenalidomide from Example 1 of the '517, then the '682 is obvious because the polymorphic forms of the previously-claimed compound are routine in pharmaceutical investigation and thus lack inventive step.

The '682 suffers from the fact that in the inventors Muller and Chen were involved in the published studies "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production" (1999) and "Selection of Novel Analogs of Thalidomide with Enhanced Tumor Necrosis Factor a Inhibitory Activity" (1996). Muller also published "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity" (1996).

The graphic below is taken from the 1999 study "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." The compound on the right designated 8a is lenalidomide, also written as 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione 4, evidencing that the compound was known years before the priority date of the '682 patent.

Scheme 2



6a 3-NO_2
6b 4-NO_2
6c 5-NO_2
6d 6-NO_2

7a X = 4-NO_2 **8a** X= 4-NH_2
7b X = 5-NO_2 **8b** X= 5-NH_2
7c X = 6-NO_2 **8c** X= 6-NH_2
7d X = 7-NO_2 **8d** X= 7-NH_2

Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

D'Amato (1994) helps establish that analogues of thalidomide inhibit angiogenesis: "Other thalidomide analogs that have been shown to be teratogenic in rodents (17), including phthaloylglutamic anhydride (PGA) and phthaloylglutamic acid (PG acid), were also analyzed. […]Evaluation of thalidomide analogs demonstrated a correlation between teratogenicity and antiangiogenic potential."

Corral (1999) describes inhibition of TNFα by IMiDs® (a registered trademark of Celgene specifically referring to thalidomide, lenalidomide, and pomalidomide) are an effective treatment against multiple myeloma well before the priority date: "The collaboration between Rockefeller University and Celgene Corporation scientists has led to the discovery of two different classes of immunomodulators derived from thalidomide and selected for their potent anti-TNFα inhibitory activity. […] IMiDs® are potent inhibitors of monocyte inflammatory cytokine production and also are strong costimulators of T cell activity."

Muller (1999) points out that amino substitution also produces inhibition of TNFα. "The amino substituted isoindolinone analogs were prepared as illustrated Scheme 2. […] The nitro groups were hydrogenated to the desired amino compound as described above to afford 8a-d. […] In summary, we have discovered three high potency inhibitors of TNFα by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide."

Davies and Muller (2001) demonstrate that thalidomide analogues are useful in the treatment of multiple myeloma. "Previously, the direct anti-MM activity of Thal and its analogues (immunomodulatory drugs, IMiDs®) on MM cells was demonstrated, suggesting multiple mechanisms of action."

Clearly the analogues or derivatives of thalidomide, such as lenalidomide and its various forms, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the polymorphs claimed by Celgene's EP '682 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Brittain, Harry G., ed. Polymorphism in pharmaceutical solids. CRC Press, 2009.
2. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
3. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
4. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
5. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.

6. Lentzsch, Suzanne, et al. "S-3-Amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice." Cancer Research 62.8 (2002): 2300-2305.

7. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.

8. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 (1996): 3238-3240.

Patent No.	Title	Assignee	Priority Date File Date
US6316471	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 11/13/2001
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patent on Polymorphs of Lenalidomide

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US8431598	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Jaworsky et al	09/04/2003 05/26/2011 09/04/2023

Commentary

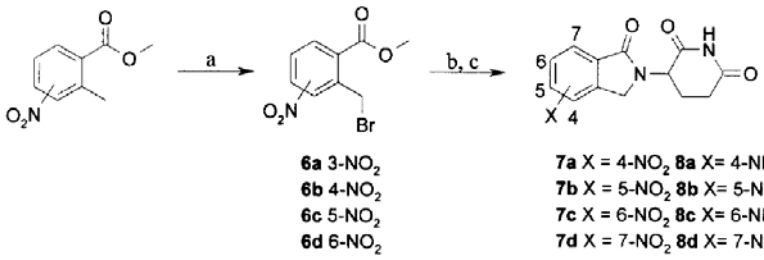
Celgene's '598 patent claims multiple forms of lenalidomide. The claims include calorimetric melting points, diffraction patterns, and multiple crystalline forms. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '598 patent had initial rejections in the USPTO for being obvious in light of Celgene's U.S. Pat. No. 7,855,217, which is a family member of the '682 patent under review, and the '598 patent's family member U.S. Pat. No. 8,193,219 (find analysis below). The examiner stated that the '598 patent was not "patentably distinct." The '598 patent was also initially rejected under Section 35 U.S.C. 112, first paragraph, for failing to describe the invention adequately to enable any person skilled in the art to reproduce the invention.

The '598 suffers from the fact that in the inventors Muller and Chen were involved in the published studies "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production" (1999) and "Selection of Novel Analogs of Thalidomide with Enhanced Tumor Necrosis Factor a Inhibitory Activity" (1996). Muller also published "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity" (1996).

The graphic below is taken from the 1999 study "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." The compound on the right designated 8a is lenalidomide, also written as 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione 4, evidencing that the compound was known years before the priority date of the '598 patent.

Scheme 2



Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

D'Amato (1994) helps establish that analogues of thalidomide inhibit angiogenesis: "Other thalidomide analogs that have been shown to be teratogenic in rodents (17), including phthaloylglutamic anhydride (PGA) and phthaloylglutamic acid (PG acid), were also analyzed. […]Evaluation of thalidomide analogs demonstrated a correlation between teratogenicity and antiangiogenic potential."

Corral (1999) describes inhibition of TNFα by IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment against multiple myeloma well before the priority date: "The collaboration between Rockefeller University and Celgene Corporation scientists has led to the discovery of two different classes of immunomodulators derived from thalidomide and selected for their potent anti-TNFα inhibitory activity. […] IMiDs® are potent inhibitors of monocyte

inflammatory cytokine production and also are strong costimulators of T cell activity."

Muller (1999) points out that amino substitution also produces inhibition of TNFα. "The amino substituted isoindolinone analogs were prepared as illustrated Scheme 2. […] The nitro groups were hydrogenated to the desired amino compound as described above to afford 8a-d. […] In summary, we have discovered three high potency inhibitors of TNFα by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide."

Davies and Muller (2001) demonstrate that thalidomide analogues are useful in the treatment of multiple myeloma. "Previously, the direct anti-MM activity of Thal and its analogues (immunomodulatory drugs, IMiDs®) on MM cells was demonstrated, suggesting multiple mechanisms of action."

Clearly the analogues or derivatives of thalidomide, such as lenalidomide and its various forms, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the polymorphs claimed by Celgene's '598 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
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6. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 (1996): 3238-3240.

Patent No.	Title	Assignee	Priority Date File Date
US8193219	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Celgene Corporation	09/04/2003 10/03/2011
US7855217	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Celgene Corporation	09/04/2003 12/15/2008
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995

Patent No.	Title	Assignee	Priority Date File Date
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patent on Polymorphs of Lenalidomide

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US7977357	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Jaworsky et al	09/04/2003 07/23/2008 09/04/2023

Commentary

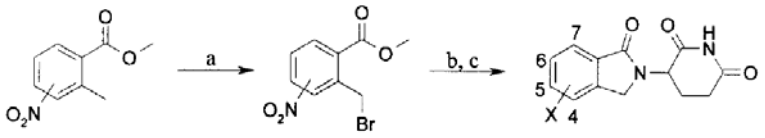
Celgene's '357 patent claims polymorphic forms of lenalidomide. The claims include calorimetric melting points, diffraction patterns and crystalline forms of lenalidomide. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '357 patent had initial rejections in the USPTO under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter of the invention. The '357 patent was also rejected under the first paragraph of 35 U.S.C. 112 for not enabling the scope of the claims.

The '357patent suffers from the fact that in the inventors Muller and Chen were involved in the published studies "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production" (1999) and "Selection of Novel Analogs of Thalidomide with Enhanced Tumor Necrosis Factor a Inhibitory Activity" (1996). Muller also published "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity" (1996).

The graphic below is taken from the 1999 study "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." The compound on the right designated 8a is lenalidomide, also written as 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione 4, evidencing that the compound was known years before the priority date of the '357 patent.

Scheme 2



6a 3-NO_2
6b 4-NO_2
6c 5-NO_2
6d 6-NO_2

7a X = 4-NO_2 **8a** X= 4-NH_2
7b X = 5-NO_2 **8b** X= 5-NH_2
7c X = 6-NO_2 **8c** X= 6-NH_2
7d X = 7-NO_2 **8d** X= 7-NH_2

Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

D'Amato (1994) helps establish that analogues of thalidomide inhibit angiogenesis: "Other thalidomide analogs that have been shown to be teratogenic in rodents (17), including phthaloylglutamic anhydride (PGA) and phthaloylglutamic acid (PG acid), were also analyzed. […]Evaluation of thalidomide analogs demonstrated a correlation between teratogenicity and antiangiogenic potential."

Corral (1999) describes inhibition of TNFα by IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment against multiple myeloma well before the priority date: "The collaboration between Rockefeller University and Celgene Corporation scientists has led to the discovery of two different classes of immunomodulators derived from thalidomide and selected for their potent anti-TNFα inhibitory activity. […] IMiDs® are potent inhibitors of monocyte inflammatory cytokine production and also are strong costimulators of T cell activity."

Muller (1999) points out that amino substitution also produces inhibition of TNFα. "The amino substituted isoindolinone analogs were prepared as illustrated Scheme 2. […] The nitro groups were hydrogenated to the desired amino compound as described above to afford 8a-d. […] In summary, we have discovered three high potency inhibitors of TNFα by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide."

Davies and Muller (2001) demonstrate that thalidomide analogues are useful in the treatment of multiple myeloma. "Previously, the direct anti-MM activity of Thal and its analogues (immunomodulatory drugs, IMiDs®) on MM cells was demonstrated, suggesting multiple mechanisms of action."

Clearly the analogues or derivatives of thalidomide, such as lenalidomide and its various forms, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the polymorphs claimed by Celgene's '357 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
4. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
5. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.
6. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 (1996): 3238-3240.

Patent No.	Title	Assignee	Priority Date File Date
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992

Patent No.	Title	Assignee	Priority Date File Date
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patent on Polymorphs of Lenalidomide

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US7465800	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Jaworsky et al	09/04/2003 09/03/2004 04/27/2027

Commentary

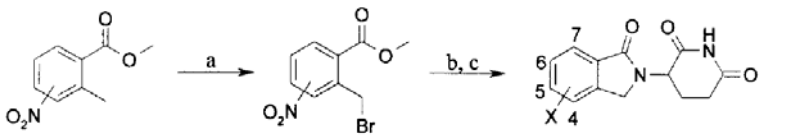
Celgene's '800 patent claims polymorphic forms of lenalidomide. The claims include diffraction patterns, hemihydrates, and calorimetric melting points. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '800 patent had initial rejections in the USPTO under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter of the invention. The '800 patent was also rejected under the first paragraph of 35 U.S.C. 112 for failing to describe the invention adequately to enable a person skilled in the art to reproduce the invention. Multiple claims (originally claims 4-5 and 41-43) were rejected for being substantial duplicates of each other.

The '800 patent suffers from the fact that in the inventors Muller and Chen were involved in the published studies "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production" (1999) and "Selection of Novel Analogs of Thalidomide with Enhanced Tumor Necrosis Factor a Inhibitory Activity" (1996). Muller also published "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity" (1996).

The graphic below is taken from the 1999 study "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." The compound on the right designated 8a is lenalidomide, also written as 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione 4, evidencing that the compound was known years before the priority date of the '800 patent.

Scheme 2



6a 3-NO_2 **7a** X = 4-NO_2 **8a** X= 4-NH_2
6b 4-NO_2 **7b** X = 5-NO_2 **8b** X= 5-NH_2
6c 5-NO_2 **7c** X = 6-NO_2 **8c** X= 6-NH_2
6d 6-NO_2 **7d** X = 7-NO_2 **8d** X= 7-NH_2

Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

D'Amato (1994) helps establish that analogues of thalidomide inhibit angiogenesis: "Other thalidomide analogs that have been shown to be teratogenic in rodents (17), including phthaloylglutamic anhydride (PGA) and phthaloylglutamic acid (PG acid), were also analyzed. […]Evaluation of thalidomide analogs demonstrated a correlation between teratogenicity and antiangiogenic potential."

Corral (1999) describes inhibition of TNFα by IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment against multiple myeloma well before the priority date: "The collaboration between Rockefeller University and Celgene Corporation scientists has led to the discovery of two different classes of immunomodulators derived from thalidomide and selected for their potent anti-TNFα inhibitory activity. […] IMiDs® are potent inhibitors of monocyte inflammatory cytokine production and also are strong costimulators of T cell activity."

Muller (1999) points out that amino substitution also produces inhibition of TNFα. "The amino substituted isoindolinone analogs were prepared as illustrated Scheme 2. […] The nitro groups were hydrogenated to the desired amino compound as described above to afford 8a-d. […] In summary, we have discovered three high potency inhibitors of TNFα by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide."

Davies and Muller (2001) demonstrate that thalidomide analogues are useful in the treatment of multiple myeloma. "Previously, the direct anti-MM activity of Thal and its analogues (immunomodulatory drugs, IMiDs®) on MM cells was demonstrated, suggesting multiple mechanisms of action."

Clearly the analogues or derivatives of thalidomide, such as lenalidomide and its various forms, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the polymorphs claimed by Celgene's '800 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
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5. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.
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US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
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US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
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US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966

Patent No.	Title	Assignee	Priority Date File Date
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patenton Polymorphs of Lenalidomide

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US8193219	Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	Jaworsky et al	09/04/2003 10/03/2011 09/04/2023

Commentary

Celgene's '219 patent claims polymorphic forms of lenalidomide. The claims include diffraction patterns and dosing regimens. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The '219 patent had initial rejections in the USPTO under 35 U.S.C. 101 for double patentingclaims 1-17 of the '357 patent. The original claims 40-44 were rejected for obviousness in light of claims 16-17 of the '357 patent.The '219 patent was also rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter of the invention. The '219 patent was also rejected under the first paragraph of 35 U.S.C. 112 for failing to describe the invention adequately to enable any person skilled in the art to reproduce the invention.

The '219 patent suffers from the fact that in the inventors Muller and Chen were involved in the published studies "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production" (1999) and "Selection of Novel Analogs of Thalidomide with Enhanced Tumor Necrosis Factor a Inhibitory Activity" (1996). Muller also published "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity" (1996).

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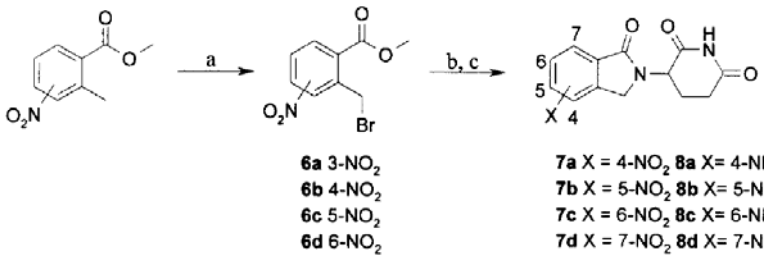
Scheme 2



6a 3-NO_2
6b 4-NO_2
6c 5-NO_2
6d 6-NO_2

7a X = 4-NO_2 **8a** X= 4-NH_2
7b X = 5-NO_2 **8b** X= 5-NH_2
7c X = 6-NO_2 **8c** X= 6-NH_2
7d X = 7-NO_2 **8d** X= 7-NH_2

Reagents: (a) light, NBS, CCl_4, reflux; (b) **3**, Et_3N, DMF, 80 °C; (d) H_2, 10% Pd/C, MeOH

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Corral (1999) describes inhibition of TNFα by IMiDs® (a registered trademark of Celgene which specifically refers to thalidomide, lenalidomide, and pomalidomide) are an effective treatment against multiple myeloma well before the priority date: "The collaboration between Rockefeller University and Celgene Corporation scientists has led to the discovery of two different classes of immunomodulators derived from thalidomide and selected for their potent anti-TNFα inhibitory activity. […] IMiDs® are potent inhibitors of monocyte

inflammatory cytokine production and also are strong costimulators of T cell activity."

Muller (1999) points out that amino substitution also produces inhibition of TNFα. "The amino substituted isoindolinone analogs were prepared as illustrated Scheme 2. […] The nitro groups were hydrogenated to the desired amino compound as described above to afford 8a-d. […] In summary, we have discovered three high potency inhibitors of TNFα by 4-amino substitution of thalidomide, EM-12, and a-methylthalidomide."

Davies and Muller (2001) demonstrate that thalidomide analogues are useful in the treatment of multiple myeloma. "Previously, the direct anti-MM activity of Thal and its analogues (immunomodulatory drugs, IMiDs®) on MM cells was demonstrated, suggesting multiple mechanisms of action."

Clearly the analogues or derivatives of thalidomide, such as lenalidomide and its various forms, were well established and could have been reproduced by a person skilled in the art. Based on this information, it seems clear that the polymorphs claimed by Celgene's '219 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. Corral, Laura G., and Gilla Kaplan. "Immunomodulation by thalidomide and thalidomide analogues." Annals of the rheumatic diseases 58.suppl 1 (1999): I107-I113.
2. Corral, Laura G., et al. "Selection of novel analogs of thalidomide with enhanced tumor necrosis factor alpha inhibitory activity." Molecular Medicine2.4 (1996): 506.
3. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
4. Davies, Faith E., et al. "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood 98.1 (2001): 210-216.
5. Muller, George W., et al. "Amino-substituted thalidomide analogs: potent inhibitors of TNFα production." Bioorganic & medicinal chemistry letters 9.11 (1999): 1625-1630.
6. Muller, George W., et al. "Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity 1." Journal of medicinal chemistry 39.17 (1996): 3238-3240.

Patent No.	Title	Assignee	Priority Date File Date
US7977357	Polymorphic forms of 3-(4-amino-1-oxo-1, 3 dihydro-isoindo1-2-yl)-piperidine-2,6-dione	Celgene Corporation	09/04/2003 07/23/2008
US6281230	Isoindolines, method of use, and pharmaceutical compositions	Celgene Corporation	07/24/1996 04/06/2000
US6270766	Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease	The Kennedy Institute of Rheumatology	10/08/1992 08/01/1996
US6235756	Methods and compositions for inhibition of angiogenesis by thalidomide	The Children's Medical Center Corporation	03/01/1993 08/22/1997
US6110941	Compounds analogous to thalidomide from the class comprising piperidine-2,6-diones	Gruenenthal GmbH	02/01/1997 01/29/1998
US5712291	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 06/06/1995
US5635517	Method of reducing TNF.alpha. levels with amino substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo-and 1,3-dioxoisoindolines	Celgene Corporation	07/24/1996 07/24/1996
US5629327	Methods and compositions for inhibition of angiogenesis	Childrens Hospital Medical Center Corp.	03/01/1993 12/15/1993
US5605684	Topical thalidomide compositions for surface of mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 06/07/1995
US5593990	Methods and compositions for inhibition of angiogenesis	The Children's Medical Center Corporation	03/01/1993 01/13/1995

Patent No.	Title	Assignee	Priority Date File Date
US5443824	Topical thalidomide compositions for surface or mucosal wounds, ulcerations, and lesions	Daniel J. Piacquadio	03/14/1994 03/14/1994
US5385901	Method of treating abnormal concentrations of TNF .alpha.	The Rockefeller University	02/14/1991 10/02/1992
US3563986	4 - PHTHALIMIDO - N - HETEROCYCLIC AMINO METHYL OR PIPERIDINO HYDRAZINO PIPERIDINE DIONES 2,6	ERNST FRANKUS	10/12/1965 05/09/1966
US3560495	1-HETEROCYCLIC AMINO METHYL OR 1-HETEROCYCLIC HYDRAZINO METHYL-3-PHTHALIMIDO OR (3',6'-DITHIA-3',4',5',6'-TETRAHYDROPHTHALIMIDO)-PYRROLIDINEDIONES-2,5 OR PIPERIDINEDIONES-2,6	ERNST FRANKUS	05/08/1965 05/09/1966
US2830991	Products of the amino-piperidine-2-6-dione series	GRUENENTHAL CHEMIE	05/17/1954 05/16/1955

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US6045501	Methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug	Elsayed et al	08/28/1998 08/28/1998 08/28/2018

Commentary

Celgene's '501 patent claims a method of approving a prescription for a teratogenic drug utilizing a computer to register pharmacists, pharmacies, and patients. The claims include providing counseling and drug hazard information to patients and authorizing a prescription to a woman only after determining that she is not pregnant. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, pharmacist, and pharmacy information in a computer was described and in use earlier than Celgene's 1998 priority date. In particular, Dishman (1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 1998 priority date. Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy.

The step of providing counseling and drug hazard data to patients was obvious well before 1998 through common practice as well as prior art. In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '501 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
3. Dishman, Benjamin R., et al. "Pharmacists' role in clozapine therapy at a Veterans Affairs medical center." American Journal of Health-System Pharmacy 51.7 (1994): 899-901.
4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.
5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
6. Koren, Gideon, and Anne Pastuszak. "Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during

the first trimester." Teratology 41.6 (1990): 657-661.

7. Love, D. J., D. C. Schalk, and M. C. Morgan. "Computerized relational database for monitoring clozapine therapy." American Journal of Health-System Pharmacy 50.8 (1993): 1657-1662.
8. Mitchell, Allen A., Carla M. Van Bennekom, and Carol Louik. "A pregnancy-prevention program in women of childbearing age receiving isotretinoin." New England Journal of Medicine 333.2 (1995): 101-106.
9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
10. Stitt, Frank W. "The Problem-Oriented Medical Synopsis: a patient-centered clinical information system." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
11. Suermondt, H. J., et al. "Automated identification of relevant patient information in a physician's workstation." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
12. Van Dyne, M. M., et al. "Using machine learning and expert systems to predict preterm delivery in pregnant women." Artificial Intelligence for Applications, 1994., Proceedings of the Tenth Conference on. IEEE, 1994.

Patent No.	Title	Assignee	Priority Date File Date
US5265010	Method and apparatus for performing patient documentation	Koninklijke Philips N.V.	05/15/1990 05/15/1990
US5672154	Method and apparatus for controlled individualized medication	MiniDoci Uppsala AB	08/27/1992 02/27/1995
US5558638	Patient monitor and support system	Matria Healthcare, Inc.	04/30/1993 04/30/1993
US5473537	Method for evaluating and reviewing a patient's condition	Behavioral Algorithms, Inc.	07/30/1993 04/12/1995
US5833599	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 04/09/1996
US6317719	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 11/10/1998
US7297111	Computerized medical diagnostic and treatment advice system	Clinical Decision Support, LLC	12/29/1993 03/09/2005
US5845255	Prescription management system	Cybear, LLC	10/28/1994 10/02/1997
US7072840	Prescription management system	Cybear, LLC	10/28/1994 11/30/1998
US7483839	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7519540	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7574370	Prescription management system	Cybear, LLC	10/28/1994 08/30/2001
US7606723	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/16/2004
WO9613790	PRESCRIPTION MANAGEMENT SYSTEM	MedEsystem Corporation	10/28/1994 10/27/1995
US5758095	Interactive medication ordering system	Presqriber LLC	02/24/1995 02/24/1995
US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995
US6055507	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 08/20/1998
US6063026	Medical diagnostic analysis system	Carbon Based Corporation	12/07/1995 03/22/1996

Patent No.	Title	Assignee	Priority Date File Date
US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
US5950630	System and method for improving compliance of a medical regimen	Michael T. Portwood	12/12/1996 12/12/1996
US6240394	Method and apparatus for automatically generating advisory information for pharmacy patients	inVentiv Health Inc.	12/12/1996 12/12/1996
US6322502	Medical information system	iMD Soft Ltd.	12/30/1996 06/29/1999
US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US6315720	Methods for delivering a drug to a patient while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug	Williams et al	10/23/2000 10/23/2000 10/23/2020

Commentary

Celgene's '720 patent claims a method of approving a prescription for a teratogenic drug utilizing a computer to register pharmacists, pharmacies, and patients. The claims include providing counseling and drug hazard information to patients and authorizing a prescription to a woman only after determining that she is not pregnant. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, pharmacist, and pharmacy information in a computer was described and in use earlier than Celgene's 2000 priority date. In particular, Dishman (1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 2000 priority date.Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy.

The step of providing counseling and drug hazard data to patients was obvious well before 2000 through common practice as well as prior art. In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '720 patent would be obvious to a person of ordinary skill in the art.

In addition to the above obviousness arguments, Celgene's '720 patent could be invalidated using a double-patenting argument. The '720 patent fails to sufficiently differentiate itself from Celgene's earlier '501 patent.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
3. Dishman, Benjamin R., et al. "Pharmacists' role in clozapine therapy at a Veterans Affairs medical center." American Journal of Health-System Pharmacy 51.7 (1994): 899-901.
4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.

5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
6. Koren, Gideon, and Anne Pastuszak. "Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester." Teratology 41.6 (1990): 657-661.
7. Love, D. J., D. C. Schalk, and M. C. Morgan. "Computerized relational database for monitoring clozapine therapy." American Journal of Health-System Pharmacy 50.8 (1993): 1657-1662.
8. Mitchell, Allen A., Carla M. Van Bennekom, and Carol Louik. "A pregnancy-prevention program in women of childbearing age receiving isotretinoin." New England Journal of Medicine 333.2 (1995): 101-106.
9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
10. Stitt, Frank W. "The Problem-Oriented Medical Synopsis: a patient-centered clinical information system." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
11. Suermondt, H. J., et al. "Automated identification of relevant patient information in a physician's workstation." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
12. Van Dyne, M. M., et al. "Using machine learning and expert systems to predict preterm delivery in pregnant women." Artificial Intelligence for Applications, 1994., Proceedings of the Tenth Conference on. IEEE, 1994.

Patent No.	Title	Assignee	Priority Date File Date
US5265010	Method and apparatus for performing patient documentation	Koninklijke Philips N.V.	05/15/1990 05/15/1990
US5672154	Method and apparatus for controlled individualized medication	MiniDoci Uppsala AB	08/27/1992 02/27/1995
US5558638	Patient monitor and support system	Matria Healthcare, Inc.	04/30/1993 04/30/1993
US5473537	Method for evaluating and reviewing a patient's condition	Behavioral Algorithms, Inc.	07/30/1993 04/12/1995
US5833599	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 04/09/1996
US6317719	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 11/10/1998
US7297111	Computerized medical diagnostic and treatment advice system	Clinical Decision Support, LLC	12/29/1993 03/09/2005
US5845255	Prescription management system	Cybear, LLC	10/28/1994 10/02/1997
US7072840	Prescription management system	Cybear, LLC	10/28/1994 11/30/1998
US7483839	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7519540	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7574370	Prescription management system	Cybear, LLC	10/28/1994 08/30/2001
US7606723	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/16/2004
WO9613790	PRESCRIPTION MANAGEMENT SYSTEM	MedEsystem Corporation	10/28/1994 10/27/1995
US5758095	Interactive medication ordering system	Presqriber LLC	02/24/1995 02/24/1995
US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995

Patent No.	Title	Assignee	Priority Date File Date
US6055507	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 08/20/1998
US6063026	Medical diagnostic analysis system	Carbon Based Corporation	12/07/1995 03/22/1996
US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
US5950630	System and method for improving compliance of a medical regimen	Michael T. Portwood	12/12/1996 12/12/1996
US6240394	Method and apparatus for automatically generating advisory information for pharmacy patients	inVentiv Health Inc.	12/12/1996 12/12/1996
US6322502	Medical information system	iMD Soft Ltd.	12/30/1996 06/29/1999
US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US6561976	Methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug	Elsayed et al	08/28/1998 09/26/2001 08/28/2018

Commentary

Celgene's '976 patent claims a method of approving a prescription for a teratogenic drug utilizing a computer to register pharmacists, pharmacies, and patients. The claims include providing counseling and drug hazard information to patients and authorizing a prescription to a woman only after determining that she is not pregnant. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, pharmacist, and pharmacy information in a computer was described and in use earlier than Celgene's 1998 priority date. In particular, Dishman (1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 1998 priority date. Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy.

The step of providing counseling and drug hazard data to patients was obvious well before 1998 through common practice as well as prior art.In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '976 patent would be obvious to a person of ordinary skill in the art.

In addition to the above obviousness arguments, Celgene's '976 patent could be invalidated using a double-patenting argument. The '976 patent fails to sufficiently differentiate itself from Celgene's earlier '501 patent.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
3. Dishman, Benjamin R., et al. "Pharmacists' role in clozapine therapy at a Veterans Affairs medical center." American Journal of Health-System Pharmacy 51.7 (1994): 899-901.
4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.

5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
6. Koren, Gideon, and Anne Pastuszak. "Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester." Teratology 41.6 (1990): 657-661.
7. Love, D. J., D. C. Schalk, and M. C. Morgan. "Computerized relational database for monitoring clozapine therapy." American Journal of Health-System Pharmacy 50.8 (1993): 1657-1662.
8. Mitchell, Allen A., Carla M. Van Bennekom, and Carol Louik. "A pregnancy-prevention program in women of childbearing age receiving isotretinoin." New England Journal of Medicine 333.2 (1995): 101-106.
9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
10. Stitt, Frank W. "The Problem-Oriented Medical Synopsis: a patient-centered clinical information system." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
11. Suermondt, H. J., et al. "Automated identification of relevant patient information in a physician's workstation." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
12. Van Dyne, M. M., et al. "Using machine learning and expert systems to predict preterm delivery in pregnant women." Artificial Intelligence for Applications, 1994., Proceedings of the Tenth Conference on. IEEE, 1994.

Patent No.	Title	Assignee	Priority Date File Date
US5265010	Method and apparatus for performing patient documentation	Koninklijke Philips N.V.	05/15/1990 05/15/1990
US5672154	Method and apparatus for controlled individualized medication	MiniDoci Uppsala AB	08/27/1992 02/27/1995
US5558638	Patient monitor and support system	Matria Healthcare, Inc.	04/30/1993 04/30/1993
US5473537	Method for evaluating and reviewing a patient's condition	Behavioral Algorithms, Inc.	07/30/1993 04/12/1995
US5833599	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 04/09/1996
US6317719	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 11/10/1998
US7297111	Computerized medical diagnostic and treatment advice system	Clinical Decision Support, LLC	12/29/1993 03/09/2005
US5845255	Prescription management system	Cybear, LLC	10/28/1994 10/02/1997
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US7483839	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7519540	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7574370	Prescription management system	Cybear, LLC	10/28/1994 08/30/2001
US7606723	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/16/2004
WO9613790	PRESCRIPTION MANAGEMENT SYSTEM	MedEsystem Corporation	10/28/1994 10/27/1995
US5758095	Interactive medication ordering system	Presqriber LLC	02/24/1995 02/24/1995
US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995

Patent No.	Title	Assignee	Priority Date File Date
US6055507	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 08/20/1998
US6063026	Medical diagnostic analysis system	Carbon Based Corporation	12/07/1995 03/22/1996
US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
US5950630	System and method for improving compliance of a medical regimen	Michael T. Portwood	12/12/1996 12/12/1996
US6240394	Method and apparatus for automatically generating advisory information for pharmacy patients	inVentiv Health Inc.	12/12/1996 12/12/1996
US6322502	Medical information system	iMD Soft Ltd.	12/30/1996 06/29/1999
US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US6561977	Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated	Williams et al	10/23/2000 09/27/2001 10/23/2020

Commentary

Celgene's '977 patent claims a method of approving a prescription for a teratogenic drug utilizing a computer to register pharmacists, pharmacies, and patients. The claims include providing counseling and drug hazard information to patients and authorizing a prescription to a woman only after determining that she is not pregnant. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, pharmacist, and pharmacy information in a computer was described and in use earlier than Celgene's 2000 priority date.In particular, Dishman (1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 2000 priority date. Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy.

The step of providing counseling and drug hazard data to patients was obvious well before 1998 through common practice as well as prior art. In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '977 patent would be obvious to a person of ordinary skill in the art.

In addition to the above obviousness arguments, Celgene's '977 patent could be invalidated using a double-patenting argument. The '977 patent fails to sufficiently differentiate itself from Celgene's earlier '501 patent.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
3. Dishman, Benjamin R., et al. "Pharmacists' role in clozapine therapy at a Veterans Affairs medical center." American Journal of Health-System Pharmacy 51.7 (1994): 899-901.
4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.

5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
6. Koren, Gideon, and Anne Pastuszak. "Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester." Teratology 41.6 (1990): 657-661.
7. Love, D. J., D. C. Schalk, and M. C. Morgan. "Computerized relational database for monitoring clozapine therapy." American Journal of Health-System Pharmacy 50.8 (1993): 1657-1662.
8. Mitchell, Allen A., Carla M. Van Bennekom, and Carol Louik. "A pregnancy-prevention program in women of childbearing age receiving isotretinoin." New England Journal of Medicine 333.2 (1995): 101-106.
9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
10. Stitt, Frank W. "The Problem-Oriented Medical Synopsis: a patient-centered clinical information system." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
11. Suermondt, H. J., et al. "Automated identification of relevant patient information in a physician's workstation." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
12. Van Dyne, M. M., et al. "Using machine learning and expert systems to predict preterm delivery in pregnant women." Artificial Intelligence for Applications, 1994., Proceedings of the Tenth Conference on. IEEE, 1994.

Patent No.	Title	Assignee	Priority Date File Date
US5265010	Method and apparatus for performing patient documentation	Koninklijke Philips N.V.	05/15/1990 05/15/1990
US5672154	Method and apparatus for controlled individualized medication	MiniDoci Uppsala AB	08/27/1992 02/27/1995
US5558638	Patient monitor and support system	Matria Healthcare, Inc.	04/30/1993 04/30/1993
US5473537	Method for evaluating and reviewing a patient's condition	Behavioral Algorithms, Inc.	07/30/1993 04/12/1995
US5833599	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 04/09/1996
US6317719	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 11/10/1998
US7297111	Computerized medical diagnostic and treatment advice system	Clinical Decision Support, LLC	12/29/1993 03/09/2005
US5845255	Prescription management system	Cybear, LLC	10/28/1994 10/02/1997
US7072840	Prescription management system	Cybear, LLC	10/28/1994 11/30/1998
US7483839	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7519540	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7574370	Prescription management system	Cybear, LLC	10/28/1994 08/30/2001
US7606723	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/16/2004
WO9613790	PRESCRIPTION MANAGEMENT SYSTEM	MedEsystem Corporation	10/28/1994 10/27/1995
US5758095	Interactive medication ordering system	Presqriber LLC	02/24/1995 02/24/1995
US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995

Patent No.	Title	Assignee	Priority Date File Date
US6055507	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 08/20/1998
US6063026	Medical diagnostic analysis system	Carbon Based Corporation	12/07/1995 03/22/1996
US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
US5950630	System and method for improving compliance of a medical regimen	Michael T. Portwood	12/12/1996 12/12/1996
US6240394	Method and apparatus for automatically generating advisory information for pharmacy patients	inVentiv Health Inc.	12/12/1996 12/12/1996
US6322502	Medical information system	iMD Soft Ltd.	12/30/1996 06/29/1999
US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US6755784	Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated	Williams et al	10/23/2000 03/07/2003 10/23/2020

Commentary

Celgene's '784 patent claims a method of approving a prescription for a teratogenic drug utilizing a computer to register pharmacists, pharmacies, and patients. The claims include providing counseling and drug hazard information to patients and authorizing a prescription to a woman only after determining that she is not pregnant. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, pharmacist, and pharmacy information in a computer was described and in use earlier than Celgene's 2000 priority date. In particular, Dishman (1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 2000 priority date. Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy.

The step of providing counseling and drug hazard data to patients was obvious well before 2000 through common practice as well as prior art. In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '784 patent would be obvious to a person of ordinary skill in the art.

In addition to the above obviousness arguments, Celgene's '784 patent could be invalidated using a double-patenting argument. The '784 patent fails to sufficiently differentiate itself from Celgene's earlier '501 patent.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
3. Dishman, Benjamin R., et al. "Pharmacists' role in clozapine therapy at a Veterans Affairs medical center." American Journal of Health-System Pharmacy 51.7 (1994): 899-901.
4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.

5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
6. Koren, Gideon, and Anne Pastuszak. "Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester." Teratology 41.6 (1990): 657-661.
7. Love, D. J., D. C. Schalk, and M. C. Morgan. "Computerized relational database for monitoring clozapine therapy." American Journal of Health-System Pharmacy 50.8 (1993): 1657-1662.
8. Mitchell, Allen A., Carla M. Van Bennekom, and Carol Louik. "A pregnancy-prevention program in women of childbearing age receiving isotretinoin." New England Journal of Medicine 333.2 (1995): 101-106.
9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
10. Stitt, Frank W. "The Problem-Oriented Medical Synopsis: a patient-centered clinical information system." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
11. Suermondt, H. J., et al. "Automated identification of relevant patient information in a physician's workstation." Proceedings of the Annual Symposium on Computer Application in Medical Care. American Medical Informatics Association, 1993.
12. Van Dyne, M. M., et al. "Using machine learning and expert systems to predict preterm delivery in pregnant women." Artificial Intelligence for Applications, 1994., Proceedings of the Tenth Conference on. IEEE, 1994.

Patent No.	Title	Assignee	Priority Date File Date
US5265010	Method and apparatus for performing patient documentation	Koninklijke Philips N.V.	05/15/1990 05/15/1990
US5672154	Method and apparatus for controlled individualized medication	MiniDoci Uppsala AB	08/27/1992 02/27/1995
US5558638	Patient monitor and support system	Matria Healthcare, Inc.	04/30/1993 04/30/1993
US5473537	Method for evaluating and reviewing a patient's condition	Behavioral Algorithms, Inc.	07/30/1993 04/12/1995
US5833599	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 04/09/1996
US6317719	Providing patient-specific drug information	Lexi-Comp, Inc.	12/13/1993 11/10/1998
US7297111	Computerized medical diagnostic and treatment advice system	Clinical Decision Support, LLC	12/29/1993 03/09/2005
US5845255	Prescription management system	Cybear, LLC	10/28/1994 10/02/1997
US7072840	Prescription management system	Cybear, LLC	10/28/1994 11/30/1998
US7483839	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7519540	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/30/2001
US7574370	Prescription management system	Cybear, LLC	10/28/1994 08/30/2001
US7606723	Computerized prescription system for gathering and presenting information relating to pharmaceuticals	Cybear, LLC	10/28/1994 08/16/2004
WO9613790	PRESCRIPTION MANAGEMENT SYSTEM	MedEsystem Corporation	10/28/1994 10/27/1995
US5758095	Interactive medication ordering system	Presqriber LLC	02/24/1995 02/24/1995
US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995

Patent No.	Title	Assignee	Priority Date File Date
US6055507	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 08/20/1998
US6063026	Medical diagnostic analysis system	Carbon Based Corporation	12/07/1995 03/22/1996
US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
US5950630	System and method for improving compliance of a medical regimen	Michael T. Portwood	12/12/1996 12/12/1996
US6240394	Method and apparatus for automatically generating advisory information for pharmacy patients	inVentiv Health Inc.	12/12/1996 12/12/1996
US6322502	Medical information system	iMD Soft Ltd.	12/30/1996 06/29/1999
US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997

Celgene Patent on Approval Methods for Drug Distribution

Patent No.	Title	Inventor	Priority Date File Date Expiration Date
US8315886	Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated	Williams et al	10/23/2000 12/13/2010 10/23/2020

Commentary

Celgene's '886 patent claims a method of approving a prescription for a potentially contraindicated drug utilizing a computer to register physicians, pharmacies, and patients. The claims include placing patients into risk groups and authorizing a prescription only after determining that the risk of a side effect is below an acceptable level. After reviewing this patent, M·CAM believes Celgene's filing is obvious in light of prior art.

The steps of registering patient, physician, and pharmacy information in a computer was described and in use earlier than Celgene's 2000 priority date. In particular, Dishman(1994), Honigfield (1996), and Love (1993) describe such databases as part of the Clozaril National Registry. Additionally, U.S. Pat. No. 6,322,502, owned by iMD Soft Ltd., claims a medical information system for storing patient and pharmacist data. Stitt (1993), Suermondt (1993), and Van Dyne (1994) also describe patient databases in which extensive medical data is stored, including pregnancy data.

The step of limiting prescriptions of a teratogenic drug to non-pregnant women had also been established before Celgene's 2000 priority date. Honigfield and Love teach restricting access to drugs based on blood-testing, while Mitchell (1995) and Powell (1994) teach excluding pregnancy from therapy with isotretinoin and thalidomide. Additionally, U.S. Pat. Nos. 7,072,840; 7,483,839; 7,574,370; and 7,606,723 (owned by Cybear, LLC) describe a prescription creation system utilizing a patient condition database which can establish drug limitations based on pregnancy. U.S. Pat. Nos. 5,473,537 (owned by Behavioral Algorithms, Inc.) and 5,772,585 (owned by EMC, Inc) describe systems for storing and analyzing patient demographic, habit, and behavior data. These systems, in light of Mitchell and Powell, render the risk determination and prescription limitation steps in the '886 patent obvious.

The step of providing counseling and drug hazard data to patients was obvious well before 2000 through common practice as well as prior art. In particular, Koren (1990) and Mitchell describe providing counseling and drug risk information to women who are or could become pregnant. Additionally, U.S. Pat. No. 6,240,394 (owned by inVentiv Health Inc.) claims the automated generation of advisory information to patients receiving drugs based on stored patient data.

Based on this information, it seems clear that the methods claimed by Celgene's '886 patent would be obvious to a person of ordinary skill in the art.

Selected Prior Art

1. "Healthpoint Introduces Clinical Information System To Increase Practice Productivity And Enhance Care, HealthpointAcs Unveiled At Himss Annual Convention", Business Wire, Mar. 5, 1996, 3 pages.
2. D'Amato, ROBERT J., et al. "Thalidomide is an inhibitor of angiogenesis." Proceedings of the National Academy of Sciences 91.9 (1994): 4082-4085.
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4. Freeman, David J., and L. Kola Oyewumi. "Will routine therapeutic drug monitoring have a place in clozapine therapy?." Clinical pharmacokinetics 32.2 (1997): 93-100.

5. Honigfield, Gilbert. "Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis." Psychiatric Services (1996).
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9. Powell, R. J., and J. M. Gardner-Medwin. "Guideline for the clinical use and dispensing of thalidomide." Postgraduate medical journal 70.830 (1994): 901.
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US5619991	Delivery of medical services using electronic data communications	Alcatel-Lucent USA, Inc.	04/26/1995 04/26/1995
US5832449	Method and system for dispensing, tracking and managing pharmaceutical trial products	TrialCard, Inc.	11/13/1995 11/13/1995

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US6108635	Integrated disease information system	Interleukin Genetics, Inc.	05/22/1996 04/30/1997
US5772585	System and method for managing patient medical records	EMC, Inc	08/30/1996 08/30/1996
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US6234964	Disease management system and method	Clinical Decision Support, LLC	03/13/1997 03/13/1998
US6067523	System and method for reporting behavioral health care data	Harcourt Assessment, Inc.	07/03/1997 07/03/1997
US6108665	System and method for optimizing behavioral health care collection	Harcourt Assessment, Inc.	07/03/1997 07/03/1997