Paper No. _____
Filed: April 22, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS VI LLC

PETITIONER

V.

CELGENE CORPORATION

PATENT OWNER

CASE NO.: UNASSIGNED
PATENT NO. 6,045,501
FILED: AUGUST 28, 1998
ISSUED: APRIL 4, 2000
INVENTORS: MARC ELSAYED, BRUCE WILLIAMS

TITLE: METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE PREVENTING THE EXPOSURE OF A FOETUS OR OTHER CONTRAINDICATED INDVIDUAL TO THE DRUG

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 6,045,501

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

TABLE OF EXHIBITS

Exhibit No.	Description
Exhibit 1001	U.S. Patent No. 6,045,501 to Marc Elsayed and Bruce Williams, filed on Aug. 28, 1998, and issued on Apr. 4, 2000 ("The '501 Patent")
Exhibit 1002	Declaration of Jeffrey Fudin, R.Ph., B.S., Pharm.D., DAAPM, FCCP, FASHP ("*Fudin Decl.*")
Exhibit 1003	U.S. Patent No. 5,619,991 to Neil J.A. Sloane, filed on Apr. 26, 1995, and issued on Apr. 15, 1997 ("*Sloane*")
Exhibit 1004	U.S. Patent No. 6,045,501 Prosecution History ("'501 prosecution history")
Exhibit 1005	"Guideline for the clinical use and dispensing of thalidomide," R.J. Powell and J.M.M Gardner-Medwin, *Postgrad Med. J.* (1994) 79, 901–904 ("*Powell*")
Exhibit 1006	"A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin," Allen A. Mitchell *et al.*, *New Eng. J. Med.* (Jul. 13, 1995) 333:2, 101–06 ("*Mitchell*")
Exhibit 1007	"Pharmacists' role in clozapine therapy at a Veterans Affairs medical center," Benjamin R. Dishman *et al.*, *Am. J. Hosp. Pharm.* (Apr. 1, 1994) 51, 899–901 ("*Dishman*")
Exhibit 1008	"CDC Meeting: 03/26/1997 Minutes and Agenda Regarding Thalidomide" ("*CDC*")
Exhibit 1009	"Effects of the Clozapine National Registry System on Incidence of Deaths Related to Agranulocytosis," Gilbert Honigfeld, *Psychiatric Services* (Jan. 1996) 47:1, 52–56 ("*Honigfeld*")
Exhibit 1010	"Development of the Clozaril Patient Management System," Bijan Bastani *et al.*, Psychopharmacology (1989) 99: S 122–S 125 ("*Bastani*")
Exhibit 1011	"The Return of Thalidomide: Are Birth Defects Surveillance Systems Ready?," Quanhe Yang *et al.*, *Am. J. Med. Genetics* (1997) 73:251–258 ("*Yang*")
Exhibit 1012	"Assessing the Effectiveness of a Computerized Pharmacy System," Reed M. Gardner *et al.*, Decision Support Systems in Critical Care, 1994, M.M. Schabot *et al.*, eds. ("*Gardner*")
Exhibit 1013	"Federal Register Notices," 62:53, 13158 (Mar. 19, 1997) ("*Federal Register*")

Exhibit No.	Description
Exhibit 1014	Curriculum Vitae for Jeffrey Fudin, R.Ph., B.S., Pharm.D., DAAPM, FCCP, FASHP ("*Fudin CV*")
Exhibit 1015	"Thalidomide: Potential Benefits and Risks, An Open Public Scientific Workshop, Program and Abstracts," Office of the Director National Institutes of Health (Sept. 9–10, 1997) ("*NIH*")
Exhibit 1016	"Center for Drug Evaluation and Research Approval Package for: Application Number NDA 20-785 Approval Letter(s)," Sept. 19, 1997, and Jul. 16, 1998 ("*FDA Thalomid Approval Letters*")
Exhibit 1017	"NIH News Advisory: NIH Will Hold Public Scientific Workshop on Thalidomide: Potential Benefits and Risks," Office of the Director National Institutes of Health (Sept. 5, 1997) ("*NIH Press Release*")
Exhibit 1018	"Passage of Chemicals into Human and Animal Semen: Mechanisms and Significance," Thaddeus Mann and Cecelia Lutwak-Mann, CRC Critical Reviews in Toxicology (1982) 11:1, 1–14 ("*Mann*")

I. INTRODUCTION

Petitioner Coalition For Affordable Drugs VI LLC requests an *Inter Partes* Review ("IPR") of Claims 1–10 of U.S. Patent No. 6,045,501 (the "'501 Patent") (Ex. 1001) in accordance with 35 U.S.C. §§311–319 and 37 C.F.R. § 42.100 *et seq*.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A))

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '501 Patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR challenging the Claims of the '501 Patent on the grounds identified in this Petition.

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

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

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs VI LLC, Hayman Credes Master Fund, L.P. ("Credes"), Hayman Orange Fund SPC – Portfolio A ("HOF"), Hayman Capital Master Fund, L.P. ("HCMF"), Hayman Capital Management, L.P. ("HCM"), Hayman Offshore Management, Inc. ("HOM"), Hayman Investments, L.L.C. ("HI"), nXn Partners, LLC ("nXnP"), IP Navigation Group, LLC ("IPNav"), J. Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively, "RPI"). The RPI hereby certify the following information: CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative

general partner of Credes and HCMF. HI is the general partner of HCM. J. Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes, HOF and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is 98.5% member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the 98.5% member of IPNav. Other than HCM and J. Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HOF, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition will be borne by HCM, CFAD, Credes, HOF and/or HCMF.

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

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '501 Patent has been the subject of the following lawsuits: *Celgene Corp. v. Barr Laboratories, Inc. et al.*, DNJ-2:07-cv-00286 (filed Jan. 18, 2007), *Celgene Corp. v. Barr Laboratories, Inc. et al.*, DNJ-2:07-cv-04050 (filed Aug. 23, 2007), *Celgene Corp. v. Barr Laboratories, Inc. et al.*, DNJ-2:07-cv-05485 (filed Nov. 14, 2007), *Celgene Corp. v. Barr Laboratories, Inc. et al.*,

DNJ-2:08-cv-03357 (filed Jul. 3, 2008), *Celgene Corp. v. Natco Pharma Ltd.*, DNJ-2:10-cv-05197 (filed Oct. 8, 2010), and *Celgene Corp. v. Lannett Holdings, Inc. et al.*, DNJ-2:15-cv-00697 (filed Jan. 30, 2015).

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead counsel is Sarah E. Spires, Reg. No. 61,501, sarah.spires@skiermontpuckett.com. Back-up counsel are Ki O, Reg. No. 68,952, ki.o@skiermontpuckett.com; Dr. Parvathi Kota, Reg. No. 65,122, parvathi.kota@skiermontpuckett.com; and Paul J. Skiermont (*pro hac vice* requested), paul.skiermont@skiermontpuckett.com, 2200 Ross Ave. Ste. 4800W, Dallas, Texas 75201, P: 214-978-6600/F: 214-978-6601. Petitioner consents to electronic service.

IV. PAYMENT OF FEES (37 C.F.R. § 42.15(a) AND § 42.103))

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506293. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

The '501 Patent is titled "Methods for Delivering a Drug to a Patient While Preventing the Exposure of a Foetus or Other Contraindicated Individual to the Drug." The underlying application, U.S. Patent Application Serial No. 09/143,569, was filed on August 28, 1998, identifying Marc Elsayed and Bruce Williams as the inventors.

The ’501 Patent claims methods for delivering a drug, including a teratogenic drug, to a patient while preventing the exposure of a fetus or other contraindicated individuals to the drug. (Ex. 1001, Abstract, 3:21–23.) “A teratogenic drug is an agent that, upon administration to the mother or father, may disturb the normal growth and development of an embryo or fetus.” (Ex. 1002 ¶ 1919.) The ’501 Patent discloses methods to “monitor[] and control[]” the distribution of such drugs and other potentially hazardous drugs. (Ex. 1001 at 1:13–17.)

The background section of the ’501 specification admits that prior “methods for controlling the distribution of drugs have been developed in connection with” a known teratogenic drug (isotretinoin, or Accutane®), including a “pregnancy prevention program.” (Ex. 1001 at 1:48–55.) It references a study from the Slone Epidemiology Unit of Boston University that surveyed patients to assess the success of the isotretinoin program and found it to be effective. (Ex. 1001 at 1:52–57.)

“The invention of the ’501 Patent was purportedly conceived in the context of the introduction of an FDA-approved version of thalidomide, a known teratogenic drug beneficial for treating a variety of diseases, including a form of leprosy.” (Ex. 1002 ¶ 2222.) Claim 1 of the ’501 Patent can be summarized in three simple steps: (1) “registering in a computer readable storage medium” information about qualified prescribers, authorized pharmacies, and patients, including patients’ ability to become pregnant or impregnate, (2) identifying and counseling a subpopulation of those patients that can become pregnant or impregnate as to the risks of the

teratogenic drug, and (3) authorizing delivery of the drug by registered pharmacies only to non-pregnant registered patients while monitoring the subpopulation for pregnancy. (Ex. 1001 at 2:9–37; Ex. 1002 ¶ 23.) While the claims of the '501 Patent are focused on teratogenic drugs, the specification makes clear that the inventors were also contemplating "other potentially hazardous drugs" that could "also be distributed in accordance with embodiments of this invention…in such a fashion that person for whom such drugs are contraindicated will not receive them." (Ex. 1001 at 3:10–17.)

In one embodiment, "[i]f the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered…the pharmacy will be ineligible to dispense the drug." (Ex. 1001 at 5:54–64.) For teratogenic drugs, "the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods…" (Ex. 1001 at 6:37–40.) In another embodiment, the patient must sign an informed consent form prior to receiving the drug. (Ex. 1001 at 7:33–38.) After counseling, the patient may receive limited amounts of the drug from a registered pharmacy, and not receive refills without a renewal prescription from a prescriber, subject to conditions like a negative pregnancy test. (Ex. 1001 at 8:53–65.)

Claim 1, the only independent claim in the '501 Patent, provides:

> A method for delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus comprising:

a. registering in a computer readable storage medium prescribers who are qualified to prescribe said drug;

b. registering in said medium pharmacies to fill prescriptions for said drug;

c. registering said patients in said medium, including information concerning the ability of female patients to become pregnant and the ability of male patients to impregnate females;

d. retrieving from said medium information identifying a subpopulation of said female patients who are capable of becoming pregnant and male patients who are capable of impregnating females;

e. providing to the subpopulation, counseling information concerning the risks attendant to fetal exposure to said drug;

f. determining whether patients comprising said subpopulation are pregnant; and

g. in response to a determination of non-pregnancy for said patients, authorizing said registered pharmacies to fill prescriptions from said registered prescribers for said non-pregnant registered patients.

(Ex. 1001 at 10:43–67.)

During prosecution, the only references of record were four U.S. Patents. "None of this art of record related to the Accutane® pregnancy prevention program or the Clozaril® restricted distribution model, both well known in the art as methods to avoid the delivery of potentially hazardous drugs to contraindicated individuals." (Ex. 1002 ¶ 2525.) The examiner initially rejected the applicants' claims as obvious in view of one of those references, U.S. Patent No. 5,619,991 ("*Sloane*"). In an Office Action dated October 7, 1999, the examiner noted *Sloan*e discloses a "method for

delivering drugs to patients in need of a drug while avoiding delivery of said drug to a foetus comprising registering qualified prescriber in a computer readable storage medium, registering pharmacies to fill prescriptions, registering patients and patient data, providing counseling information to a patient. . .determining whether the patient is pregnant, and authorization of prescriptions to be filled." (Ex. 1004 at 1004-0063.)

In response, Applicants argued the "critical feature" of independent Claim 1 was that "the methods may be used, *e.g.*, to deliver a teratogenic drug to patients in need of the drug **while avoiding the delivery of the drug to a foetus**." (Ex. 1004 at 1004-0075 (original emphasis).) They also argued "*Sloane* is utterly silent regarding the use of computer readable storage media to deliver to patients potentially dangerous drugs, for example, teratogenic drugs, while at the same time avoiding their delivery to persons to whom the drugs are contraindicated, for example, foetuses." (Ex. 1004 at 1004-0076.) Applicants argued that *Sloane* does not teach how its methods could be used to provide checks and balances to insure only registered prescribers or pharmacies have access. (Ex. 1004 at 1004-0077.) The claims were then allowed.

A. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Unless otherwise noted, Petitioner contends that the claim terms of the '501 Patent are presumed to take on the ordinary and customary meaning that they would have to one of ordinary skill in the art at the time of the invention.

1. "Registering"

"Registering" means: "recording in a written format (including by mail, facsimile transmission, online transmission) information relating to a person or entity (such as a prescriber, pharmacy, or patient). (Ex. 1001, 4:10-49, 5:1-23, 6:25-52; Ex. 1002 ¶ 30.)

2. "Determination of non-pregnancy"

"Determination of non-pregnancy" means: "the process of establishing that a patient is not pregnant, for example, through consultation, examination, self-report, or chemical test." (Ex. 1001 at 7:45–62; Ex. 1002 ¶ 31.)

3. "The risks attendant to fetal exposure"

"The risks attendant to fetal exposure" means: "exposure to danger, harm, or loss associated with the drug if a fetus is subjected to it through use by the mother or the father." (Ex. 1001 at 6:30–34; Ex. 1002 ¶ 32.)

B. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Petitioners request IPR under 35 U.S.C. § 311 of Claims 1–10 of the '501 Patent, and cancellation of these ten claims as unpatentable.

2. Statutory Grounds of Challenge

Petitioners request IPR of Claims 1–10 of the '501 Patent in view of the following references, each of which is prior art to the '501 Patent under 35 U.S.C. §§ 102(a) and (b) or 103. The Examiner did not consider any of the prior art listed in the following chart. Claims 1–10 are unpatentable under 35 U.S.C. § 103:

Ground	Proposed Rejections for the '501 Patent	Exhibit Number(s)
1	Claims 1–10 are obvious under 35 U.S.C. § 103(a) over *Powell* and *Mitchell* in view of *Dishman*.	Exs. 1005, 1006, 1007
2	Claims 1–10 are obvious under 35 U.S.C. § 103(a) over *NIH* in view of *Honigfeld*.	Exs. 1015, 1009

C. Overview of the State of the Art and Summary of Prior Art References

1. State of the Relevant Art as of August 1998

"By August of 1998, persons of ordinary skill in the art understood that teratogenic drugs may cause birth defects, and were aware that such drugs either already used, or needed, restrictive safeguards before prescription." (Ex. 1002 ¶ 33.) For example, one drug marketed using methods to prevent its use in pregnant patients was isotretinoin, marketed under the trade name Accutane®. (Ex. 1006 at 101; Ex. 1002 ¶ 34.) "This drug, suspected to be a potent teratogen based on animal testing, became part of a manufacturer-sponsored Pregnancy Prevention Program ("PPP"). (Ex. 1002 ¶ 34 (citing Ex. 1006 at 101).) The PPP had multiple components, including the distribution to physicians of a kit containing informed consent documents and information for patient counseling. (Ex. 1006 at 101.) "In particular, patients were warned against the teratogenic risk of Accutane and the need to prevent pregnancy while taking the drug. Patients were also advised as to the proper methods of birth control available." (Ex. 1002 ¶ 35 (citing Ex. 1006 at 103).)

"In addition to the Accutane PPP, another well-known restricted drug distribution program in existence prior to 1998 regulated clozapine (trade name Clozaril®). In early 1997, medical professionals made the observation that the methods used to control prescriptions for clozapine, an anti-psychotic with potential adverse effects indicated by white blood cell counts ("WBCs"), could be copied for thalidomide." (Ex. 1002 ¶ 36.) In particular, such methods included "comprehensive data collection," including keeping records of pre-approved physicians and pharmacists to prescribe and dispense the drug and patients taking the drug. (Ex. 1010 at 122.) "The patients were required to submit to weekly testing for WBCs and could only have a prescription for clozapine filled if the test results were within a certain range." (Ex. 1002 ¶ 36 (citing Ex. 1010 at 122).)

Thalidomide was developed in 1957 in Germany, as a sedative, under the trade name Contergan. (Ex. 1002 ¶ 37.) "However, shortly after it was first marketed it became apparent that thalidomide caused severe birth defects in infants whose mothers took the drug while pregnant. As a result, it was generally taken off of most markets in 1962." (Ex. 1002 ¶ 38.) Thalidomide was reintroduced in professional circles in the United States in the 1990s, and on July 16, 1998, the FDA approved the drug to treat a rare form of leprosy, erythema nodosum leprosum (ENL). (Ex. 1002 ¶ 39.) To ensure the safety of the product, the FDA invoked the restricted distribution provisions under Subpart H of its regulations (21 C.F.R. § 314.520), which are

directed to products with safety issues that cannot be addressed under ordinary approval conditions. (Ex. 1002 ¶ 40, citing Ex. 1016.)

"In pharmacy schools, the history of thalidomide is taught to support case studies that show what could happen without proper monitoring and evaluation of drug product properties by adequate and acceptable laboratory, animal, and human studies." (Ex. 1002 ¶ 4145.) In fact, the tragedy of the birth defects caused by thalidomide in the 1950s "sensitized manufacturers, governments, health professionals, and the public to the problem of birth defects and possible teratogenicity of drugs." (Ex. 1002 ¶ 41 (quoting Ex. 1011 at 251).) These individuals and entities "recognized, by 1997, that '[i]f thalidomide becomes widely available, stringent control measures must be taken to prevent the exposure of pregnant women, though the proportion of women at risk may be small' and that '[p]atient and physician educational campaigns and public awareness of the teratogenic effects of the thalidomide would no doubt play a crucial role in minimizing the teratogenic impact...'" (Ex. 1002 ¶ 42 (quoting Ex. 1011 at 252, 257).) Manufacturers of pharmaceuticals were also especially interested in strict controls to avoid liability for any fetal harm as a result of treatment with thalidomide. (Ex. 1002 at 43.)

"In March of 1997, the Centers for Disease Control and Prevention convened a meeting specifically to discuss an approach for the introduction of thalidomide to U.S. markets." (Ex. 1002 ¶ 44.) This meeting was announced in the Federal Register, and in the announcement, the organizers specified that the purpose was to "enable

academic and public health professionals to discuss strategies to prevent birth defects due to exposure to thalidomide and other human teratogens…to review existing strategies for limiting intrauterine exposure to human teratogens, and to discuss and provide individual input on new approaches for preventing birth defects due to future teratogens such as thalidomide." (Ex. 1002 ¶ 44 (quoting Ex. 1013, March 19, 1997 Federal Register (emphasis added)).) The announcement specifically outlined certain methods to be evaluated, such as the "(1)…Accutane Pregnancy Prevention Program, (2) use and limitations of drug registries, (3) contraception efficacy, (4) ethical issues on teratogen exposure, and (5) measures to assure appropriate use of pharmaceuticals." (*Id.*) The agenda and minutes summarized these topics. (Ex. 1008.)

Thus, doctors, pharmacists, and regulators interested in bringing thalidomide back to the market with restrictions to protect fetuses from its teratogenic effects "were aware of both the Accutane Pregnancy Prevention Program, as well as the clozapine restricted distribution program." (Ex. 1002 ¶ 47.)

It was also well known in the art prior to 1998 that prescription records can be and were kept in computerized systems. (Ex. 1012 at 175, Fig. 12.1; Ex. 1002 ¶ 48.) Such records included information about the patient, including their name, age, birthdate, sex, height, weight, allergies, and other health-related measures. (Ex. 1002 ¶ 49–50.) Pharmacies used such systems to track their patients dating back to, at the latest, 1975. (Ex. 1012 at Ch. 12; Ex. 1002 ¶ 48.) Physicians and pharmacists use this data to determine (1) whether a patient should be prescribed and provided a certain

drug given its profile, and (2) how long a patient should take the medication. (Ex. 1002 ¶ 54.) They also isolated certain groups of patients, such as contraindicated individuals, based on computerized sorting of these records. (Ex. 1002 ¶ 53.)

"Thus, in the case of thalidomide or any other teratogenic drug, a person of ordinary skill in the art would have been motivated to combine well-known prior art restricted drug distribution methods, including counseling-based avoidance of pregnancy, and a computerized tracking system that allows only registered access to prescriptions when certain conditions (*e.g.*, non-pregnancy) are met." (Ex. 1002 ¶ 55.) *See also*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (U.S. 2007) (where "there is a design need or market pressure to solve a problem and there are finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp").

2. Summary of the Petition's Prior Art References

a. Powell

The *Powell* publication constitutes prior art under 35 U.S.C. § 102(b) because it was published in the December 1994 volume of the Postgraduate Medical Journal, which is more than one year prior to the '501 Patent's priority date. During the prosecution of the '501 Patent, the examiner did not have *Powell*.

Powell discloses guidelines "designed to promote the safest possible clinical use and dispensing of thalidomide." (Ex. 1005 at 901.) "In particular, it sets out several criteria for the clinical use of thalidomide, including the exclusion of patients who are

pregnant or wish to become pregnant." (Ex. 1002 ¶ 56 (citing Ex. 1005 at 901).) It recommends obtaining "informed consent" in writing and, subsequent to treatment, the monitoring of patients taking the drug. (Ex. 1002 ¶ 56 (citing Ex. 1005 at 902).)

Powell describes in detail the counseling to be provided to patients treated with thalidomide. Each patient should be given an information sheet detailing the "contraindications, warnings, and precautions associated with the use of the drug." (Ex. 1005 at 902.) A sample information sheet is provided in the reference, and it includes a paragraph detailing "[d]amage to babies" that could result from thalidomide. (Ex. 1002 ¶ 57 (citing Ex. 1005 at Fig. 1).)

In addition, the *Powell* reference discloses that the subgroup of "[w]omen with childbearing potential" must agree to (1) take a pregnancy test within two weeks of starting treatment to ensure they are not pregnant, (2) "take reliable contraceptive precautions" during and for a period after treatment, and (3) "stop taking thalidomide immediately should they miss a period" and consult their physician. (Ex. 1002 ¶ 58 (citing Ex. 1005 at 901–02).) All patients must "agree to return any unused supply of thalidomide to the prescribing physician." (Ex. 1002 ¶ 58 (citing Ex. 1005 at 902).)

b. Mitchell

The *Mitchell* publication constitutes prior art under 35 U.S.C. § 102(b) because it was published on July 13, 1995 in The New England Journal of Medicine, which is more than one year prior to the '501 Patent's priority date. During the prosecution of the '501 Patent, the examiner did not have *Mitchell*.

Mitchell discloses a pregnancy prevention program implemented to minimize pregnancies among women treated with the known teratogenic drug isotretinoin. This Pregnancy Prevention Program sought "to keep the drug available while minimizing the teratogenic hazard." (Ex. 1006 at 105.) The program, which was targeted at both prescribers and patients, instructed prescribers to "warn patients of risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next normal menstrual period." (Ex. 1002 ¶ 60 (citing Ex. 1006 at 101).) It also included materials such as information brochures and contraceptive information for patients. (Ex. 1006 at 101.) Prescribers and pharmacists received periodic communications from program managers to reinforce the materials. (Ex. 1006 at 101.)

"*Mitchell* describes counseling patients in relation to the teratogenic effects of isotretinoin." (Ex. 1002 ¶ 61.) Some implementations of the program included warnings about the "need to have a negative blood pregnancy test before starting therapy…and to use effective birth control one month before starting therapy, during therapy, and one month after completing it." (Ex. 1006 at 103.)

c. Dishman

The *Dishman* publication constitutes prior art under 35 U.S.C. § 102(b) because it was published on April 1, 1994 in the American Journal of Hospital Pharmacy, which is more than one year prior to the '501 Patent's priority date. During the prosecution of the '501 Patent, the examiner did not have *Dishman*.

"*Dishman* discloses a program for controlling the dispensing of clozapine, an antipsychotic drug, to veterans." (Ex. 1002 ¶ 62.) "Clozapine treatment is associated with a number of serious and potentially fatal serious side effects." (Ex. 1002 ¶ 62.) The program described in *Dishman* was instituted by the Department of Veterans Affairs ("VA") in 1994 because the VA understood the need to develop a clozapine monitoring program to prevent contraindicated individuals from receiving the drug. (Ex. 1002 ¶ 64 (citing Ex. 1007 at 900).)

Dishman discloses that, in order for the authorized prescription and use of Clozaril®, prescribers and patients must register with the Clozaril® National Registry, which required weekly monitoring of white blood cell counts of each patient and limited the amount of medicine dispensed at one time. (Ex. 1007 at 900.) This process "require[d] the cooperation and coordinated efforts of the patient, physician, laboratory, and pharmacy." (Ex. 1007 at 899.)

The VA's implementation of the program, as described in *Dishman*, established a National Clozapine Coordinating Center ("NCCC") to "review each clozapine candidate's file before granting approval for use and weekly tracking…" (Ex. 1007 at 900.) Prior to receiving approval to receive the drug, each patient had to undergo an extensive evaluation and documentation to identify contraindications, including pregnancy. (Ex. 1007 at 900.) The NCCC also mandated that each hospital have a computerized clozapine prescription lockout system, which tied the hospital's laboratory database to the outpatient pharmacy dispensing software. (Ex. 1002 ¶ 64

(citing Ex. 1007 at 900).) Thus, clozapine prescriptions could only be processed when certain pre-defined clinical criteria were met – specifically, when white blood cell counts were within defined limits. (Ex. 1002 ¶ 65 (citing Ex. 1007 at 899.) *Dishman* explained that patients were screened by the pharmacist to determine eligibility for treatment with clozapine. (Ex. 1007 at 900.) "A POSA, reading *Dishman*, would have understood that pharmacists sent information to the NCCC and after approval, the patient would be enrolled in the hospital's clozapine tracking system through which therapy could begin." (Ex. 1002 ¶ 66 (citing Ex. 1007 at 900).)

d. *NIH*

The *NIH* publication, which comprises a program and abstracts for "an open public scientific workshop" sponsored by the U.S. National Institutes of Health ("NIH"), Food and Drug Administration ("FDA"), and the Centers for Disease Control and Prevention ("CDC"), constitutes prior art under 35 U.S.C. § 102(a) because it was "sufficiently accessible, at least to the public interested in the art" before August 28, 1998 to qualify as a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). The question of sufficient public accessibility is a legal determination based on underlying fact issues, subject to a case-by-case analysis. *See, e.g.*, *In re Wyer*, 655 F.2d 221, 224 (C.C.P.A. 1981).

NIH was available no later than September 5, 1997, as established by, a press release (Ex. 1017) from the NIH. (Ex. 1002 at 68.) The press release states that "A complete agenda and background information on the meeting, along with an

extensive bibliography on thalidomide research is available on the Internet…" (Ex. 1017.) An introduction to the reference notes: "This book is designed for the use of participants in the workshop and as a pertinent reference document for anyone interested in the workshop subject. We are grateful to the authors who have summarized their materials and made them available in a timely fashion." (Ex. 1015 at 15 (emphasis added).) During prosecution the examiner did not have *NIH*.

NIH includes several abstracts related to various aspects of the potential use of thalidomide in the United States. An objective of the workshop was "to provide effective risk-communication and risk-management procedures to the relevant health care providers and patients about the potential benefits and risks associated with the use of thalidomide..." (Ex. 1015 at 1.)

"The abstracts cover numerous topics for the risk reduction and monitoring of patients treated with thalidomide. Such topics include (1) warnings against use by women capable of becoming pregnant, (2) required pregnancy testing before treatment, (3) mandatory use of contraception for men and women, (4) physician and pharmacist education, (5) patient education, and (6) tracking of patients in a database." (Ex. 1002 ¶ 72 (citing Ex. 1015 at 21, 33, 35, 47, 53–54).) *NIH* included recommendations relating to involvement of pharmacists (and others): "This joint effort should include the patient, the prescribing health care provider, other appropriate health care providers, the pharmacist, the pharmaceutical company,

professional societies, and regulators." (Ex. 1015, 53–54.) Portions of *NIH* also disclose the Accutane Pregnancy Prevention Program. (Ex. 1015, 31.)

Finally, *NIH* includes a consent form template and an informational patient brochure for use with thalidomide treatment. The consent form includes a detailed, nearly full page section warning against "Birth Defects" and an agreement by "females able to bear children" that they will "have a negative pregnancy test before, during, and one month after stopping thalidomide." (Ex. 1015 at 0113–19.) The brochure bears a prominent "Avoid Pregnancy" illustration on the cover, and contains warnings to both men and women that they must use contraception to avoid birth defects. It also includes a drawing of a malformed infant. (Ex. 1015 at 0120–21.)

e. Honigfeld

The *Honigfeld* publication constitutes prior art under 35 U.S.C. § 102(b) because it was published January 1996, in the journal Psychiatric Services, which is more than one year prior to the '501 Patent's priority date. During the prosecution of the '501 Patent, the examiner did not have *Honigfeld*.

The *Honigfeld* reference discloses procedures for dispensing a drug that is available only through "treatment systems registered with the national registry" for the drug. (Ex. 1002 ¶ 78 (citing Ex. 1009 at 52).) In particular, the reference discusses a registry for Clozaril® that allows pretreatment authorization for a patient to be treated with the drug "only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression." (Ex. 1009 at 52.) Also, "[d]istribution of the

medication is limited to pharmacies which agree to follow the 'no blood-no drug guidelines." (Ex. 1009 at 53.) The registry described by *Honigfeld* functions by receiving data and entering it "into an integrated, computerized database maintained by the manufacturer." (Ex. 1009 at 53.) Patients' records in the registry include an "identifying code number and initials, the physician's identification, the pharmacy's identification, daily dosage of clozapine in milligrams, and white blood cell test dates and results." (Ex. 1009 at 53.) The registry goal is "reduce the chances of reexposure to the medication by persons at increased risk" of adverse effects. (Ex. 1009 at 54.)

D. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is apparent from the cited art. Further, a person of ordinary skill in the field of the invention of the '501 Patent, as of August 1998, the earliest possible priority date, would typically have either a Pharm. D. or a BS in pharmacy with approximately 5—10 years of related experience and a license to practice as a registered pharmacist in any one or more of the United States. (Ex. 1002 ¶ 15.) A person of ordinary skill in the art "may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others on the team, to solve a given problem. For example, a formulator, dissolution expert and a clinician may be part of the team." (*Id* at ¶ 16.)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: Claims 1–10 of U.S. Patent No. 6,045,501 to Elsayed *et al.* are obvious under 35 U.S.C. § 103(a) over *Powell* and *Mitchell* in view of *Dishman*.

1. Claim 1 is obvious over *Powell*, *Mitchell* and *Dishman.*

One of ordinary skill in the art prior to August 28, 1998, when seeking to treat patients with thalidomide, would first look to *Powell* for guidance on "the clinical use and dispensing" of thalidomide, (Ex. 1005 at 901) and would garner from it recommendations for "delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus," as described in the preamble of Claim 1. *Powell* is a printed publication in a medical journal on the precise topic of preventing pregnancy in connection with the use of thalidomide, a known teratogenic, and therefore "would be a natural starting point for a pharmacist or medical professional." (Ex. 1002 ¶ 8791.) Although they appear in the form of recommendations, the disclosed methods of *Powell* are enabled because a person of ordinary skill in the art "would understand how to practice [them] at the time of publication without undue experimentation," in view of the nature of the methods and the state of the art. (Ex. 1002 ¶ 88.)

At the time that *Powell* was published, "a person of ordinary skill in the art would have understood how to implement *Powell's* teachings in clinical and pharmacy settings," especially in view of such a person's knowledge of the Accutane® Pregnancy Prevention Program described in *Mitchell* and the Clozaril® controlled distribution model outlined in *Dishman*. (Ex. 1002 ¶ 88.) Such a person "would also recognize that *Powell* and *Dishman* would address the shortcomings of the Accutane® program that was well known in the art and disclosed in *Mitchell*—namely, that the use

of the registry was not mandatory for all patients, and that the system did not involve verification by pharmacists that a patient was authorized to receive the drug." (Ex. 1002 ¶ 89.) Indeed, a POSA would seek those references to solve such problems. (*Id.*)

First, a "person of ordinary skill would have understood from *Powell* and *Mitchell* the desirability, when treating patients with teratogenic drugs, of "'identifying a subpopulation of said female patients who are capable of becoming pregnant and male patients who are capable of impregnating females,'" as required by **Claim 1(d)** of the '501 Patent. (Ex. 1002 ¶ 91.) To start, *Powell* teaches that "women of childbearing potential" should be excluded if they "wish to become pregnant," "have not practised a reliable form of contraception for 1 year," "are unwilling to take reliable contraceptive precautions," and/or "are considered not capable of complying with the requirements for reliable contraception." (Ex. 1005 at 901901.)

Similarly, *Mitchell* discloses measures, such as warnings on the packaging that were directed "specifically at women." (Ex. 1006 at 101.) *Mitchell* further teaches that "women of childbearing age (12 to 59 years of age)" are a particularly significant subgroup of patients for isotretinoin treatment. (Ex. 1006 at 102.) The subjects of the study presented in *Mitchell* were limited to this subgroup of women, and the success of the PPP was analyzed in relation to counseling provided to the subgroup. (Ex. 1006 at 102.) "A person of ordinary skill in the art would have understood from these disclosures that the subgroup of female patients that are capable of becoming pregnant should be isolated for counseling." (Ex. 1002 ¶ 94.)

In addition, a person of ordinary skill in the art "would have included in the subpopulation any individual that could be affected by the teratogenic nature of the drug, because the purpose of the programs of *Powell* and *Mitchell* is to minimize birth defects." (Ex. 1002 ¶ 95.) By 1998, "it was apparent that the sperm of male patients could be damaged by teratogenic drugs and consequently result in birth defects, if the male was to impregnate a female." (Ex. 1002 ¶ 96 (citing Ex. 1018 at 7–8.) One of ordinary skill in the art would have understood that "a subgroup of male patients capable of impregnating females could be defined as men born after a certain year and could be obtained from the patient's birth date, a record invariably present in computerized records for dispensing drugs." (Ex. 1002 ¶ 97.) Therefore, "[b]ecause a person of ordinary skill in the art prescribing or dispensing thalidomide would seek to 'avoid[] the delivery of said drug to a foetus,' it would have been obvious to include males who could impregnate females within the subgroup." (Ex. 1002 ¶ 98 (citing Ex. 1001 Claim 1).) *See In re Preda*, 401 F.2d 825, 826 (CCPA 1968) ("it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom")*; In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (element considered disclosed in a prior art reference if it is "within the knowledge of a skilled artisan").

Second, *Powell* and *Mitchell* teach "providing to the subpopulation[] counseling information concerning the risks attendant to fetal exposure to said drug," as required by **Claim 1(e)**. *Powell* explicitly states that a prescriber of thalidomide "must inform

the patient of any contraindications, warnings and precautions associated with the use of the drug." (Ex. 1005 at 902.) Figure 1 of *Powell* consists of a sample Patient Information Sheet, and paragraph 3 reads: "3. *Damage to babies*: This is very important for all women considering thalidomide. Thalidomide is toxic to the developing baby, especially in the early months of pregnancy." (Ex. 1005, Fig. 1. (underlining added).) *Powell* further discloses detailed methods for counseling that involve "informed consent" and agreements to use contraception from patients. (Ex. 1005 at 901–02.) For example, *Powell* states that "[f]ully informed consent should be obtained using a written consent form and a signed agreement…Women of childbearing potential who discontinue treatment with thalidomide should agree to take reliable contraceptive precautions for 3 months after discontinuing thalidomide…" (Ex. 1005 at 901–02 (emphasis added).) "This disclosure parallels the '501 Patent's description of its invention that 'preferably involves requiring the patient to fill out an informed consent' (Ex. 1001 at 7:33–38) and to agree to 'use at least one form of birth control, with female patients agreeing to use at least two forms…'" (Ex. 1002 ¶ 103 (citing Ex. 1001 at 7:45–48).)

Similarly, in *Mitchell's* PPP, physicians were given instructions "to warn patients of risks" involved in treatment with the teratogenic drug and "communication between physicians and patients regarding the drug's teratogenic risk and the need to prevent pregnancy" was encouraged. (Ex. 1006 at 105101, 105.) Patients were given an "information brochure," "contraceptive information," and "a consent form."

(Ex. 1006 at 101.) They were further warned, through the packaging, "about the risks of becoming pregnant while taking isotretinoin" and were given "line drawings of malformations associated with isotretinoin." (*Id.*)(Ex. 1006 at 101.) "Thus, the method of counseling a subpopulation of patients to be treated with thalidomide regarding birth defects would have been obvious to a person of ordinary skill in the art from a reading of *Powell* and *Mitchell*." (Ex. 1002 ¶ 105.)

Third, a person of ordinary skill in the art would have recognized that *Powell* and *Mitchell* disclose "determining whether patients comprising said subpopulation are pregnant" prior to the dispensation of thalidomide, as required by **Claim 1(f)** of the '501 Patent. (Ex. 1002 ¶ 106.) *Powell* states that "[p]regnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy." (Ex. 1005 at 901.) *Mitchell* teaches that doctors should "obtain negative pregnancy tests" prior to treatment. (Ex. 1006 at 101.) "It would have been apparent to a person of ordinary skill in the art, upon reading either of these two references, that 'the prescriber should give the patient a pregnancy test…prior to and during treatment with the teratogenic drug' in order to make the claimed determination." (Ex. 1001 at 7:17–21; Claim 1(f); Ex. 1002 ¶ 109.)

Fourth, a person of ordinary skill in the art would have further understood from *Powell* that "written records should be kept relating to prescribers, patients, and pharmacies, similar to the requirements of elements **(a) through (c) in Claim 1** of the '501 Patent." (Ex. 1002 ¶ 111.) For example, *Powell* recommends that these

"[r]ecords should include the amount of thalidomide that has been made, the form of the finished product, the 'named patient', the prescribing doctor and the person to whom it has been supplied." (Ex. 1005 at 904.) *Powell* further discloses that:

> the order [for thalidomide] should be made in writing with the name of the patient, the prescribing doctor and the hospital address and telephone number. The letter should include a statement that the doctor is familiar with the use of thalidomide and its side effects, including peripheral neuropathy and teratogenicity. Also, a written assurance should be obtained that the drug will only be dispensed by the hospital pharmacist to the 'named patient' in accordance with the prescription.

(Ex. 1005 at 904 (emphasis added).)

While keeping these records in a "computer readable storage medium" is not explicitly mentioned in *Powell*, it would have been obvious to a person of ordinary skill in the art, as a matter of routine optimization, that electronic records of this information would be useful and easy to achieve through the entry into a computer. *See In re Venner,* 262 F.2d 91, 95 (CCPA 1958) (automation of known manual processes is obvious); *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955). For example, "[o]ne of the advantages of having computer records is ease in sharing and storing information, including for purposes such as communicating with managed care organizations." (Ex. 1002 ¶ 114.)

Armed with these disclosures from *Powell* and *Mitchell* described above, "a person of ordinary skill in the art would have been motivated to look to the system

disclosed in *Dishman* to further implement a computerized registry for avoiding birth defects from a teratogenic drug." (Ex. 1002 ¶ 115.) *Dishman* describes a registry for clozapine. "Clozapine is a potent anti-psychotic with the potential for serious side effects, and prior to 1998, it was well recognized that a successful system existed in the United States to maintain control over the dispensation of the drug…A person of ordinary skill in the art would have sought resources, such as *Dishman*, that described ways to restrict access to drugs that could be potentially hazardous," particularly such a method that had "proven successful" prior to 1998. (Ex. 1002 ¶ 116–117.)

Thus, "[i]t would have been obvious for a person of ordinary skill in the art to implement the methods used by the Clozaril® program for teratogenic drugs." (Ex. 1002 ¶ 118.) *See Innovention Toys, LLC v. MGA Entm't Inc.*, 637 F. 3d 1314, 1321 (Fed. Cir. 2011) ("[a] reference is reasonably pertinent if…it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 1740 (2007) ("patent's subject matter can be proved obvious . . . by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims").

First, the *Dishman* reference teaches "registering in a computer readable storage medium prescribers who are qualified to prescribe said drug," "registering in said medium pharmacies to fill prescriptions for said drug," and "registering said patients

in said medium…" as required by **(a) through (c) in Claim 1** of the '501 Patent. In particular, *Dishman* states that:

> The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry, which requires weekly monitoring of each patient's white blood cell (WBC) count and limits medication dispensing to a one-week supply. The registry permits community and hospital pharmacies to dispense clozapine only upon the pharmacist's verification that the WBC count is within acceptable limits.

(Ex. 1007 at 899 (emphasis added).) While the reference does not explicitly state that the pharmacists must be registered, "[o]ne of ordinary skill in the art would have understood that, in order to obtain and maintain the pharmacist's verification data relating to the pharmacy and its procedures would need to be collected and stored as part of the registry." (Ex. 1002 ¶ 121 (citing Ex. 1007 at 899 ("This complicated process requires the cooperation and coordinated efforts of the patient, physician, laboratory, and pharmacy.")).)

Second, the *Dishman* reference "discloses the storage of the registry data on a computer readable medium," as required throughout **Claim 1** of the '501 Patent. (Ex. 1002 ¶ 123.) For example, the "NCCC requires that each hospital have a computerized clozapine prescription lockout system…[that] ties the hospital's laboratory database to the outpatient pharmacy dispensing software." (Ex. 1007 at 900 (emphasis added).) "A person of ordinary skill in the art would have understood from the *Dishman* reference that this computerized system would include data from the

registered prescribers, patients, and pharmacies in order to determine which prescriptions should be 'locked out.'" (Ex. 1002 ¶ 124.) As *Dishman* shows, such a system includes "clinical and demographic information" for patients to be treated with clozapine. (Ex. 1007 at 900.)

Third, it "would have been obvious to a person of ordinary skill in the art, upon reading *Dishman,* that a method for delivering a teratogenic drug to a patient while avoiding the delivery of it to a fetus as described in Claim 1 should include, 'in response to a determination of non-pregnancy for said patients, authorizing said registered pharmacies to fill prescriptions from said registered prescribers…'" (Ex. 1002 ¶ 126 (citing Ex. 1001 **Claim 1(g)**).) In the methods described in *Dishman*, "[t]he program will allow clozapine prescriptions to be processed only when WBC counts are within the defined limits…[T]he lockout system prevents the filling of any clozapine prescription if the computer notices three consecutive drops in WBC count." (Ex. 1007 at 900 (emphasis added).) "This disclosure teaches that, in a program for treating patients with a teratogenic or otherwise hazardous drug, the availability of the drug should be conditioned upon certain medical criteria being met. In the case of a teratogenic drug, the relevant medical criterion is a determination that the patient is not pregnant." (Ex. 1002 ¶ 128.) An analogous restriction is described in the '501 Patent as part of an embodiment: "After the patient has received counseling . . . and has also filled out and signed an informed consent form, and it is determined

that the drug…is not contraindicated for the patient…the prescriber may prescribe the drug to the patient." (Ex. 1002 ¶ 129; Ex. 1001 at 8:53–59.)

This identification of an "at risk" subgroup and avoiding the prescription and dispensing of the drug to that group, as disclosed in *Dishman*, is precisely the kind of method that the inventors of the '501 Patent sought to patent. As previously described, during the prosecution of the patent, the applicants specifically distinguished their invention over the prior art by stating that the prior art did not show procedures for identifying an at-risk subpopulation and then prescribing a drug to patients while avoiding the at-risk subpopulation. (Ex. 1004 at 1004-0077–78.) However, as discussed, such procedures are plainly taught by *Dishman*. Thus, "[i]n view of the guidelines taught by *Powell*, it would have been obvious to a person of ordinary skill in the art to implement the methods disclosed in *Mitchell* and *Dishman* for safe dispensation of potentially hazardous drugs." (Ex. 1002 ¶ 131.)

2. Dependent Claims 2–10 are obvious.

The additional elements of the dependent claims of the '501 Patent do not add any points of novelty. Instead, a person of ordinary skill in the art would find the additional elements of those claims obvious in light of *Powell* and *Mitchell* and the knowledge of a person of ordinary skill in the art.

Powell expressly discloses guidelines for the "clinical use and dispensing of thalidomide," (Ex. 1005 at 901 (emphasis added); Ex. 1002 ¶ 133.) as required by **Claim 2**. *Mitchell* also teaches using the disclosed methods of the PPP in the context

of thalidomide; the reference postulates that "[t]he experience gained with isotretinoin can serve as a basis for considering how [thalidomide] should be used and monitored, with a view to ensuring that pregnancies and malformations are reduced to an absolute minimum." (Ex. 1006 at 105 (emphasis added); Ex. 1002 ¶ 134.)

Claim 3 of the '501 Patent refers to "registering information concerning male patients who are capable of impregnating females and including such males within said subpopulation." This claim does not introduce any new element to Claim 1, as the additional language "simply mimics a portion of the elements of Claim 1." (Ex. 1002 ¶ 136.) Thus, for the same reasons as described in Claim 1(d), this claim would have been obvious to a person of ordinary skill in the art. (Ex. 1002 ¶ 136.)

Powell and *Mitchell* disclose the use of "pregnancy testing" for the determination of pregnancy, as required by **Claim 4**. The *Powell* reference states that "[p]regnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy." (Ex. 1005 at 901.) *Mitchell* teaches physicians to "obtain negative pregnancy tests" prior to commencing treatment and that, in the Accutane® PPP, 60 percent of women surveyed "had had some type of pregnancy test." (Ex. 1006 at 102.) "It would have been obvious to a person with ordinary skill in the art, through these prior art disclosures as well as general knowledge in the field, that the determination of pregnancy required in Claim 1 could be achieved through pregnancy testing." (Ex. 1002 ¶ 140.)

For the additional requirement in **Claim 5** that "the issuance and fulfillment of said prescriptions are recorded in said computer readable storage medium," a person of ordinary skill in the art, upon reading *Dishman*, would have found the element to be obvious. For example, *Dishman* describes that "[t]he NCCC requires that each hospital have a computerized clozapine prescription lockout system…[which] ties the hospital's laboratory database to the outpatient pharmacy dispensing software." (Ex. 1007 at 900.) "Based on this disclosure, a person of ordinary skill in the art would have concluded that the issuance and fulfillment of prescriptions would be recorded in the computerized database in order for the clozapine prescription lockout system to operate." (Ex. 1002 ¶ 143.)

Similarly, the added element in **Claim 6** is explicitly taught by *Dishman.* Claim 6 of the '501 Patent requires that "refilling of said prescriptions is authorizable only in response to information contained on said computer readable storage medium." As discussed above, in the registry system disclosed in *Dishman*, "[t]he lockout system ties the hospital's laboratory database to the outpatient pharmacy dispensing software." (Ex. 1007 at 900.) The program will allow clozapine prescriptions to be processed only when WBC counts are within the defined limits…. [T]he lockout system prevents the filling of any clozapine prescription if the computer notices three consecutive drops in the WBC count." (Ex. 1007 at 900 (emphasis added).) "A person of ordinary skill in the art would have understood the disclosure of *Dishman* to refer to computer-recorded data relating to white blood cell counts, and that any prescription

refill for clozapine would be authorized only in response to an appropriate count… It would be obvious to apply this method to the clinical use of a teratogenic drug in relation to the avoidance of treating pregnant patients." (Ex. 1002 ¶ 147.) According to the prosecution history, such a system of "checks and balances" is precisely what the applicants for the '501 Patent sought to claim. (Ex. 1004 at 1004-0077.)

A person of ordinary skill in the art would have also found obvious the additional requirement of **Claim 7** that prescriptions be filled "for no more than about 28 days." (Ex. 1002 ¶ 152.) "Limiting the amount of dispensed drug in order to control its use was a concept well known to a person of ordinary skill in the art in August of 1998, as is exemplified by at least *Powell*." (Ex. 1002 ¶ 149.) For example, *Powell* discloses that, initially, "follow-up visits" with prescribing physicians "should be at monthly intervals or less." (Ex. 1005 at 902.) "A person of ordinary skill in the art would understand that the follow up visits would be required before additional drug was dispensed." (Ex. 1002 ¶ 150.) In addition, "*Powell* teaches further limiting the availability of the drug by recommending that 'orders to provide a stock for a hospital pharmacy should not be accepted. However, an amount to provide for 3 months prescription for a 'named patient' could be supplied to be held in the pharmacy.'" (Ex. 1002 ¶ 151 (citing Ex. 1005 at 904 (emphasis added).)

Moreover, "[o]ne of ordinary skill in the art would have arrived at a 28-day restriction based on general knowledge in the field. An average woman's menstrual cycle is approximately 28 days…In the context of treatment with a teratogenic drug

where the avoidance of pregnancy is of paramount importance, it would be obvious to a person of ordinary skill in the art to tie the amount of drug prescribed and dispensed to a time period commensurate with the menstrual cycle." (Ex. 1002 ¶ 153.) In fact, oral contraceptives are prescribed for 28-days, and therefore "the claimed time period aligns with other prescribing habits of physicians." (Ex. 1002 ¶ 154.)

The *Powell* and *Mitchell* references also teach the filling of prescriptions "together with distribution of literature warning of the effects of said drug upon foetuses," as required by **Claim 8**. In *Powell*, "[e]ach patient being treated with thalidomide should be given an information sheet (Figure 1)… which contains information relating to its proposed use and warnings about the potential, severe side effects of thalidomide." (Ex. 1005 at 902 and Fig. 1.) That information sheet contains a section explicitly discussing potential birth defects. (Ex. 1005 at Fig. 1.) In *Mitchell*, patients were provided with "an information brochure," written "warnings about the risks of becoming pregnant," and "line drawings of malformations associated with isotretinoin." (Ex. 1006 at 101.) These disclosures, along with pre-existing practices in the field, would have made it "obvious to distribute literature warning of birth defects with the filling of prescriptions for the drug." (Ex. 1002 ¶ 159.)

The requirement of **Claim 9** that patients be provided with "contraception counseling" is also divulged in *Powell* and *Mitchell*. "A person of ordinary skill in the art would have understood that a prescriber should discuss contraception with patients and '[p]atients should be specifically excluded' if they are 'unwilling to take reliable

contraceptive precautions.'" (Ex. 1002 ¶ 161 (citing Ex. 1005 at 901).) The *Powell* reference further teaches that "[w]omen of childbearing potential who discontinue treatment with thalidomide should agree to take reliable contraceptive precautions for three months after discontinuing thalidomide." (Ex. 1005 at 902.) The sample patient information sheet in *Powell* also contains indications of patient counseling on contraception: "[i]f you wish to consider thalidomide you must be prepared to use adequate contraception through the duration of thalidomide therapy and for 3 months after…Your doctor can advise you about adequate contraception." (Ex. 1005 at Fig. 1.) Similarly, in the PPP of *Mitchell*, patients are expressly provided with "contraceptive information" and information about "a contraception referral program." (Ex. 1006 at 101.) Therefore, "it would have been obvious to a person of ordinary skill in the art that such counseling would be beneficial in the clinical use of a teratogen." (Ex. 1002 ¶ 164.)

Finally, **Claim 10** of the '501 Patent adds the element that "patients who are capable of becoming pregnant" are provided with a contraceptive device. But this addition, too, "would have been obvious to a person of ordinary skill the art." (Ex. 1002 ¶ 166.) "[W]hile the *Powell* reference does not explicitly state that patients should be provided with a contraceptive device, its discussion on counseling and encouraging of contraception is extensive. For instance, as described above, *Powell* mandates exclusion from treatment who refuse to or cannot use a form of contraception." (Ex. 1002 ¶ 166–67 (citing Ex. 1005 at 901).) The sample information sheet for patients

provided in the reference warns patients that "[i]f you wish to consider thalidomide you must be prepared to use adequate contraception through the duration of thalidomide therapy and for 3 months after…Your doctor can advise you about adequate contraception." (Ex. 1005 at Fig. 1.)

Mitchell discloses the step of providing contraception. In particular, in the program described in *Mitchell*, patients are provided with "the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling)." (Ex. 1006 at 101.) "A person of ordinary skill in the art would have understood from this disclosure that the other physician would, after ensuring that it is medically appropriate, provide contraception—either in device or drug form…Therefore, in light of these teachings, a person of ordinary skill in the art would have recognized the value of providing contraception to patients directly." (Ex. 1002 ¶ 170.)

3. Claim Chart for Ground 1 Showing Exemplary Citations in *Powell, Mitchell, and Dishman*

Element	Prior Art
1pre. A method for delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus comprising:	*Powell* teaches methods for delivering a teratogenic drug to patients in need of the drug while avoiding delivery of drug to a foetus: Ex. 1005 at 901 ("This guideline is designed to promote the safest possible clinical use and dispensing of thalidomide."); *Id.* ("Pregnancy should be excluded before instituting therapy with thalidomide…").

a. registering in a computer readable storage medium prescribers who are qualified to prescribe said drug;	*Powell* teaches records of the prescribers that prescribe the teratogenic drug: Ex. 1005 at 904 ("Records should include the amount of thalidomide that has been made, the form of the finished product, the 'named patient,' the prescribing doctor and the person to whom it has been supplied."); *Id.* ("the supplier should require that the order [for thalidomide] should be made in writing with the name of the patient, the prescribing doctor and the hospital address and telephone number. The letter should include a statement that the doctor is familiar with the use of thalidomide and its side effects, including peripheral neuropathy and teratogenicity. Also, a written assurance should be obtained that the drug will only be dispensed by the hospital pharmacist to the 'named patient' in accordance with the prescription."). *Dishman* teaches a computerized program for registering qualified prescribers: Ex. 1007 at 899 ("The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry."); *Id.* at Abstract ("A program in which pharmacists have an active role in prescribing and dispensing psychoactive drugs."); *Id.* at 899 ("Some pharmacists in our institution have specialized training in psychiatry and have acquired clinical privileges that allow them to prescribe psychotropic medications and order laboratory tests."); *Id.* at 900 ("The VA Central Office established a National Clozapine Coordinating Center (NCCC). Physicians at the NCCC review each clozapine candidate's file before granting approval for use and review weekly tracking sheets that report patient status. Each VA medical center is required to establish a clozapine treatment team, headed by the chief of the psychiatry service and including representatives from the psychiatry, pharmacy, laboratory, medicine, and nursing services. The clozapine treatment team reviews new applications for clozapine use and provides clinical and demographic information for all new patients to the NCCC."); *Id.* at 900 ("The NCCC requires that each hospital have a computerized clozapine prescription lockout system … [that] ties the hospital's laboratory database to the outpatient pharmacy dispensing software."). Ex. 1002 ¶¶ 111-113, 119-120, 123-125.

b. registering in said medium pharmacies to fill prescriptions for said drug;	*Dishman* teaches computerized program for registering pharmacies: Ex. 1007 at 899 ("The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry, which requires weekly monitoring of each patient's white blood cell (WBC) count and limits medication dispensing to a one-week supply. The registry permits community and hospital pharmacies to dispense clozapine only upon the pharmacist's verification that the WBC count is within acceptable limits."); *Id.* at Abstract ("A program in which pharmacists have an active role in prescribing and dispensing psychoactive drugs."); *Id.* at 899 ("This complicated process requires the cooperation and coordinated efforts of the patient, physician, laboratory, and pharmacy."); *Id.* at 900, ("Each VA medical center is required to establish a clozapine treatment team, headed by the chief of the psychiatry service and including representatives from the psychiatry, pharmacy, laboratory, medicine, and nursing services."); *Id.* ("The NCCC requires that each hospital have a computerized clozapine prescription lockout system. The lockout system ties the hospital's laboratory database to the outpatient pharmacy dispensing software."). Ex. 1002 ¶¶ 120-122.
c. registering said patients in said medium, including information concerning the ability of female patients to become pregnant and the ability of male patients to impregnate females;	*Dishman* discloses computerized programs for registering patients: Ex. 1007 at 899 ("The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry…"); *Id.* at 900 ("The VA Central Office established a National Clozapine Coordinating Center (NCCC). Physicians at the NCCC review each clozapine candidate's file before granting approval for use and review weekly tracking sheets that report patient status."); *Powell* teachs information concerning the ability of female patients to become pregnant: Ex. 1005 at 901 ("Pregnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy."); *Powell* teaches written records of the patients:

	Ex. 1005 at 904 ("Records should include the amount of thalidomide that has been made, the form of the finished product, the 'named patient,' the prescribing doctor and the person to whom it has been supplied."); *Id.* at ¶ 5 ("the supplier should require that the order [for thalidomide] should be made in writing with the name of the patient, the prescribing doctor and the hospital address and telephone number. The letter should include a statement that the doctor is familiar with the use of thalidomide and its side effects, including peripheral neuropathy and teratogenicity. Also, a written assurance should be obtained that the drug will only be dispensed by the hospital pharmacist to the 'named patient' in accordance with the prescription."). Ex. 1002 ¶¶ 111-112, 119-120.
d. retrieving from said medium information identifying a subpopulation of said female patients who are capable of becoming pregnant and male patients who are capable of impregnating females;	*Dishman* discloses computerized programs for registering patients: *See* Claim Chart Element 1c *Dishman* excerpts. *Powell* teaches identifying a subpopulation of said female patients who are capable of becoming pregnant: Ex. 1005 at 901, ¶ 3 ("Patients should be specifically excluded from treatment with thalidomide for any of the following reasons: a. Unwilling to sign a consent form. b. Unable to understand the potential risk from the use of thalidomide. c. Unlikely to be able to comply with the prescribing instructions. d. Women who wish to become pregnant. e. Women of childbearing potential: i. who have not practised a reliable form of contraception for 1 year; ii. who are unwilling to take reliable contraceptive precautions; iii. who are considered not capable of complying with the requirements for reliable contraception. Reliable contraceptive methods include the contraceptive pill, an intrauterine device, surgical sterilization of patient or sole partner. Female patients who do not normally practise contraception because of a history of infertility should do so whilst taking thalidomide.").

	Mitchell teaches identifying a subpopulation of said female patients who are capable of becoming pregnant: Ex. 1006 at 901 ("a 10-capsule blister pack that contained information directed specifically at women . . . includ[ing] warning about the risks of becoming pregnant while taking isotretinoin or during the month after treatment…"); *Id.* at 102 ("The subjects were women of childbearing age (12 to 59 years of age) who were being treated with isotretinoin.") Ex. 1002 ¶¶ 91-98.
e. providing to the subpopulation, counseling information concerning the risks attendant to fetal exposure to said drug;	*Powell* teaches providing to the subpopulation[] counseling information concerning the risks attendant to fetal exposure to said drug: Ex. 1005 at 901-902 ("Fully informed consent should be obtained using a written consent form and a signed agreement. … Women of childbearing potential who discontinue treatment with thalidomide should agree to take reliable contraceptive precautions for 3 months after discontinuing thalidomide."); *Id.* at 902 ("Each patient being treated with thalidomide should be given an information sheet (Figure 1). … A sample patient information sheet is provided, which contains information relating to its proposed use and warnings about the potential, severe side effects of thalidomide. It should be updated as required."); *Id.* at 903 [Fig. 1] ("Damage to babies: This is very important for all women considering thalidomide. Thalidomide is toxic to the developing baby…If you wish to consider thalidomide, you must be prepared to use adequate contraception throughout the duration of thalidomide therapy and for 3 months after it has finished…Your doctor can advise you about adequate contraception.") *Mitchell* teaches providing to the subpopulation[] counseling information concerning the risks attendant to fetal exposure to said drug: Ex. 1006 at 101 ("The materials included guidelines for physicians (instructing them, for example, to warn patients of risks . . ."); *Id.* at 105 ("the program encourages communication between

	physicians and patients regarding the drug's teratogenic risk and the need to prevent pregnancy . . ."); *Id.* at 101 ("They also included a patient-qualification checklist, an information brochure for patients, contraceptive information, information about and the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling), and a consent form."). Ex. 1002 ¶¶ 100-102, 104.
f. determining whether patients comprising said subpopulation are pregnant; and	*Powell* teaches determining whether patients comprising said subpopulation are pregnant: Ex. 1005 at 901 ("Pregnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy."); *Id.* at 901-2 ("A pregnancy test should be provided."). *Mitchell* teaches determining whether patients comprising said subpopulation are pregnant: Ex. 1006 at 101 ("The materials included guidelines for physicians []instructing them, for example, to . . . obtain negative pregnancy tests . . ."). Ex. 1002 ¶¶ 107-108.
g. in response to a determination of non-pregnancy for said patients, authorizing said registered pharmacies to fill prescriptions from said registered prescribers for said non-pregnant registered patients.	*Dishman* teaches both registered pharmacies and prescribers require authorization in order to dispense the drug: Ex. 1007 at 899 ("The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry."); *Id.* at 900 ("The program will allow clozapine prescriptions to be processed only when WBC counts are within the defined limits … the lockout system prevents the filling of any clozapine prescription if the computer notices three consecutive drops in the WBC count."). *Powell* teaches that thalidomide should only be dispensed to a patient who is not pregnant: Ex. 1005 at 901 ("Pregnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy."). Ex. 1002 ¶¶ 127-128.

2. The method of claim 1 wherein said drug is thalidomide.	*Powell* discloses the guidelines for treatment of patients with thalidomide: Ex. 1006 at Title ("Guideline for the clinical use and dispensing of Thalidomide.").
3. The method of claim 1 further comprising including in said registering information concerning male patients who are capable of impregnating females and including said males within said subpopulation.	*See* Claim Chart for Claim elements 1(c) to 1(e). Ex. 1002 ¶ 136.
4. The method of claim 1 wherein said determination comprises pregnancy testing.	*Powell* discloses pregnancy testing for thalidomide treatment: Ex. 1005 at 901 ("Pregnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy."); *Id.* at 901 ("A pregnancy test should be provided and, if positive, appropriate counselling should be given."). *Mitchell* teaches pregnancy testing: Ex. 1006 at 101 ("The materials included guidelines for physicians []instructing them, for example, to . . . obtain negative pregnancy tests . . .")
5. The method of claim 1 wherein the issuance and fulfillment of said prescriptions are recorded in said computer	*Dishman* teaches computerized systems for recording issuance and fulfillment of prescriptions: Ex. 1007 at 900 ("The NCCC requires that each hospital have a computerized clozapine prescription lockout system. The lockout system ties the hospital's laboratory database to the outpatient pharmacy dispensing software. The program will allow clozapine prescriptions to be processed only when WBC counts are within the defined limits. At our institution, the lockout system prevents the filling of any clozapine prescription if the computer notices

readable storage medium.	three consecutive drops in the WBC count."); *Id.* at 899 ("The manufacturer, Sandoz, requires all prescribers and patients to be registered with the Clozaril National Registry."); *Id.* at 900 ("The VA Central Office established a National Clozapine Coordinating Center (NCCC). Physicians at the NCCC review each clozapine candidate's file before granting approval for use and review weekly tracking sheets that report patient status.") Ex. 1002 ¶¶ 142-143.
6. The method of claim 1 wherein refilling of said prescriptions is authorizable only in response to information contained on said computer readable storage medium.	*Dishman* teaches computerized systems for refilling the prescriptions: Ex. 1007 at 900 ("The NCCC requires that each hospital have a computerized clozapine prescription lockout system. The lockout system ties the hospital's laboratory database to the outpatient pharmacy dispensing software. The program will allow clozapine prescriptions to be processed only when WBC counts are within the defined limits. At our institution, the lockout system prevents the filling of any clozapine prescription if the computer notices three consecutive drops in the WBC count."). Ex. 1002 ¶¶ 145-147.
7. The method of claim 1 wherein said prescriptions are filled for no more than about 28 days.	*Powell* discloses prescriptions are filled for no more than about 28 days: Ex. 1005 at 902 ("Follow-up visits should be at monthly intervals or less for the first 3 months to enable the clinician to detect side effects/early signs of toxicity."); *Id.* at 904 ("Orders to provide a stock for a hospital pharmacy should not be accepted. However, an amount to provide for 3 months prescription for a 'named patient' could be supplied to be held in the pharmacy."). Ex. 1002 ¶¶ 149-154.
8. The method of claim 1 wherein said prescriptions are filled together with distribution of literature warning of the	*Powell* teaches filling prescriptions together with distribution of literature warning of the effects of said drug upon foetuses: Ex.1005 at 902 ("Each patient being treated with thalidomide should be given an information sheet (Figure 1).… which contains information relating to its proposed use and warnings about the potential, severe side effects of thalidomide. It should be updated

effects of said drug upon foetuses.	as required."); *Id.* at 903, Figure 1 (reproduced at Claim element 1(e)). *Mitchell* teaches filling prescriptions together with distribution of literature warning of the effects of said drug upon foetuses: Ex. 1006 at 101 ("They also included . . . an information brochure for patients . . . the manufacturer replaced traditional medication bottles with a 10-capsule blister pack that contained information directed specifically at women: the package included warnings about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon behind each capsule, and line drawings of malformations associated with isotretinoin.") Ex. 1002 ¶¶ 156-158.
9. The method of claim 1 further comprising providing said patients with contraception counseling.	*Powell* teaches contraception counseling: Ex.1005 at 901 ("Patients should be specifically excluded from treatment with thalidomide … [if w]omen of childbearing potential … who are unwilling to take reliable contraceptive precautions."); *Id.* at 902 ("Women of childbearing potential who discontinue treatment with thalidomide should agree to take reliable contraceptive precautions for 3 months after discontinuing thalidomide."); *Id.* at 902 ("Each patient being treated with thalidomide should be given an information sheet … which contains information relating to its proposed use and warnings about the potential, severe side effects of thalidomide. It should be updated as required."); *Id.* at 903, Figure 1 (reproduced at Claim element 1(e)). *Mitchell* teaches contraception counseling: Ex. 1006 at 101 ("They also included . . . contraceptive information, information about and the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling) . . .") Ex. 1002 ¶¶ 161-163.
10. The method of claim 1 further comprising: h.	*Powell* teaches providing contraception: Ex. 1005 at Figure 1 ("[i]f you wish to consider thalidomide you must be prepared to use adequate contraception through the

providing to said patients who are capable of becoming pregnant a contraceptive device or formulation.	duration of thalidomide therapy and for 3 moths after…Your doctor can advise you about adequate contraception.") *Mitchell* teaches providing contraception: Ex. 1006 at 101 (""the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling)…" Ex. 1002 ¶¶ 166-169.

B. Ground 2: Claims 1–10 of U.S. Patent No. 6,045,501 to Elsayed *et al.* are obvious under 35 U.S.C. § 103(a) over *NIH* in view of *Honigfeld*.

1. Independent Claim 1 is obvious over *NIH* and *Honigfeld.*

As described above, one of ordinary skill in the art in August of 1998, "aware of the potential harm of treating patients with a drug known to cause birth defects," would have been "interested in methods for drug delivery that would avoid exposure to embryos and fetuses." (Ex. 1002 ¶ 172.) Such an individual would have "looked to guidance from prominent national organizations such as the NIH, FDA, and CDC, and specifically to any publications from these groups that discussed treatment with thalidomide." (Ex. 1002 ¶ 173.)

The *NIH* reference describes methods developed and recommended by various health care professionals and regulators, including the "Thalidomide Working Group," an FDA initiative. (Ex. 1002 ¶ 174.) "The methods disclosed in *NIH* include the isolation of a subgroup of male and female patients that could become pregnant or impregnate, counseling the group regarding the teratogenic risks of the drug, and establishing non-pregnancy of each patient prior to treatment, just as required by

Claim 1(d) through (f)." (*Id.* at 175.) "A person of ordinary skill in the art would have combined these teachings with the well-known Pregnancy Prevention Program for the teratogen Accutane® (Ex. 1015 at 31, 55, 61), and the clozapine registry methods disclosed in *Honigfeld* (Ex. 1009), because those programs were recognized methods to avoid the delivery of drugs to contraindicated individuals." (Ex. 1002 ¶ 176.) Moreover, such a person "would have sought to implement the methods described in *NIH* and *Honigfeld* in order to improve upon the non-mandatory registration and unrestricted pharmacy methods of the Accutane® program." (Ex. 1002 ¶ 177.)

First, the *NIH* reference teaches the identification of a "subpopulation" of patients "who are capable of becoming pregnant" or "capable of impregnating females," as required by **Claim 1(d)**. The disclosures in the *NIH* reference teach using "a database of individual patients taking thalidomide," and a "person of ordinary skill in the art reviewing this reference would have understood that such a database would include such demographic information about patients as sex and age." (Ex. 1002 ¶ 179, citing Ex. 1015 at 35).) Further, a "person of ordinary skill in the art would have understood that information about ability to become pregnant or impregnate would also be included because the reference teaches further steps involving '<u>women of childbearing potential</u>' and 'fertile women'" (Ex. 1002 ¶ 180 (quoting Ex. 1015 at 1, 21, 53) (emphasis added).) "Males are also considered part of the subgroup because the disclosure in *NIH* states that '[m]ale thalidomide users should use condoms' and that 'a male who has not had a vasectomy…must abstain from reproductive sexual

intercourse, or use two highly effective birth control methods…'" (Ex. 1002 ¶ 181 (quoting Ex. 1015 at 47 and 0113–19).) "Therefore, the *NIH* reference teaches retrieving information about patients to identify the subpopulation described in claim 1." (Ex. 1002 ¶ 182.)

Second, the *NIH* reference discloses counseling the subpopulation "concerning the risks attendant to fetal exposure to said drug," as required by **Claim 1(e)**. Specifically, the methods in *NIH* include "[e]nsur[ing] that all patients are counseled about the teratogenicity of thalidomide" and giving patients "a consent form and a patient education brochure" that discusses the "known teratogenic effects of thalidomide." (Ex. 1015 at 35, 53 (emphasis added).) In addition, the consent form provided as a template within the reference includes an almost full page section entitled "Birth Defects" which explicitly describes the types of birth defects that have been observed "in babies exposed to thalidomide during pregnancy." (Ex. 1015 at 011–19.) The patient information brochure provided contains warnings for both male and female patients, as well as a diagram of a malformed baby, relating to the birth defects that could result from use of thalidomide. (Ex. 1015 at 0120–21.) Therefore, "the counseling step of claim 1 would have been obvious to a person of ordinary skill in the art prior to the priority date of the '501 Patent." (Ex. 1002 ¶ 187.)

Third, a determination of non-pregnancy prior to starting treatment, as required by **Claim 1(f)**, is a part of the methods presented in *NIH*. In particular, *NIH* teaches "monthly pregnancy tests before, during, and after the course of thalidomide

treatment." (Ex. 1015 at 1.) The abstracts disclose a requirement that "[a] pregnancy test must be performed and found negative before treatment [with thalidomide] is initiated." (Ex. 1015 at 21; see also at 47, 51, 61.) "A person of ordinary skill in the art would therefore have understood that pregnancy should be excluded by such testing prior to beginning the course of treatment." (Ex. 1002 ¶ 191.)

"In further seeking a way to implement [these three sets of] teachings of the *NIH* reference, a person of ordinary skill in the art would have been motivated to look to methods of applying them with respect to other potentially harmful drugs, such as clozapine…One of ordinary skill in the art would have sought methods that involved computerized databases, because prior to 1998, the use of computers allowed improved ways to organize, sort, and share information in a medical and pharmacy setting." (Ex. 1002 ¶ 193.) *See In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1380 (Fed. Cir. 2007) ("One skilled in the art would naturally look to prior art addressing the same problem as the invention at hand…"). Such methods are described by *Honigfeld*, which discloses "procedures for distribution of clozapine…[in which] the medication is available in the U.S. only through treatment systems registered with the national registry…" (Ex. 1002 ¶ 194 (quoting Ex. 1009 at 52).)

First, *Honigfeld* discloses "registering in a computer readable storage medium prescribers who are qualified to prescribe said drug," as required by **Claim 1(a).** For instance, in the program described in *Honigfeld*, "[a]ll data coming to the clozapine national registry are entered into an integrated, computerized database…" (Ex. 1009

at 53 (emphasis added).) "A computerized database constituted 'a computer readable storage medium' in the understanding of a person of ordinary skill in the art at the time of filing of the '501 Patent." (Ex. 1002 ¶ 197.) The data entered into this database includes "the physician's identification" for each patient. (Ex. 1009 at 53.) "The physician must be authorized to treat with clozapine; initial contact with the registry is made by 'physicians who are seeking clearance to start a specific patient on clozapine.'" (Ex. 1002 ¶ 199 (quoting Ex. 1009 at 53).)

Second, the step of "registering in said medium pharmacies to fill prescriptions for said drug," (**Claim 1(b)**) is disclosed by *Honigfeld*. The computerized database described in the reference further includes "the pharmacy's identification" for each patient. (Ex. 1009 at 53.) Further, *Honigfeld* teaches that "[d]istribution of the medication is limited to registered pharmacies…" (Ex. 1009 at 53.) A person of ordinary skill in the art would have found obvious, from a review of *Honigfeld,* that pharmacies should be registered in the computerized database. (Ex. 1002 ¶ 203.)

Third, *Honigfeld* includes recording information related to patients into the database (**Claim 1(c)**)**.** For example, the registry includes each "patient's identifying code number and initials . . . [the] daily dosage of clozapine in milligrams, and white blood cell test dates and results." (Ex. 1009 at 205.) "In *Honigfeld*, the patient records did not specifically reference Claim 1(c) "information concerning the ability of female patients to become pregnant . . . [or] the ability of male patients to impregnate females," because those parameters did not affect the authorization to dispense the

drug. Instead, in the clozapine program, it was the white blood cell test results that determined whether a patient could take the drug." (Ex. 1002 ¶ 206.) "A person of ordinary skill in the art would have understood that, in the case of a teratogenic drug, information concerning a patient's ability to become pregnant or impregnate would be the relevant information recorded in the system." (Ex. 1002 ¶ 207.)

Fourth, *Honigfeld* teaches that, in response to the appropriate test results, registered pharmacies are authorized to fill prescriptions for clozapine—just as in **Claim 1(g)** of the '501 Patent. The program described in *Honigfeld* consists of "a national patient registry system that provides the medication only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression…" (Ex. 1009 at 52 (emphasis added).) The reference further states that "[d]istribution of the medication is limited to registered pharmacies, which agree to follow the 'no blood-no drug' guidelines." (Ex. 1009 at 53 (emphasis added).) *NIH* discusses ongoing pregnancy testing "every 30 days" after starting treatment, to ensure thalidomide treatment is warranted each time, and "condition[ing] the dispensing of the drug on a negative pregnancy test." (Ex. 1002 ¶ 211 (citing Ex. 1015 at 47).)

"The specification of the '501 Patent includes discussion of this very procedure; a patient can be prescribed the drug in question only after 'it is determined that the drug which is to be prescribed is not contraindicated for the patient.'" (Ex. 1002 ¶ 212 (quoting Ex. 1001 at 8:53–59).) Additionally, the inventors of the '501 Patent sought to patent the same idea—that an "at risk" subgroup be identified and

then denied treatment unless certain patient-related criteria are met. (Ex. 1004, *File History* at 1004-0077–78.) "Thus, it would have been apparent to an ordinarily skilled artisan to dispense thalidomide only upon confirmation that the patient is not pregnant." (Ex. 1002 ¶ 213.) As a result, based on *NIH* (recommending measures to avoid use of a teratogenic by pregnant patients and citing Accutane® PPP) in view of *Honigfeld* (a registry system which authorizes prescriptions based on the results of patient testing), "a person of ordinary skill in the art would have found Claim 1 of the '501 Patent to be obvious." (Ex. 1002 ¶ 214.)

2. Dependent Claims 2–10 are obvious.

The dependent claims of the '501 Patent fail to add limitations that render the invention of the '501 Patent non-obvious. The additional elements of Claims 2–10 are disclosed in *NIH* or *Honigfeld*. *NIH* discusses the use of thalidomide as the teratogenic drug in the method of Claim 1, as required by **Claim 2**. "The main topic of discussion throughout the reference is use of thalidomide in relation to its teratogenicity." (Ex. 1002 ¶ 215.) **Claim 3**, which requires "registering information concerning male patients who are capable of impregnating females and including such males within said subpopulation," would also have been obvious in view of *NIH* and *Honigfeld* and in further view of the knowledge that one skilled in the art would have had in August of 1998. "The additional language of Claim 3 is merely a duplication of language already present in Claim 1, on which it depends, and is obvious for the same reasons as the corresponding limitation in Claim 1." (Ex. 1002 ¶ 217.)

The additional step of **Claim 4**, which requires the determination of non-pregnancy of Claim 1 to be pregnancy testing, is present in multiple sections of the *NIH* reference. *NIH* teaches that a "pregnancy test must be performed and found negative before treatment [with thalidomide] is initiated." (Ex. 1015 at 21; *see also* at 1, 4, 9, 13, 14, 61.) In addition, the consent form template included in *NIH* specifies that female patients "will be required to have blood drawn for a pregnancy test before you start taking thalidomide." (*Id.* at 0113–19.) Such blood testing is among the embodiments of the '501 Patent: "female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug." (Ex. 1001 at 7:48–52.) "In view of these references and the knowledge and pre-existing practice of one of ordinary skill in the art, it would have been obvious to test for pregnancy prior to making the drug available to a patient." (Ex. 1002 ¶ 221.)

The element of **Claim 5,** "the issuance and fulfillment of said prescriptions are recorded in said computer readable storage medium," is taught by *Honigfeld*: "the medication is dispensed weekly only to patients for whom data on current white blood cell counts are available." (Ex. 1009 at 53.) Further, "[a]ll data coming to the clozapine national registry are entered into an integrated, computerized database…" (Ex. 1009 at 53.) "A person of ordinary skill in the art, when reading these disclosures, would have understood that prescriptions would be logged in order for the registry to assess when the last prescription was filled or refilled (i.e., whether a week had

passed)." (Ex. 1002 ¶ 224.) *Honigfeld* explicitly teaches the element of having prescription refills "authorizable only in response to information contained on said computer readable storage medium," as required by **Claim 6**. The "registry system" of *Honigfeld* "provides the medication only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression…" and "[d]istribution of the medication is limited to registered pharmacies, which agree to follow the 'no blood-no drug' guidelines." (Ex. 1009 at 52–53.) "One of ordinary skill in the art would understand that the method of *Honigfeld*, when applied to a teratogenic drug, requires that refills of the drug would only be available upon obtaining appropriate test results from the computerized registry." (Ex. 1002 ¶ 227.) This system of "checks and balances" is precisely the method the inventors claimed. (Ex. 1004 at 1004-0077.)

Claim 7's requirement that the prescription be filled "for no more than about 28 days" does not add novelty to the invention. For example, *Honigfeld* discloses limiting dispensation of the medication to approximately 7 days: "[t]he medication is dispensed weekly…" (Ex. 1009 at 53.) "A person of ordinary skill in the art would have understand that limiting the supply of the drug to a relatively short time period—in any case under 28 days—is desirable as a matter of general knowledge in the field, particularly in light of the average 28-day menstrual cycle that directly relates to pregnancy." (Ex. 1002 ¶ 230.) *NIH* teaches "distribution of literature warning of the effects of said drug upon foetuses," as required by **Claim 8**. *NIH* discloses the distribution of a "consent form and patient brochure" that contain information

relating to the teratogenic effects of thalidomide as well as "contraception and pregnancy testing." (Ex. 1015 at 35.) A template and sample of these documents describing the types of potential birth defects that could occur are provided. (Ex. 1015 at 0113–21.) Therefore, "[i]t would have been obvious to a person of ordinary skill in the art that written documentation of the risk of birth defects should be provided to the patient when a prescription for a teratogenic drug is filled." (Ex. 1002 ¶ 234.)

For **Claim 9**, "contraception counseling" is among the methods *NIH* discloses. *NIH* recommends mandating contraception for both males and females. For example, one abstract teaches that "[c]ontraceptive measures must be used during treatment." (Ex. 1015 at 21.) Another specifies doctors must ensure patients "are counseled about effective contraceptive methods." (Ex. 1015 at 53.) "The template for the consent form and the informational brochure in *NIH* both contain information and advice relating to contraception." (Ex. 1002 at 238.) "These disclosures, along with the general knowledge and practice of one of ordinary skill in the art, would have made the step of contraception counseling obvious prior to 1998." (Ex. 1002 ¶ 239.)

Finally, **Claim 10** requires "providing to said patients who are capable of becoming pregnant a contraceptive device of formulation." *NIH* discloses "a free contraception referral program" for patients to be treated with thalidomide." (Ex. 1015 at 51.) "A person of ordinary skill in the art would understand from this disclosure that providing contraception with the drug when dispensed would be desirable as an effective way to avoid pregnancy." (Ex. 1002, ¶¶ 242, 243.)

3. Claim Chart for Ground 2 showing exemplary citations in *NIH* and *Honigfeld*.

Element	Prior Art
1pre. A method for delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus comprising:	*NIH* teaches methods for delivering a teratogenic drug to patients in need of the drug while avoiding delivery of the drug to a foetus: Ex. 1015 at 53 ("Ensure that female patients of childbearing potential are adequately monitored during thalidomide use to reduce the risk of fetal exposure.")
a. registering in a computer readable storage medium prescribers who are qualified to prescribe said drug;	*Honigfeld* discloses a computerized national registry that requires registration of prescribers of a hazardous drug: Ex. 1009 at 53 ("All data coming into the Clozapine national registry are entered into an integrated, computerized database maintained by the manufacturer. . . . The records include . . . the physician's identification . . . daily dosage of clozapine in milligrams, and white blood cell test dates and results.") Ex. 1002 ¶¶ 196-199.
b. registering in said medium pharmacies to fill prescriptions for said drug;	*Honigfeld* discloses a computerized registry that requires registration of pharmacies to fill prescriptions for a hazardous drug: Ex. 1009 at 53 ("All data coming to the clozapine national registry are entered into an integrated, computerized database maintained by the manufacturer. . . . The records include . . . the pharmacy's identification, daily dosage of clozapine in milligrams, and white blood cell test dates and results."); *Id.* ("Distribution of the medication is limited to registered pharmacies, which agree to follow the 'no blood-no drug' guidelines."). Ex. 1002 ¶¶ 201-203.
c. registering said patients in said medium, including information concerning the ability of female	*Honigfeld* teaches computerized patient registration: Ex. 1009 at 53 ("Patients' computer records are established during the initial phone calls made by physicians who are seeking clearance to start a specific patient on clozapine. The records include the patient's identifying code number and initials, the physician's identification, the pharmacy's

patients to become pregnant and the ability of male patients to impregnate females;	identification, daily dosage of clozapine in milligrams, and white blood cell test dates and results."). *NIH* teaches information concerning the ability of female patients to become pregnant and ability of male patients to impregnate: Ex. 1015 at 53 ("Ensure that female patients of childbearing potential are adequately monitored during thalidomide use to reduce the risk of fetal exposure."); *Id.* at 0113-19 ("If you are a male who has not had a vasectomy, you must abstain from reproductive sexual intercourse, or use a condom during intercourse while receiving thalidomide, and continuing thereafter until one month after the last dose.") Ex. 1002 ¶¶ 205-207.
d. retrieving from said medium information identifying a subpopulation of said female patients who are capable of becoming pregnant and male patients who are capable of impregnating females;	*NIH* teaches the identification of a subpopulation of female patients who are capable of becoming pregnant: Ex. 1015 at 12 ("The FDA has also developed a database of individual patients to track regulatory documentation and assess safety-related trends…"); *Id.* at 21 ("The labeling states that thalidomide should not be used in pregnant or fertile women because of the risk of fetal malformations."); *Id.* at 53 ("Ensure that female patients of childbearing potential are adequately monitored during thalidomide use to reduce the risk of fetal exposure.") *NIH* teaches the identification of a subpopulation of male patients who are capable of impregnating females: *Id.* at 46 ("Male thalidomide users should use condoms."); *Id.* at 0113-19 ("If you are a male who has not had a vasectomy, you must abstain from reproductive sexual intercourse, or use a condom during intercourse while receiving thalidomide, and continuing thereafter until one month after the last dose.") Ex. 1002 ¶¶ 179-182.
e. providing to the subpopulation, counseling information concerning the	*NIH* teaches providing to the subpopulation, counseling information concerning the risks attendant to fetal exposure to said drug:

risks attendant to fetal exposure to said drug;	Ex. 1015 at 53 ("Ensure that all patients are counseled about the teratogenicity of thalidomide and female patients of childbearing potential are counseled about effective contraceptive methods."); *Id.* at 35 ("The Group has developed a consent form and a patient education brochure to inform both patients and their health care providers about using thalidomide safely…Both documents contain information about contraception and pregnancy testing based on the window of susceptibility, days 21 to 36 post-conception, when unborn children may be most susceptible to the known teratogenic effects of thalidomide."); *Id.* at 011–19 [Consent Form] ("BIRTH DEFECTS: Thalidomide causes severe birth defects in unborn babies if it is taken by females who are pregnant…Birth defects observed in babies exposed to thalidomide during pregnancy include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system, including blockage of necessary openings…Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking thalidomide…You should discuss with your doctor (Sponsor-Investigator) what the best methods of birth control are for you."); *Id.* at 0120–21 [Patient Information Brochure] ("Thalidomide may be the most infamous drug in recent history…its use by pregnant women resulted in the birth of thousands of deformed babies…WARNING FOR FEMALE PATIENTS:…You must abstain from sexual intercourse or use two highly effective birth control methods at the same time [consult your doctor] for at least one month prior to receiving thalidomide, and continuing regularly thereafter, until one month after the last dose of thalidomide…" WARNING FOR MALE PATIENTS:…You must be willing to abstain from sexual intercourse or use a condom during intercourse while you are taking thalidomide and for at least one month after the last does of thalidomide…") Ex. 1002 ¶¶ 184-187.
f. determining whether patients comprising said	*NIH* discloses determining whether patients in the subpopulation are pregnant: Ex. 1015 at 1 ("Women of childbearing potential involved in clinical research investigations are required to have monthly

subpopulation are pregnant; and	pregnancy tests before, during, and after the course of thalidomide treatment..."); *Id.* at 21 ("A pregnancy test must be performed and found negative before treatment is initiated."); *Id.* at 47 ("…the FDA recently proposed to require a negative pregnancy test at baseline, 9-10 days after starting therapy, and every 30 days thereafter."); *Id.* at 51 ("Guidelines instructed physicians to warn patients of the risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next menstrual period."); Ex. 1002 ¶¶ 189-194.
g. in response to a determination of non-pregnancy for said patients, authorizing said registered pharmacies to fill prescriptions from said registered prescribers for said non-pregnant registered patients.	*Honigfeld* teaches that registered pharmacies are authorized to fill prescriptions in response to a determination from patient testing: Ex. 1009 at 52 ("[A] national patient registry system … provides the medication only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression."); *Id.* at 53 ("The medication is dispensed weekly only to patients for whom data on current white blood cell counts are available."); *Id.* at 53 ("Distribution of the medication is limited to registered pharmacies, which agree to follow the 'no blood-no drug' guidelines."). *NIH* teaches dispensing the drug in response to a determination of non-pregnancy: Ex. 1015 at 47: ("…the FDA recently proposed to require a negative pregnancy test at baseline, 9-10 days after starting therapy, and every 30 days thereafter.") Ex. 1002 ¶¶ 209-211.
2. The method of claim 1 wherein said drug is thalidomide.	*NIH* discloses the use of the methods of claim 1 where the drug is thalidomide: *See* Claim Chart Element 1pre *NIH* excerpts.
3. The method of claim 1 further comprising including in said registering information	*NIH* teaches registering information concerning male patients who are capable of impregnating females and including said males within said subpopulation: *See NIH* excerpts from Claim Elements 1(c) to 1(e).

concerning male patients who are capable of impregnating females and including said males within said subpopulation.	Ex. 1002 ¶ 217.
4. The method of claim 1 wherein said determination comprises pregnancy testing.	*NIH* discloses pregnancy testing for thalidomide treatment. *See* Claim Element 1(f) *NIH* excerpts; Ex. 1015 at 0113–19 ("…you will be required to have blood drawn for a pregnancy test before you start taking thalidomide.")
5. The method of claim 1 wherein the issuance and fulfillment of said prescriptions are recorded in said computer readable storage medium.	*Honigfeld* discloses records of the issuance and fulfillment of prescriptions in a computer readable storage medium: Ex. 1009 at 53 ("All data coming to the clozapine national registry are entered into an integrated, computerized database maintained by the manufacturer. … Patient's computer records…include the patient's identifying code number and initials, the physician's identification, the pharmacy's identification, daily dosage of clozapine in milligrams, and white blood cell test dates and results."); *Id.* ("The medication is dispensed weekly only to patients for whom data on current white blood cell counts are available. The registry system also outlines the responsibilities of physicians, pharmacies, patients, and the medication's manufacturer and wholesale distributors in ensuring proper use of the medication."); *Id.* ("Distribution of the medication is limited to registered pharmacies, which agree to follow the 'no blood-no drug' guidelines."). Ex. 1002 ¶¶ 223-224.
6. The method of claim 1 wherein refilling of said prescriptions is authorizable only in response to information contained on said	*Honigfeld* teaches that prescription refills are authorizable only in response to information contained on the computer readable storage medium: *See* Claim Chart for Claim 5; and Ex. 1009 at 52 ("[A] national patient registry system … provides the medication only if results of patients' weekly blood tests show no evidence of significant white blood cell suppression.")

computer readable storage medium.	Ex. 1002 ¶¶ 226-227.
7. The method of claim 1 wherein said prescriptions are filled for no more than about 28 days.	*Honigfeld* teaches that prescriptions are filled for no more than about 28 days: Ex. 1009 at 53 ("The medication is dispensed weekly only to patients for whom data on current white blood cell counts are available."); Ex. 1002 ¶¶ 229-230.
8. The method of claim 1 wherein said prescriptions are filled together with distribution of literature warning of the effects of said drug upon foetuses.	*NIH* teaches the distribution of literature warning of the drug's effects on foetuses upon dispensing the drug: *See* Claim Chart for Claim Element 1(e) *NIH* excerpts. Ex. 1002 ¶¶ 232-234.
9. The method of claim 1 further comprising providing said patients with contraception counseling.	*NIH* discloses providing patients with contraception counseling. *See* Claim Chart for Claim Element 1(e) *NIH* excerpts. Ex. 1002 ¶¶ 236-239.
10. The method of claim 1 further comprising: h. providing to said patients who are capable of becoming pregnant a contraceptive device or formulation.	*NIH* teaches providing to patients who are capable of becoming pregnant a contraceptive device or formulation. Ex. 1015 at 51 ("Components included a unique blister package for the medication with prominent warnings, detailed guidelines to physicians, a patient qualification checklist, a patient information brochure, contraceptive information, a free contraception referral program, and an informed consent form."). Ex. 1002 ¶¶ 241-242.

VII. CONCLUSION

For the foregoing reasons, Petitioners respectfully request *inter partes* review of Claims 1–10 of U.S. Patent No. 6,045,501.

Respectfully submitted,

April 22, 2015

/Sarah E. Spires/

Sarah E. Spires (Reg. No. 61,501)
SKIERMONT PUCKETT LLP
2200 Ross Ave. Ste. 4800W
Dallas, Texas 75201
P: 214-978-6600/F: 214-978-6601
Lead Counsel for Petitioner

Ki O (Reg. No. 68,952)
Dr. Parvathi Kota (Reg. No. 65,122)
Paul J. Skiermont (pro hac vice requested)
SKIERMONT PUCKETT LLP
2200 Ross Ave. Ste. 4800W
P: 214-978-6600/F: 214-978-6621
Back-Up Counsel for Petitioner

CERTIFICATE OF SERVICE

I hereby certify that on April 23, 2015, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 6,045,501, including all exhibits, was served via FedEx, overnight delivery, upon the following:

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

S. Maurice Valla
BakerHostetler
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, Pennsylvania 19104-2891

Date: April 22, 2015

/Sarah E. Spires/
Sarah E. Spires