PETITIONER'S DEMONSTRATIVES

July 21, 2016
Oral Argument

Coalition for Affordable Drugs VI LLC,
Petitioner

v.

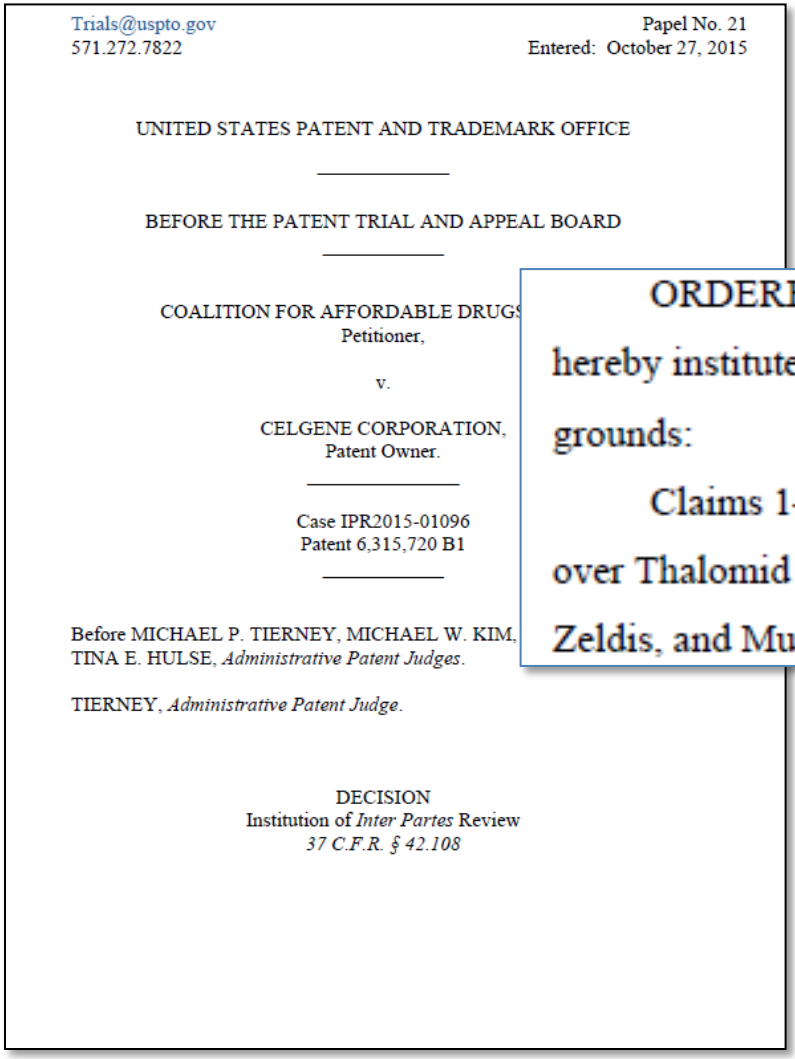
Celgene Corporation,
Patent Owner

IPR2015-01092, -01096, -01102, -01103

U.S. PATENT No. 6,315,720 GROUNDS FOR INSTITUTION OF IPR

Grounds for Institution of IPR

Institution Decision – IPR2015-01096



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Papel No. 21
Entered: October 27, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS
Petitioner,

v.

CELGENE CORPORATION,
Patent Owner.

Case IPR2015-01096
Patent 6,315,720 B1

Before MICHAEL P. TIERNEY, MICHAEL W. KIM, TINA E. HULSE, *Administrative Patent Judges*.

TIERNEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–32 of the '720 patent on the following grounds:

Claims 1–32 of the '720 patent under 35 U.S.C. § 103(a), as obvious over Thalomid PI in view of Cunningham and further in view of Keravich, Zeldis, and Mundt.

Source: Paper 21 (-01096), Institution Decision, at 23.

Grounds for Institution of IPR

Institution Decision – IPR2015-01102

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Paper No. 21
Entered: October 27, 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 IPR2015-01102
Patent 6,315,720 B1

Before MICHAEL P. TIERNEY, MICHAEL W. KIM, and TINA E. HULSE, *Administrative Patent Judges*.

TIERNEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–32 of the '720 patent on the following grounds:

Claims 1–32 of the '720 patent under 35 U.S.C. § 103(a), as obvious over Powell and Dishman in view of Cunningham and further in view of Mundt, Mann, Vanchieri, Shinn, Linnarsson, Grönroos, Soyka, Hamera, Kosten, and Menill.

Source: Paper 21 (-01102), Institution Decision, at 25.

Grounds for Institution of IPR

Institution Decision – IPR2015-01103

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Paper No. 22
Entered: October 27, 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 IPR2015-01103
Patent 6,315,720 B1

Before MICHAEL P. TIERNEY, MICHAEL W. KIM, and TINA E. HULSE, *Administrative Patent Judges*.

TIERNEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–32 of the '720 patent on the following grounds:

Claims 1–32 of the '720 patent under 35 U.S.C. § 103(a), as obvious over Mitchell and Dishman in view of Cunningham and further in view of Mundt, Mann, Vanchieri, Shinn, Linnarsson, Grönroos, Soyka, Hamera, Kosten, and Menill.

Source: Paper 22 (-01103), Institution Decision, at 25.

BURDEN OF PROOF

BURDEN OF PROOF

In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

35 U.S.C. § 316(e)

’720 Patent – Claims

’720 Patent — Claim 1

1. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;

b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;

c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;

d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and

e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled.

prior art: ’501 patent

defining patient risk groups

defining probative information

risk group assignment

determining acceptability of risk

generating prescription approval code

Source: Ex. 1001 at claims.

’720 Patent — Claim 28

Identical to claim 1, with this addition:

> wherein said adverse side effect is likely to arise in patients who take said drug in combination with at least one other drug.

Source: Ex. 1001 at claims.

’720 Patent — Dependent Claims

Patent Owner makes additional arguments for only claims 5, 10, and 17.

5. The method of claim **4** wherein said risk group assignment and said informed consent is verified by said prescriber at the time that said patient is registered in said computer readable storage medium.

6. The method of claim **5** wherein said risk group assignment and said informed consent is transmitted to said computer readable storage medium by facsimile and interpreted by optical character recognition software.

10. The method of claim **7** wherein said diagnostic testing comprises genetic testing.

17. The method of claim **16** wherein said survey is conducted telephonically using an integrated voice response system.

Source: Ex. 1001 at claims.

PERSON OF ORDINARY SKILL IN THE ART

The Institution Decision

IPR2015-01096
Patent 6,315,720 B1

Celgene's definition of a POSA is supported by the claims and specification of the '720 patent. *See generally* Ex. 1001.

Id. at 20.

For purposes of this Decision, we consider the cited prior art as representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). The prior art references, like the '720 patent specification, focus on controlling the distribution of a drug. *See, e.g.*, Ex. 1001, 1:13–16 (describing "the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled"); *see generally* Exs. 1003; 1006; 1009; 1012; 1015; 1018. Consistent with the prior art, Petitioner's Declarant, Dr. Fudin, testifies that the types of problems encountered by one of ordinary skill in the art included creating a restricted drug distribution program to prevent adverse side effects, such as teratogenic risks. Ex. 1021 ¶¶ 44–50.

On this record, we credit the testimony of Dr. Fudin and conclude that one of ordinary skill in the art encompasses a Pharm.D. or a B.S. in pharmacy with approximately 5–10 years of experience and a license to practice as a registered pharmacist.

Patent Owner disputes that Dr. Fudin has the knowledge of a person of ordinary skill in the art. Prelim. Resp. 19–21. We disagree. Dr. Fudin's educational background and experience, Pharm.D, Associate Professor of Pharmacy practice, and clinical pharmacy specialist experience, demonstrate that Dr. Fudin is qualified to testify as to the knowledge of a person of ordinary skill in the art. Ex. 1021 ¶¶ 4–14.

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Patent Owner disputes that Dr. Fudin has the knowledge of a person of ordinary skill in the art. Prelim. Resp. 19–21. We disagree. Dr. Fudin's educational background and experience, Pharm.D, Associate Professor of Pharmacy practice, and clinical pharmacy specialist experience, demonstrate that Dr. Fudin is qualified to testify as to the knowledge of a person of ordinary skill in the art. Ex. 1021 ¶¶ 4–14.

Source: Paper 21 (-01096), Institution Decision, at 8.

POSA

Dr. Frau Offers the Same Definitions as for the ’501 Patent

Q. And in all three of these declarations you offer the same definition of a POSA; correct?

A. Yes.

Q. And that's also the same definition as what you've offered in the 1092 proceeding; correct?

A. Correct.

Q. And you agree that the '501 patent is prior art to the '720 patent; correct?

MS. SHIH: Objection, relevance; and objection to the extent that you're attempting to introduce a new reference into the proceeding. Into the ground of the proceeding, to be clear.

(Pause.)

A. The '720 patent is an improvement on the 2501 patent, which I discuss in detail in my declaration submitted in IPR2015-1092.

Source: Ex. 1075 (-01096) at 306:4-21.

CLAIM CONSTRUCTION

CLAIM CONSTRUCTION

Standard:

"…broadest reasonable interpretation in light of the specification."

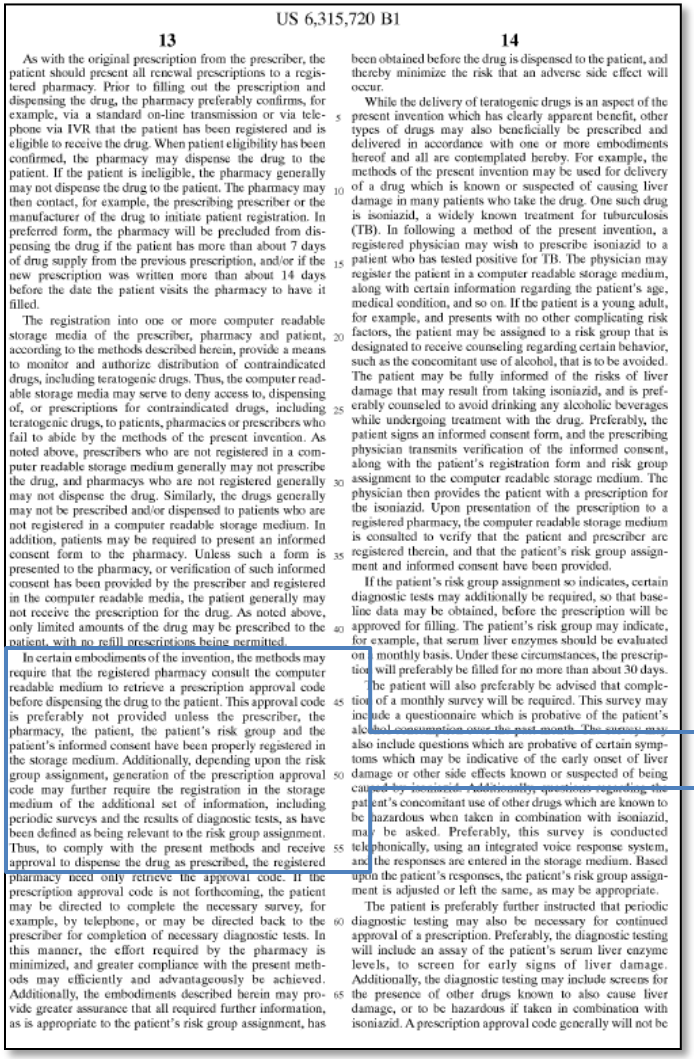
Claim term in dispute:

"prescription approval code"

Petitioner:	Patent Owner:
No construction necessary.	"code representing that an affirmative risk assessment has been made based upon risk-group assignment and the information collected from the patient, and that is generated only upon a determination that the risk of a side effect occurring is acceptable."

Source: 37 C.F.R. § 42.100(b); Paper 52 (-01096), Petitioner's Reply, at 9.

CLAIM CONSTRUCTION



US 6,315,720 B1

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As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

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While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days. The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment.

Source: Ex. 1001 (-01096) at 13:42–54.

CLAIM CONSTRUCTION

Dr. Frau's Admissions

And directing your attention to the claims which begin under Column 18, you agree that the term "affirmative risk assessment" does not appear anywhere in these claims; correct?

MS. SHIH: Objection to the form.

(Pause.)

A. Okay. Well, those words "affirmative risk assessment" do not appear on the page. The meaning is in that page.

Dr. DiPiro's Admissions

But my question relates to the words "affirmative risk assessment."

Those words do not appear in the patent, correct?

A. And I have not taken the patent in its isolation to do that, to offer that opinion in the definition.

Q. So then you acknowledge that those words don't appear in the patent, correct?

A. They don't. And again, it's not the full record that I have reviewed to construct that definition.

Source: Ex. 1075 (-01096) at 316:9-17, Ex. 1074 (-01096) at 246:15-247:1.

CLAIM CONSTRUCTION

Dr. Frau's Misapplication of the Standard

10	Q. And do you agree with me, based on what	06:31:01
11	you have in your declaration, that the broadest	
12	reasonable construction, as would be understood by	
13	a POSA in view of the specification, is the	
14	standard for claim construction?	
15	MS. SHIH: Objection, lacks foundation.	06:31:19
16	A. No, I don't agree. I don't agree -- I	
17	don't agree with -- I don't agree with your	
18	interpretation of my interpretation.	

Source: Ex. 1075 (-01096) at 204:10-18.

CLAIM CONSTRUCTION

Dr. Frau's Misapplication of the Standard

Q. Do you agree that the claims have to be viewed in light of the specification of the patent?

A. Different people can read the same paragraph in a slightly different interpretation of the wording, in the context of not only that paragraph but what follows.

And so I'm viewing this paragraph, what you're saying -- the paragraph that you mentioned as a discussion point from which the final outcome of the discussion are the claims mentioned subsequent to what is claimed.

It's just -- it's an interpretation.

06:30:30

06:30:42

Source: Ex. 1075 (-01096) at 203:21-204:9.

CLAIM CONSTRUCTION

The Prosecution History

DOCKET NO.: CELG-0188 **PATENT**

side effect occurring is acceptable. Upon a determination that the risk is acceptable, *and only upon such a determination*, a prescription approval code is generated, which must be retrieved by the pharmacy before the prescription may be filled. Thus, the prescription approval code is not merely a number that is associated with the prescription, but instead represents the fact that a determination has been made that the risk of the side effect occurring is acceptable, and that approval–an affirmative decision– has been made for the prescription to be filled. Boyer does not disclose or suggest such an approval code.

Boyer is directed to an automated system for operating a pharmacy. *See e.g.*, Claim 1. In this system, as a prescription is entered in the data record, a prescription number is generated within the computer at the data entry workstation. *See* col. 2, lines 31 to 33. As Boyer makes clear, assignment of this prescription number is one of first steps in a chain of events that follows communication of the prescription to the automated pharmacy. *See* col. 3, lines 60 to 61. Thus, the prescription number (or code, as it is alternately referred to by Boyer in Claim 15) is simply an identifier for the prescription, and is not an *approval code*, as recited in Applicants' claims. Unlike the prescription approval code of the present invention, the prescription number described in Boyer is simply a *prescription identifier*, and is in no way connected to, or reflective of, a determination that the risk of the side effect occurring has been found to be acceptable. There is simply no correlation in Boyer between the generation of the prescription number and any risk assessment, and no indication that a *prescription approval code*, as described and claimed in the instant application, must be generated and retrieved by the pharmacist before the prescription may be filled.

Any proper combination of the disclosure of Boyer with that of Elsayed and Schauss does not teach or suggest the invention defined by Applicants' claims. Accordingly, Applicants respectfully request that the rejection of Claims 1 to 27 under Section 103 be withdrawn.

- 4 -

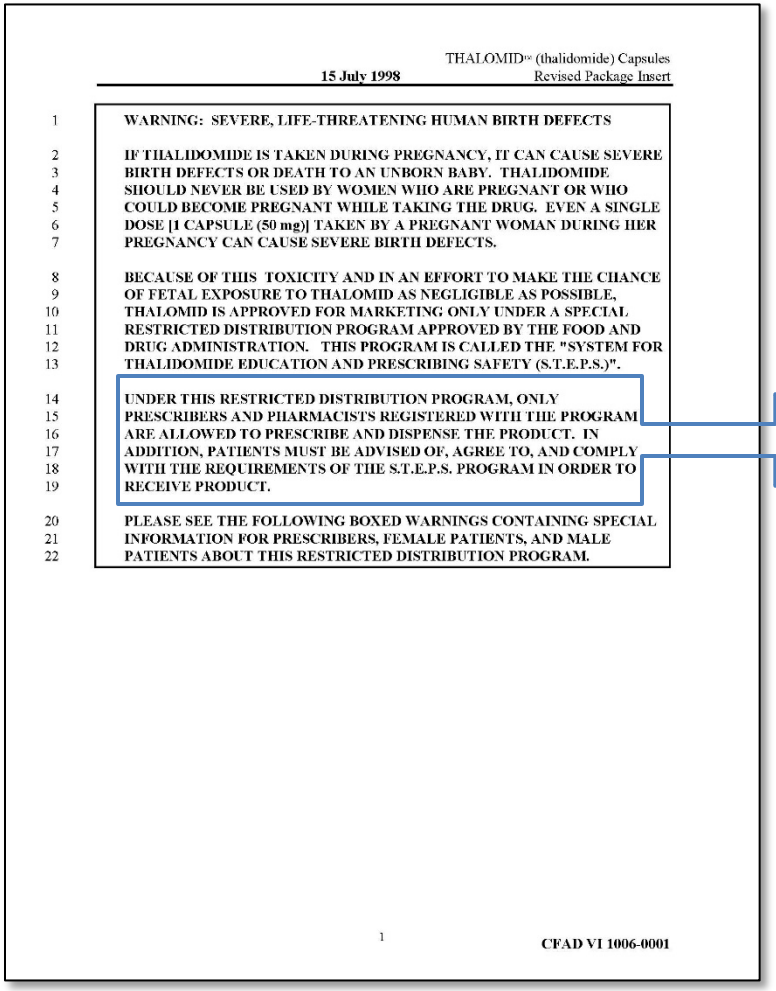
Boyer is directed to an automated system for operating a pharmacy. *See e.g.*, Claim 1. In this system, as a prescription is entered in the data record, a prescription number is generated within the computer at the data entry workstation. *See* col. 2, lines 31 to 33. As Boyer makes clear, assignment of this prescription number is one of first steps in a chain of events that follows communication of the prescription to the automated pharmacy. *See* col. 3, lines 60 to 61. Thus, the prescription number (or code, as it is alternately referred to by Boyer in Claim 15) is simply an identifier for the prescription, and is not an *approval code*, as recited in Applicants' claims. Unlike the prescription approval code of the present invention, the prescription number described in Boyer is simply a *prescription identifier*, and is in no way connected to, or reflective of, a determination that the risk of the side effect occurring has been found to be acceptable. There is simply no correlation in Boyer between the generation of the prescription number and any risk assessment, and no indication that a *prescription approval code*, as described and claimed in the instant application, must be generated and retrieved by the pharmacist before the prescription may be filled.

Source: Ex. 1002 (-01096) at 107.

PRIOR ART

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FETAL EXPOSURE TO THALOMID AS NEGLIGIBLE AS POSSIBLE, THALOMID IS APPROVED FOR MARKETING ONLY UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAM APPROVED BY THE FOOD AND DRUG ADMINISTRATION. THIS PROGRAM IS CALLED THE "SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (S.T.E.P.S.)".

UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE S.T.E.P.S. PROGRAM IN ORDER TO RECEIVE PRODUCT.

PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

1

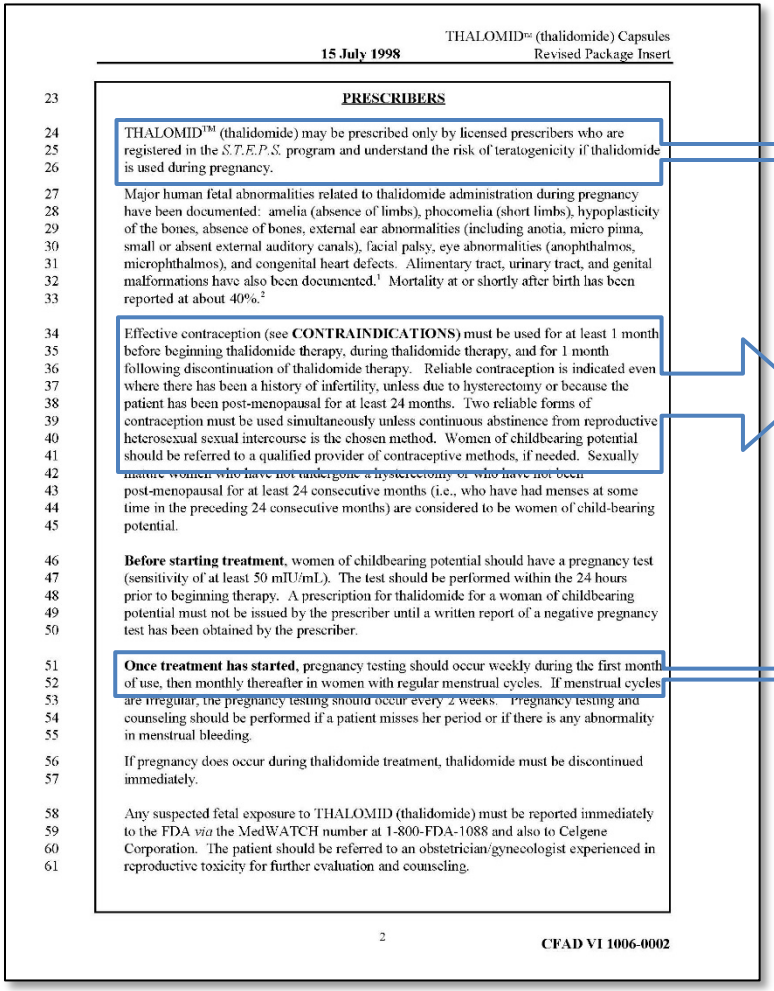
CFAD VI 1006-0001

UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE S.T.E.P.S. PROGRAM IN ORDER TO RECEIVE PRODUCT.

Source: Paper 1 (-01096), Petition, at 15, 20-21, 39, 41-42, 46; Ex. 1006 (-01096) at 1.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

PRESCRIBERS

THALOMID™ (thalidomide) may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.

Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Once treatment has started, pregnancy testing should occur weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately.

Any suspected fetal exposure to THALOMID (thalidomide) must be reported immediately to the FDA *via* the MedWATCH number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

2 CFAD VI 1006-0002

THALOMID™ (thalidomide) may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

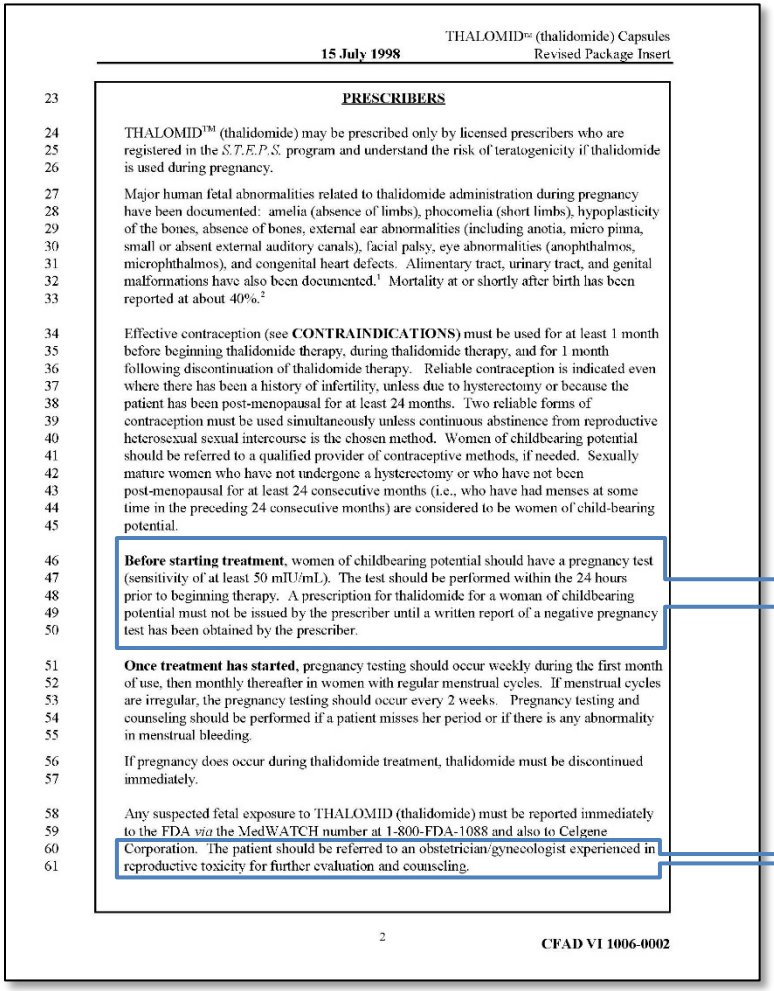
Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually

Once treatment has started, pregnancy testing should occur weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles. If menstrual cycles

Source: Paper 1 (-01096), Petition, at 16, 29-30, 36, 47-48, 52, ; Ex. 1006 (-01096) at 2.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

PRESCRIBERS

THALOMID™ (thalidomide) may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.

Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Once treatment has started, pregnancy testing should occur weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately.

Any suspected fetal exposure to THALOMID (thalidomide) must be reported immediately to the FDA *via* the MedWATCH number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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CFAD VI 1006-0002

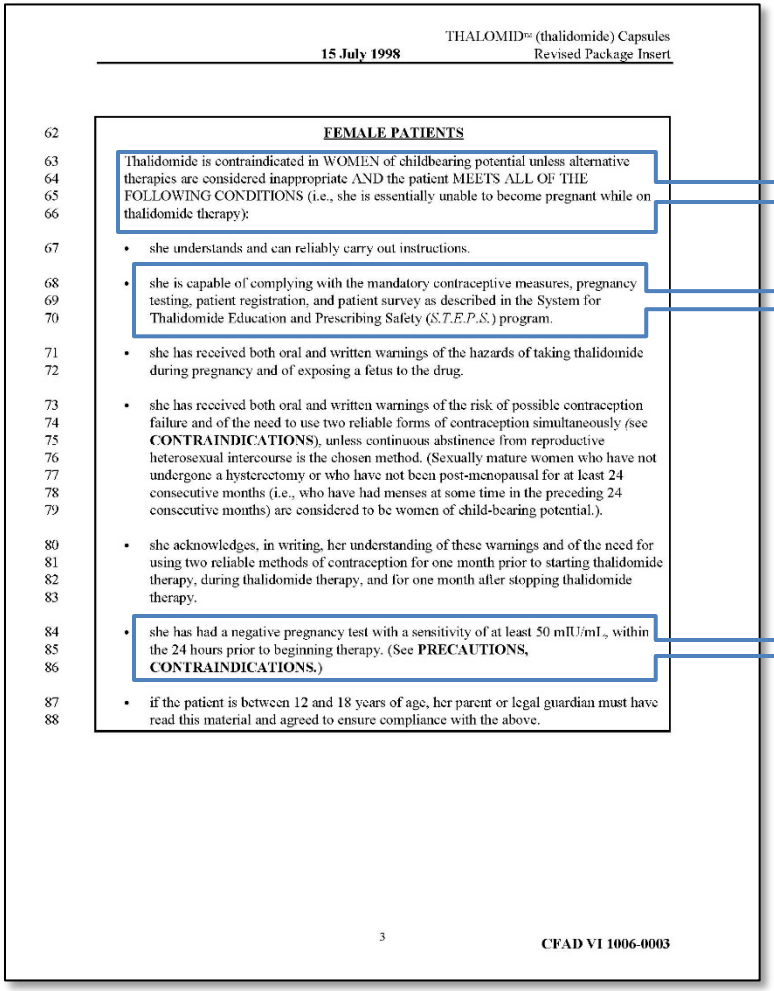
Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Source: Paper 1 (-01096), Petition, at 26, 33, 35, 41-42, 49, 57; Ex. 1006 (-01096) at 2.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
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FEMALE PATIENTS

Thalidomide is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND the patient MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is essentially unable to become pregnant while on thalidomide therapy):

- she understands and can reliably carry out instructions.
- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*) program.
- she has received both oral and written warnings of the hazards of taking thalidomide during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see **CONTRAINDICATIONS**), unless continuous abstinence from reproductive heterosexual intercourse is the chosen method. (Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.).
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for one month prior to starting thalidomide therapy, during thalidomide therapy, and for one month after stopping thalidomide therapy.
- she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL, within the 24 hours prior to beginning therapy. (See **PRECAUTIONS, CONTRAINDICATIONS.**)
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

3 **CFAD VI 1006-0003**

Thalidomide is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND the patient MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is essentially unable to become pregnant while on thalidomide therapy):

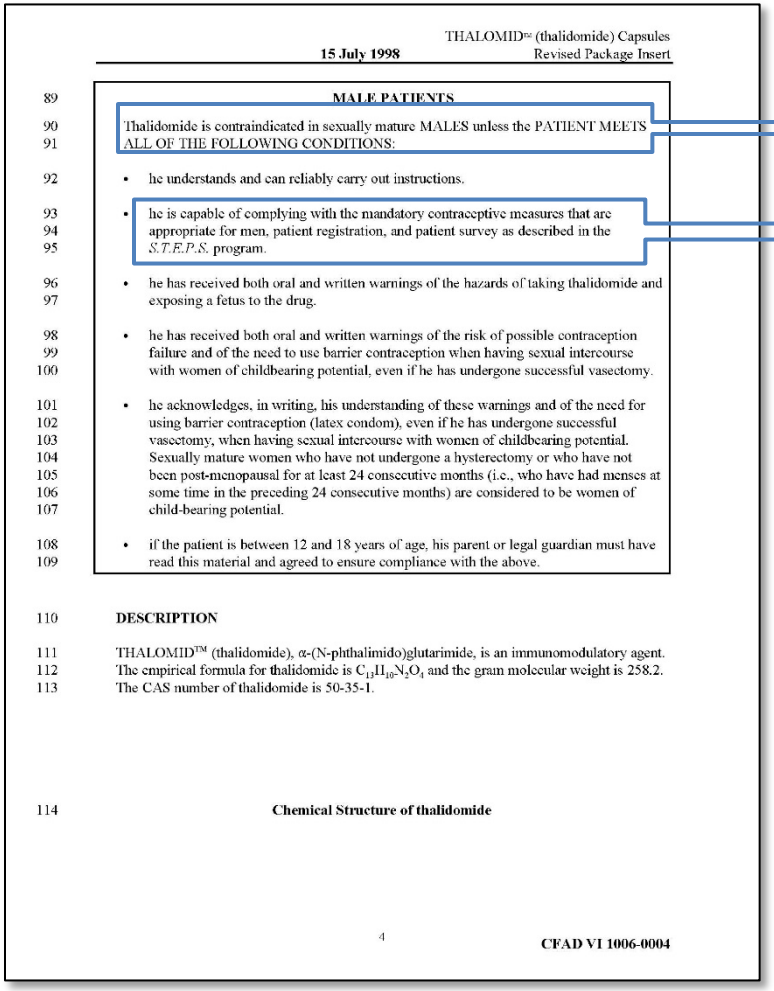
she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.*) program.

she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL, within the 24 hours prior to beginning therapy. (See **PRECAUTIONS, CONTRAINDICATIONS.**)

Source: Paper 1 (-01096), Petition, at 42-43, 50; Ex. 1006 (-01096) at 3.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
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MALE PATIENTS

Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he understands and can reliably carry out instructions.
- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.* program.
- he has received both oral and written warnings of the hazards of taking thalidomide and exposing a fetus to the drug.
- he has received both oral and written warnings of the risk of possible contraception failure and of the need to use barrier contraception when having sexual intercourse with women of childbearing potential, even if he has undergone successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need for using barrier contraception (latex condom), even if he has undergone successful vasectomy, when having sexual intercourse with women of childbearing potential. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of child-bearing potential.
- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

DESCRIPTION

THALOMID™ (thalidomide), α-(N-phthalimido)glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1.

Chemical Structure of thalidomide

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CFAD VI 1006-0004

Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.* program.

Source: Paper 1 (-01096), Petition, at 16, 37, 39-40, 44 ; Ex. 1006 (-01096) at 4.

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under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see Table 1 below). This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max} values, suggests that the poor solubility of thalidomide in aqueous media may be hindering the rate of absorption.

Table 1
Pharmacokinetic Parameter Values for THALOMID (thalidomide)
Mean (%CV)

Population/ Single Dose	AUC_0 (µg hr/mL)	C_{max} (µg/mL)	T_{max} (hrs)	Half-life (hrs)
Healthy Subjects (n=14)				
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)
Patients with Hansen's Disease (n=6)				
400 mg	46.4 (44.1%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

Co-administration of THALOMID with a high fat meal causes minor (<10%) changes in the observed AUC and C_{max} values: however, it causes an increase in T_{max} to approximately 6 hours.

Distribution

It is not known whether thalidomide is present in the ejaculate of males.
The extent of plasma protein binding of thalidomide is unknown.

Metabolism

At the present time, the exact metabolic route and fate of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. In a repeat dose study in which THALOMID (thalidomide) 200 mg was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing. This suggests that thalidomide does not induce or inhibit its own metabolism.

Elimination

As indicated in Table 1 (above) the mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism subsection, the precise metabolic fate and route of elimination of thalidomide in humans is not known at this time. Thalidomide itself has a renal clearance of 1.15 mL/minute with less than 0.7% of the dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide were undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites[8], only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was identified in the urine of subjects 12 to 24 hours after dosing.

Pharmacokinetic Data in Special Populations

HIV-seropositive Subjects: There is no apparent significant difference in measured pharmacokinetic

It is not known whether thalidomide is present in the ejaculate of males.
The extent of plasma protein binding of thalidomide is unknown.

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** Sheskin: Complete Improvement + "striking" improvement (i.e., >50% improvement)

Waters[11] reported the results of two studies, both double blind, randomized, placebo controlled, crossover trials in a total of 10 hospitalized, steroid-dependent patients with chronic ENL treated with 100 mg thalidomide or placebo (three times daily). All patients also received dapsone. The primary endpoint was reduction in weekly steroid dosage.

Table 3
Double Blind, Controlled Trial of Thalidomide in Patients with ENL: Reduction in Steroid Dosage

Reference	Duration of Treatment	No. of Patients	Number Responding	
			Thalidomide	Placebo
Waters[11]	4 weeks	9	4/5	0/4
Lep Rev 1971; 42:26	6 weeks (crossover)	8	8/8	1/8

Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a retrospective evaluation of 102 patients treated under the auspices of the U.S. Public Health Service. A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstitution of therapy.

Twenty U.S. patients between the ages of 11 and 17 years were treated with thalidomide, generally at 100 mg daily. Response rates and safety profiles were similar to that observed in the adult population.

Thirty-two other published studies containing over 1600 patients consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL with thalidomide.

INDICATIONS AND USAGE

THALOMID (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALOMID (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

THALOMID (thalidomide) is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

CONTRAINDICATIONS (See BOXED WARNINGS.)

Pregnancy: Category X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS.**) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS.**) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women

Source: Paper 1 (-01096), Petition, at 48; Ex. 1006 (-01096) at 8.

PRIOR ART

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must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also **PRECAUTIONS: DRUG INTERACTIONS**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have pregnancy testing (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours before beginning thalidomide therapy and then weekly during the first month of thalidomide therapy, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician / gynecologist experienced in reproductive toxicity for further evaluation and counseling.

THALOMID (thalidomide) is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

WARNINGS (See BOXED WARNINGS.)

Birth defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED WARNING** and **CONTRAINDICATIONS.**) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.

Drowsiness and somnolence:

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist. The correlation with cumulative dose is

irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during

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must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (*e.g.*, IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (*e.g.*, latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also **PRECAUTIONS: DRUG INTERACTIONS**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have pregnancy testing (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours before beginning thalidomide therapy and then weekly during the first month of thalidomide therapy, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician / gynecologist experienced in reproductive toxicity for further evaluation and counseling.

THALOMID (thalidomide) is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

WARNINGS (See BOXED WARNINGS.)

Birth defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED WARNING** and **CONTRAINDICATIONS.**) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.

Drowsiness and somnolence:

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist. The correlation with cumulative dose is

Birth defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED WARNING** and **CONTRAINDICATIONS.**) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.

Drowsiness and somnolence:

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short term use also exist. The correlation with cumulative dose is

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unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all. Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually, treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status. Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide.

Dizziness and orthostatic hypotension:

Patients should also be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of <750/mm^3. White blood cell count and differential should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below 750/mm^3 while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.

Increased HIV-Viral Load:

In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 $\log_{10}$ copies HIV RNA/mL, p = 0.04 compared to placebo)[7]. A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropositive[12]. The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if

Dizziness and orthostatic hypotension:

Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of <750/mm^3. White blood cell count and differential should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below 750/mm^3 while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.

Increased HIV-Viral Load:

PRIOR ART

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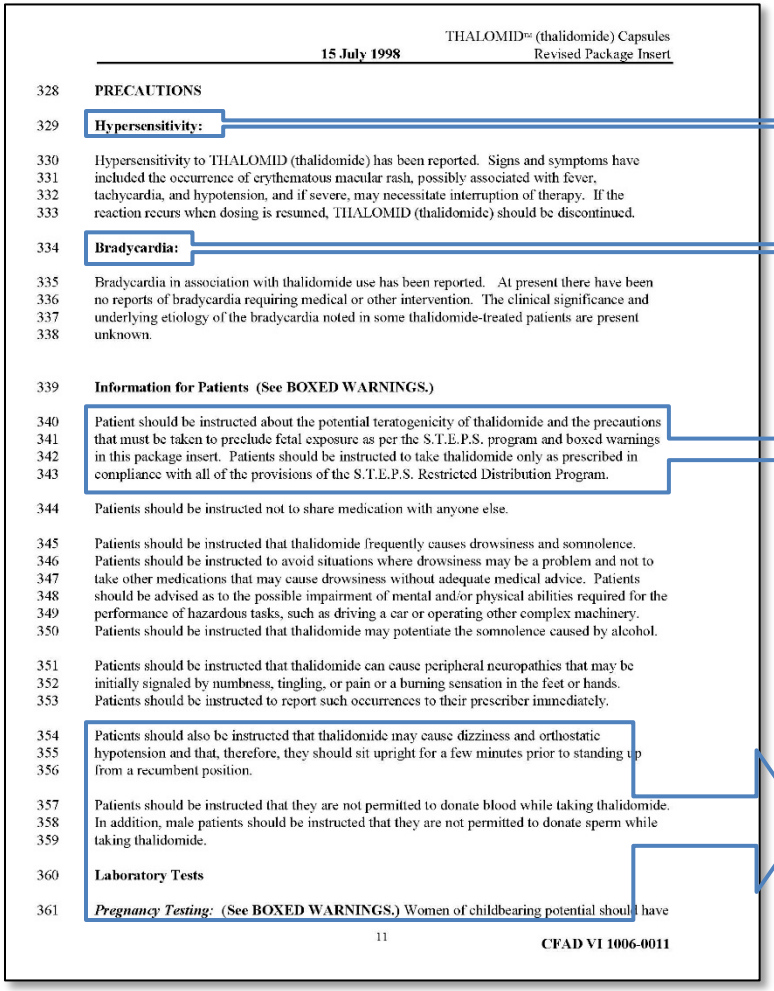

THALOMID™ (thalidomide) Capsules
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PRECAUTIONS

Hypersensitivity:

Hypersensitivity to THALOMID (thalidomide) has been reported. Signs and symptoms have included the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, THALOMID (thalidomide) should be discontinued.

Bradycardia:

Bradycardia in association with thalidomide use has been reported. At present there have been no reports of bradycardia requiring medical or other intervention. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are present unknown.

Information for Patients (See BOXED WARNINGS.)

Patient should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the S.T.E.P.S. program and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the S.T.E.P.S. Restricted Distribution Program.

Patients should be instructed not to share medication with anyone else.

Patients should be instructed that thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

Patients should be instructed that thalidomide can cause peripheral neuropathies that may be initially signaled by numbness, tingling, or pain or a burning sensation in the feet or hands. Patients should be instructed to report such occurrences to their prescriber immediately.

Patients should also be instructed that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients should be instructed that they are not permitted to donate sperm while taking thalidomide.

Laboratory Tests

Pregnancy Testing: **(See BOXED WARNINGS.)** Women of childbearing potential should have

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CFAD VI 1006-0011

Hypersensitivity:

Bradycardia:

Patient should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the S.T.E.P.S. program and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the S.T.E.P.S. Restricted Distribution Program.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients should be instructed that they are not permitted to donate sperm while taking thalidomide.

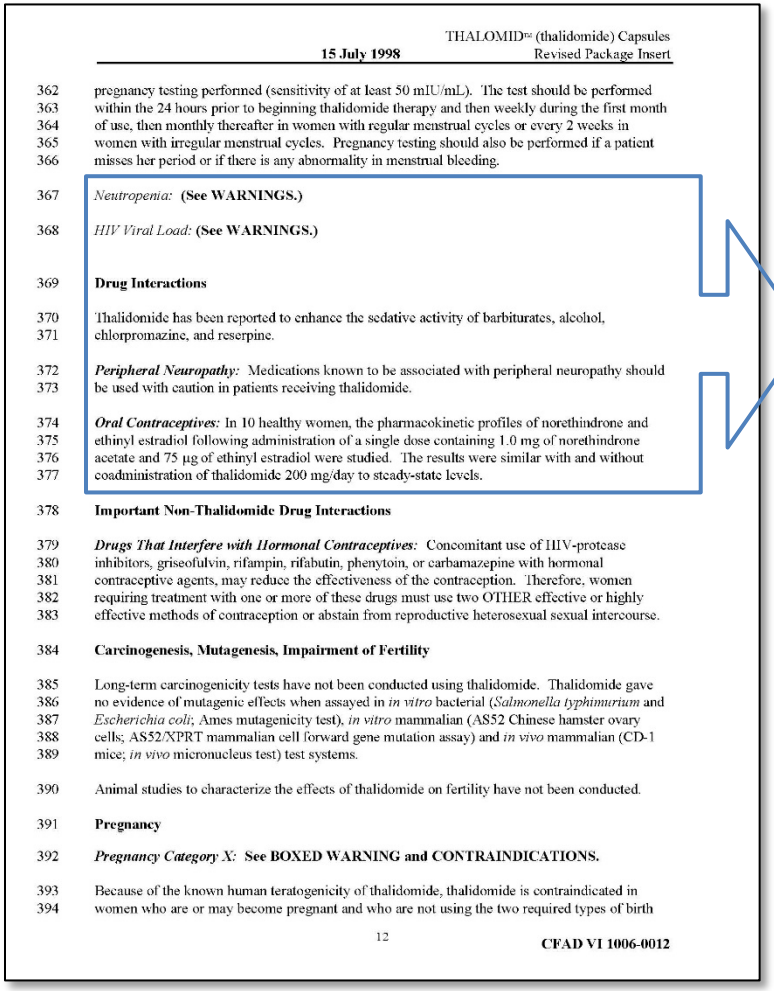
Laboratory Tests

Pregnancy Testing: **(See BOXED WARNINGS.)** Women of childbearing potential should have

Source: Paper 1 (-01096), Petition, at 29, 44-45, 48-49, 51; Ex. 1006 (-01096) at 11.

PRIOR ART

Thalomid Package Insert



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pregnancy testing performed (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing should also be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

Neutropenia: **(See WARNINGS.)**

HIV Viral Load: **(See WARNINGS.)**

Drug Interactions

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.

Peripheral Neuropathy: Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

Oral Contraceptives: In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 75 µg of ethinyl estradiol were studied. The results were similar with and without coadministration of thalidomide 200 mg/day to steady-state levels.

Important Non-Thalidomide Drug Interactions

Drugs That Interfere with Hormonal Contraceptives: Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception. Therefore, women requiring treatment with one or more of these drugs must use two OTHER effective or highly effective methods of contraception or abstain from reproductive heterosexual sexual intercourse.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity tests have not been conducted using thalidomide. Thalidomide gave no evidence of mutagenic effects when assayed in *in vitro* bacterial (*Salmonella typhimurium* and *Escherichia coli*; Ames mutagenicity test), *in vitro* mammalian (AS52 Chinese hamster ovary cells; AS52/XPRT mammalian cell forward gene mutation assay) and *in vivo* mammalian (CD-1 mice; *in vivo* micronucleus test) test systems.

Animal studies to characterize the effects of thalidomide on fertility have not been conducted.

Pregnancy

Pregnancy Category X: **See BOXED WARNING and CONTRAINDICATIONS.**

Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth

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CFAD VI 1006-0012

Neutropenia: **(See WARNINGS.)**

HIV Viral Load: **(See WARNINGS.)**

Drug Interactions

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.

Peripheral Neuropathy: Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

Oral Contraceptives: In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 75 µg of ethinyl estradiol were studied. The results were similar with and without coadministration of thalidomide 200 mg/day to steady-state levels.

Source: Paper 1 (-01096), Petition, at 35, 50-51; Ex. 1006 (-01096) at 12.

Thalomid Package Insert

control or who are not continually abstaining from reproductive heterosexual sexual intercourse. If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose [1 capsule (50 mg)] taken by a pregnant woman can cause birth defects. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician / gynecologist experienced in reproductive toxicity for further evaluation and counselling. Any suspected fetal exposure to THALOMID (thalidomide) must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Animal studies to characterize the effects of thalidomide on late stage pregnancy have not been conducted.

Use in Nursing Mothers

It is not known whether thalidomide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from thalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

No systematic studies in geriatric patients have been conducted. Thalidomide has been used in clinical trials in patients up to 90 years of age. Adverse events in patients over the age of 65 years did not appear to differ in kind from those reported for younger individuals.

ADVERSE REACTIONS

The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See **BOXED WARNINGS** and **CONTRAINDICATIONS**) The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy.

Thalidomide is associated with drowsiness / somnolence, peripheral neuropathy, dizziness / orthostatic hypotension, neutropenia, and HIV viral load increase. **(See WARNINGS.)**

Hypersensitivity to THALOMID (thalidomide) and bradycardia in patients treated with thalidomide have been reported. **(See PRECAUTIONS.)**

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials

counselling. Any suspected fetal exposure to THALOMID (thalidomide) must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Source: Paper 1 (-01096), Petition, at 41; Ex. 1006 (-01096) at 13.

PRIOR ART

Thalomid Package Insert

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia, dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop, galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, and suicide attempt.

DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence has not been reported in patients taking thalidomide. However, as with other tranquilizers / hypnotics, thalidomide too has been reported to create in patients habituation to its soporific effects.

OVERDOSAGE

There have been three cases of overdose reported, all attempted suicides. There have been no reported fatalities in doses of up to 14.4 grams, and all patients recovered without reported sequelae.

DOSAGE AND ADMINISTRATION

THALOMID MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE S.T.E.P.S. PROGRAM. THALOMID MAY ONLY BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE S.T.E.P.S. PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE S.T.E.P.S. PROGRAM.

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

For an episode of cutaneous ENL, THALOMID dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kilograms should be started at the low end of the dose range.

In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, THALOMID dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly with THALOMID. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with THALOMID should usually continue until signs and symptoms of active reaction

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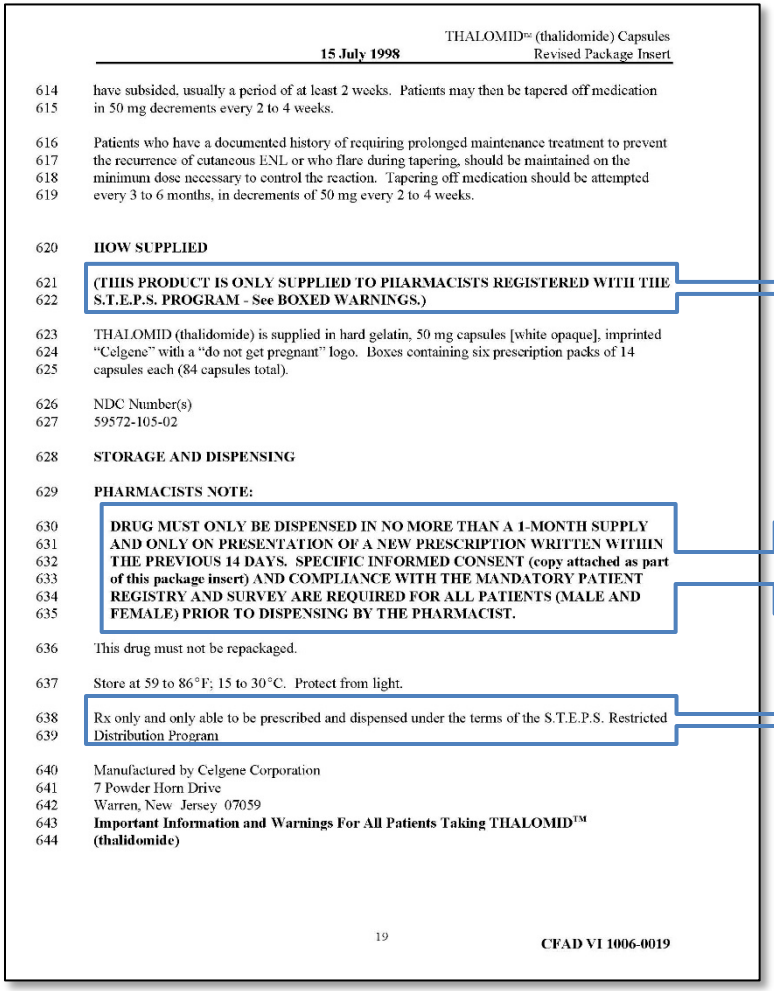
Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

Source: Paper 1 (-01096), Petition, at 21, 24, 31, 37, 47, 49; Ex. 1006 (-01096) at 18.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

HOW SUPPLIED

(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE S.T.E.P.S. PROGRAM - See BOXED WARNINGS.)

THALOMID (thalidomide) is supplied in hard gelatin, 50 mg capsules [white opaque], imprinted "Celgene" with a "do not get pregnant" logo. Boxes containing six prescription packs of 14 capsules each (84 capsules total).

NDC Number(s)
59572-105-02

STORAGE AND DISPENSING

PHARMACISTS NOTE:

DRUG MUST ONLY BE DISPENSED IN NO MORE THAN A 1-MONTH SUPPLY AND ONLY ON PRESENTATION OF A NEW PRESCRIPTION WRITTEN WITHIN THE PREVIOUS 14 DAYS. SPECIFIC INFORMED CONSENT (copy attached as part of this package insert) AND COMPLIANCE WITH THE MANDATORY PATIENT REGISTRY AND SURVEY ARE REQUIRED FOR ALL PATIENTS (MALE AND FEMALE) PRIOR TO DISPENSING BY THE PHARMACIST.

This drug must not be repackaged.

Store at 59 to 86°F; 15 to 30°C. Protect from light.

Rx only and only able to be prescribed and dispensed under the terms of the S.T.E.P.S. Restricted Distribution Program

Manufactured by Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059
Important Information and Warnings For All Patients Taking THALOMID™ (thalidomide)

19 **CFAD VI 1006-0019**

(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE S.T.E.P.S. PROGRAM - See BOXED WARNINGS.)

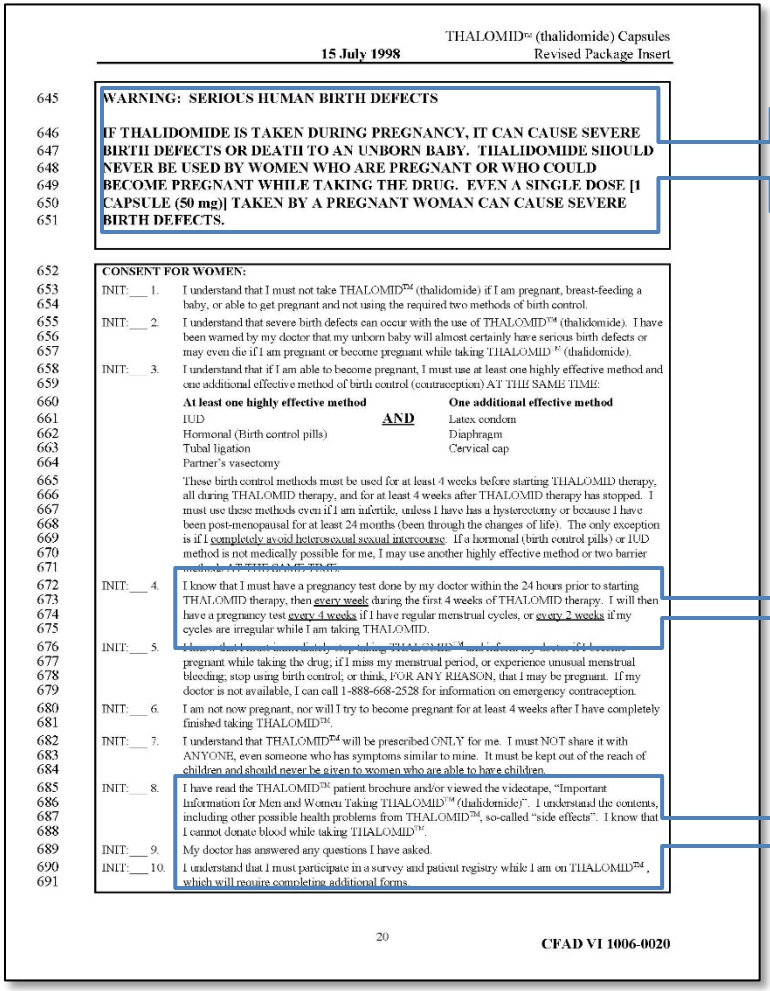
DRUG MUST ONLY BE DISPENSED IN NO MORE THAN A 1-MONTH SUPPLY AND ONLY ON PRESENTATION OF A NEW PRESCRIPTION WRITTEN WITHIN THE PREVIOUS 14 DAYS. SPECIFIC INFORMED CONSENT (copy attached as part of this package insert) AND COMPLIANCE WITH THE MANDATORY PATIENT REGISTRY AND SURVEY ARE REQUIRED FOR ALL PATIENTS (MALE AND FEMALE) PRIOR TO DISPENSING BY THE PHARMACIST.

Rx only and only able to be prescribed and dispensed under the terms of the S.T.E.P.S. Restricted Distribution Program

Source: Paper 1 (-01096), Petition, at 34, 37, 41-42, 49; Ex. 1006 (-01096) at 19.

PRIOR ART

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

WARNING: SERIOUS HUMAN BIRTH DEFECTS

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

CONSENT FOR WOMEN:

INIT:___ 1. I understand that I must not take THALOMID™ (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.

INIT:___ 2. I understand that severe birth defects can occur with the use of THALOMID™ (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking THALOMID™ (thalidomide).

INIT:___ 3. I understand that if I am able to become pregnant, I must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

At least one highly effective method		One additional effective method
IUD	**AND**	Latex condom
Hormonal (Birth control pills)		Diaphragm
Tubal ligation		Cervical cap
Partner's vasectomy		

These birth control methods must be used for at least 4 weeks before starting THALOMID therapy, all during THALOMID therapy, and for at least 4 weeks after THALOMID therapy has stopped. I must use these methods even if I am infertile, unless I have has a hysterectomy or because I have been post-menopausal for at least 24 months (been through the changes of life). The only exception is if I completely avoid heterosexual sexual intercourse. If a hormonal (birth control pills) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

INIT:___ 4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID therapy, then every week during the first 4 weeks of THALOMID therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID.

INIT:___ 5. I know that I must immediately stop taking THALOMID™ and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual menstrual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT:___ 6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID™.

INIT:___ 7. I understand that THALOMID™ will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT:___ 8. I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™, so-called "side effects". I know that I cannot donate blood while taking THALOMID™.

INIT:___ 9. My doctor has answered any questions I have asked.

INIT:___ 10. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

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WARNING: SERIOUS HUMAN BIRTH DEFECTS

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.

I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID therapy, then every week during the first 4 weeks of THALOMID therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID.

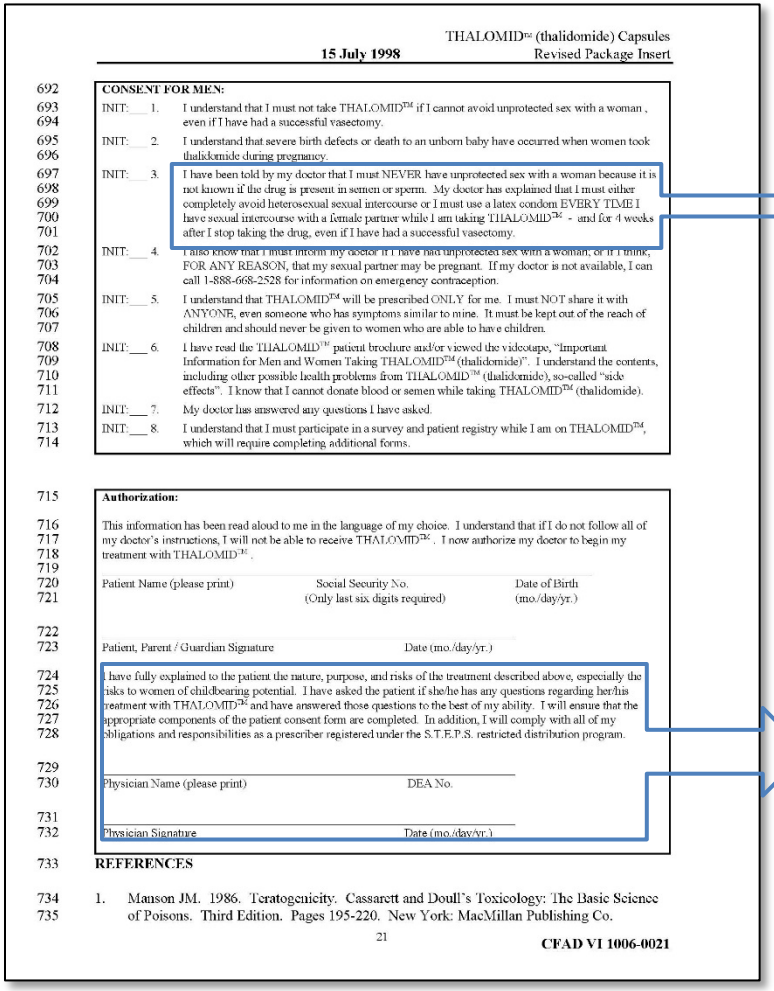
I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™, so-called "side effects". I know that I cannot donate blood while taking THALOMID™.

My doctor has answered any questions I have asked.

I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

Source: Paper 1 (-01096), Petition, at 26, 31-35, 38, 43-50; Ex. 1006 (-01096) at 20.

Thalomid Package Insert



THALOMID™ (thalidomide) Capsules
15 July 1998 Revised Package Insert

CONSENT FOR MEN:

INIT:___ 1. I understand that I must not take THALOMID™ if I cannot avoid unprotected sex with a woman , even if I have had a successful vasectomy.

INIT:___ 2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.

INIT:___ 3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.

INIT:___ 4. I also know that I must inform my doctor if I have had unprotected sex with a woman, or if I think, FOR ANY REASON, that my sexual partner may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT:___ 5. I understand that THALOMID™ will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT:___ 6. I have read the THALOMID™ patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID™ (thalidomide)". I understand the contents, including other possible health problems from THALOMID™ (thalidomide), so-called "side effects". I know that I cannot donate blood or semen while taking THALOMID™ (thalidomide).

INIT:___ 7. My doctor has answered any questions I have asked.

INIT:___ 8. I understand that I must participate in a survey and patient registry while I am on THALOMID™, which will require completing additional forms.

Authorization:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID™ . I now authorize my doctor to begin my treatment with THALOMID™ .

Patient Name (please print) | Social Security No. (Only last six digits required) | Date of Birth (mo./day/yr.)

Patient, Parent / Guardian Signature | Date (mo./day/yr.)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

Physician Name (please print) | DEA No.

Physician Signature | Date (mo./day/yr.)

REFERENCES

1. Manson JM. 1986. Teratogenicity. Cassarett and Doull's Toxicology: The Basic Science of Poisons. Third Edition. Pages 195-220. New York: MacMillan Publishing Co.

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CFAD VI 1006-0021

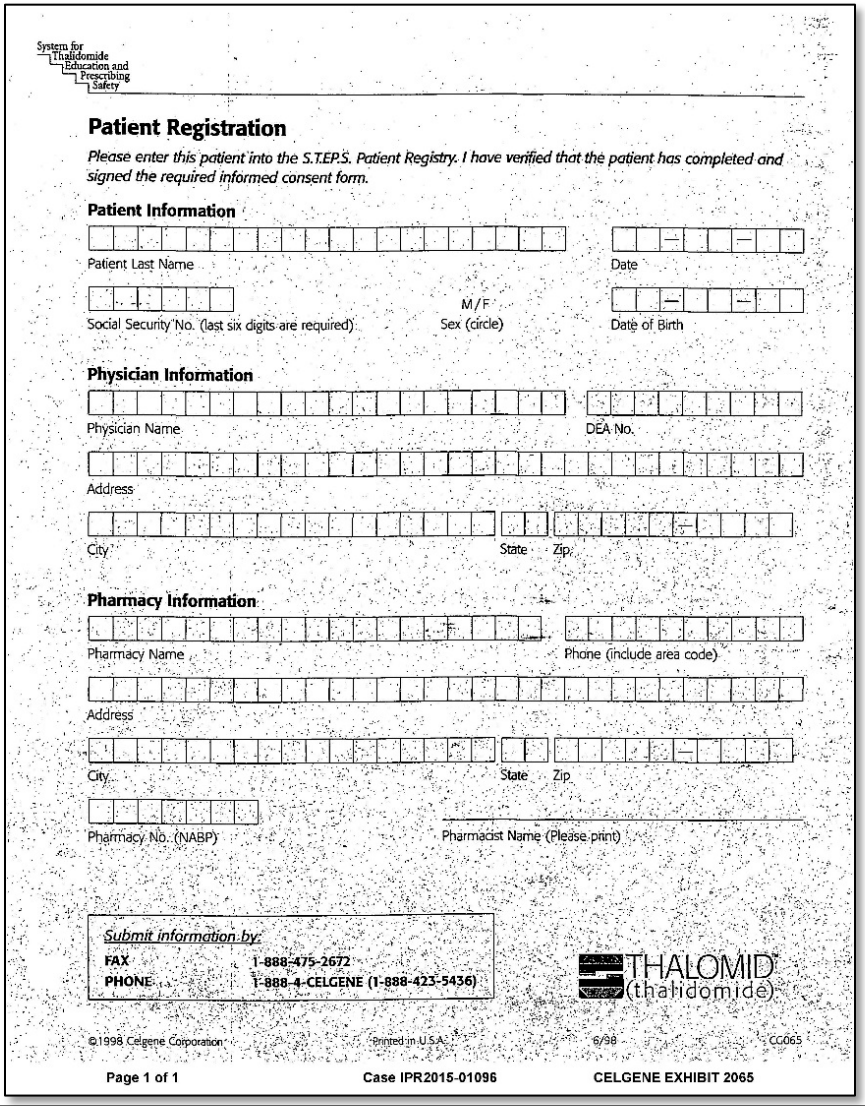
I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed. In addition, I will comply with all of my obligations and responsibilities as a prescriber registered under the S.T.E.P.S. restricted distribution program.

Physician Name (please print) DEA No.

Physician Signature Date (mo./day/yr.)

S.T.E.P.S. Materials



System for Thalidomide Education and Prescribing Safety

Patient Registration

Please enter this patient into the S.T.E.P.S. Patient Registry. I have verified that the patient has completed and signed the required informed consent form.

Patient Information

Patient Last Name

Date

Social Security No. (last six digits are required)

M/F
Sex (circle)

Date of Birth

Physician Information

Physician Name

DEA No.

Address

City

State

Zip

Pharmacy Information

Pharmacy Name

Phone (include area code)

Address

City

State

Zip

Pharmacy No. (NABP)

Pharmacist Name (Please print)

Submit information by:

FAX 1-888-475-2672

PHONE 1-888-4-CELGENE (1-888-423-5436)

THALOMID® (thalidomide)

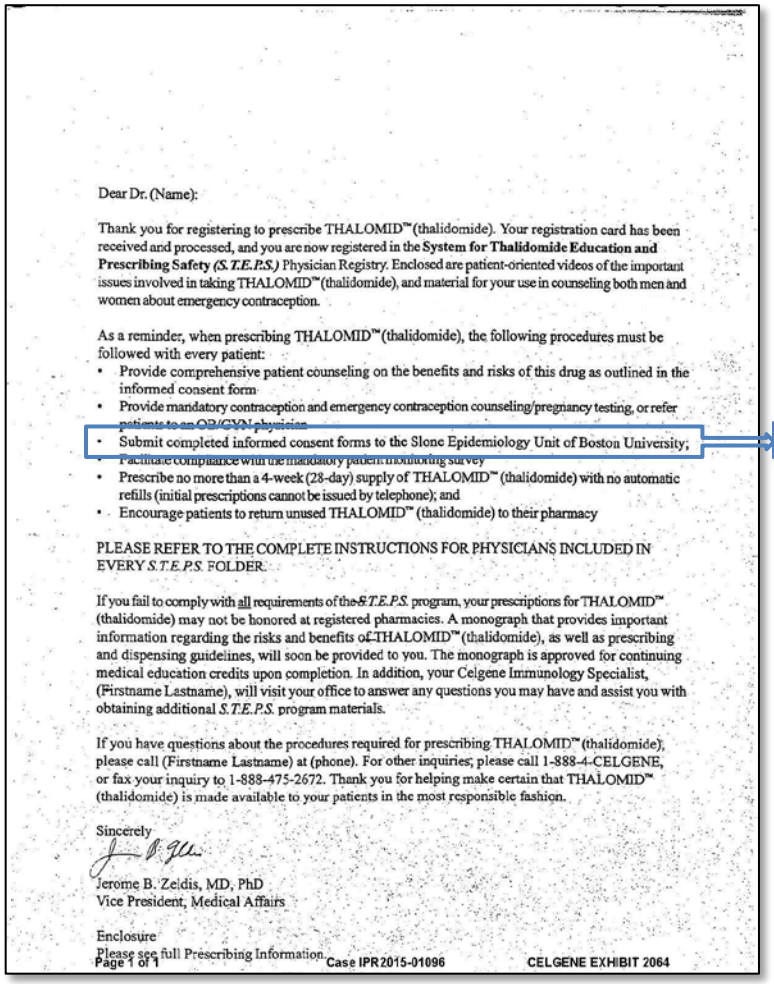
Printed in U.S.A. 6/98 CG065

Page 1 of 1 Case IPR2015-01096 CELGENE EXHIBIT 2065

Source: Ex. 2065 (-01096); Paper 52 (-01096), Reply, at 23-24.

PRIOR ART

S.T.E.P.S. Materials



Dear Dr. (Name):

Thank you for registering to prescribe THALOMID™ (thalidomide). Your registration card has been received and processed, and you are now registered in the **System for Thalidomide Education and Prescribing Safety** ***(S.T.E.P.S.)*** Physician Registry. Enclosed are patient-oriented videos of the important issues involved in taking THALOMID™ (thalidomide), and material for your use in counseling both men and women about emergency contraception.

As a reminder, when prescribing THALOMID™ (thalidomide), the following procedures must be followed with every patient:

- Provide comprehensive patient counseling on the benefits and risks of this drug as outlined in the informed consent form
- Provide mandatory contraception and emergency contraception counseling/pregnancy testing, or refer patients to an OB/GYN physician
- Submit completed informed consent forms to the Slone Epidemiology Unit of Boston University;
- Facilitate compliance with the mandatory patient monitoring survey
- Prescribe no more than a 4-week (28-day) supply of THALOMID™ (thalidomide) with no automatic refills (initial prescriptions cannot be issued by telephone); and
- Encourage patients to return unused THALOMID™ (thalidomide) to their pharmacy

PLEASE REFER TO THE COMPLETE INSTRUCTIONS FOR PHYSICIANS INCLUDED IN EVERY *S.T.E.P.S.* FOLDER.

If you fail to comply with all requirements of the *S.T.E.P.S.* program, your prescriptions for THALOMID™ (thalidomide) may not be honored at registered pharmacies. A monograph that provides important information regarding the risks and benefits of THALOMID™ (thalidomide), as well as prescribing and dispensing guidelines, will soon be provided to you. The monograph is approved for continuing medical education credits upon completion. In addition, your Celgene Immunology Specialist, (Firstname Lastname), will visit your office to answer any questions you may have and assist you with obtaining additional *S.T.E.P.S.* program materials.

If you have questions about the procedures required for prescribing THALOMID™ (thalidomide), please call (Firstname Lastname) at (phone). For other inquiries, please call 1-888-4-CELGENE, or fax your inquiry to 1-888-475-2672. Thank you for helping make certain that THALOMID™ (thalidomide) is made available to your patients in the most responsible fashion.

Sincerely

Jerome B. Zeldis, MD, PhD
Vice President, Medical Affairs

Enclosure
Please see full Prescribing Information.

Page 1 of 1 Case IPR2015-01096 CELGENE EXHIBIT 2064

- Submit completed informed consent forms to the Slone Epidemiology Unit of Boston University;

Source: Ex. 2064 (-01096); Paper 52 (-01096), Reply, at 23-24.

PRIOR ART

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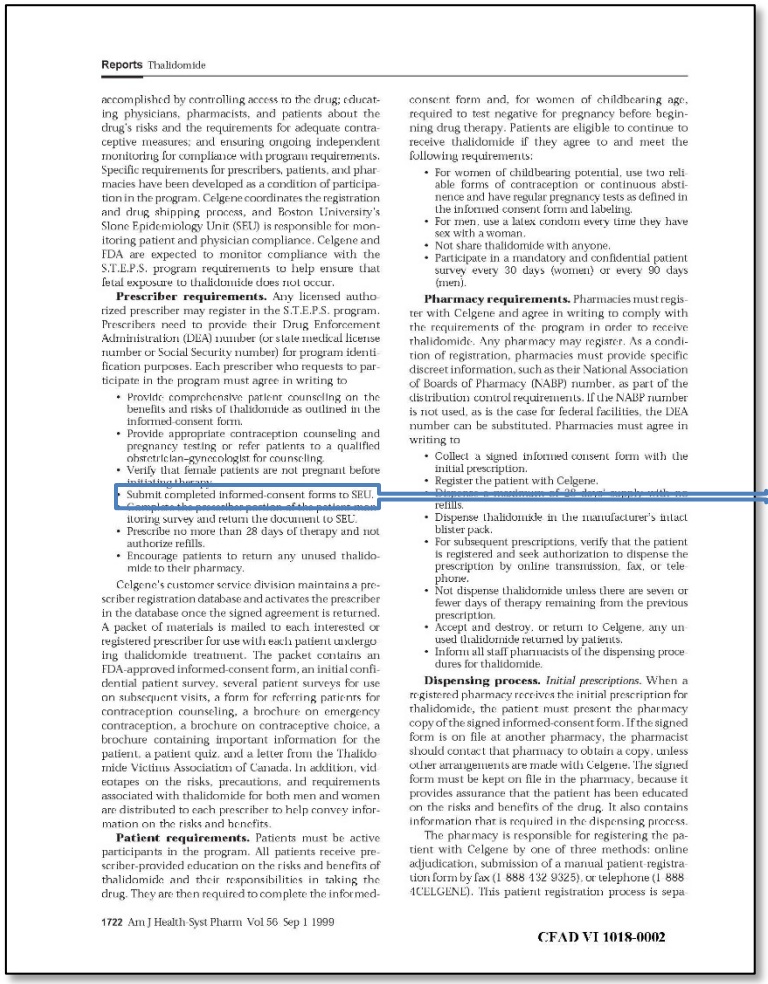

Reports Thalidomide

accomplished by controlling access to the drug; educating physicians, pharmacists, and patients about the drug's risks and the requirements for adequate contraceptive measures; and ensuring ongoing independent monitoring for compliance with program requirements. Specific requirements for prescribers, patients, and pharmacies have been developed as a condition of participation in the program. Celgene coordinates the registration and drug shipping process, and Boston University's Slone Epidemiology Unit (SEU) is responsible for monitoring patient and physician compliance. Celgene and FDA are expected to monitor compliance with the S.T.E.P.S. program requirements to help ensure that fetal exposure to thalidomide does not occur.

Prescriber requirements. Any licensed authorized prescriber may register in the S.T.E.P.S. program. Prescribers need to provide their Drug Enforcement Administration (DEA) number (or state medical license number or Social Security number) for program identification purposes. Each prescriber who requests to participate in the program must agree in writing to

- Provide comprehensive patient counseling on the benefits and risks of thalidomide as outlined in the informed-consent form.
- Provide appropriate contraception counseling and pregnancy testing or refer patients to a qualified obstetrician–gynecologist for counseling.
- Verify that female patients are not pregnant before initiating therapy.
- Submit completed informed-consent forms to SEU. Complete the prescriber portion of the patient monitoring survey and return the document to SEU.
- Prescribe no more than 28 days of therapy and not authorize refills.
- Encourage patients to return any unused thalidomide to their pharmacy.

Celgene's customer service division maintains a prescriber registration database and activates the prescriber in the database once the signed agreement is returned. A packet of materials is mailed to each interested or registered prescriber for use with each patient undergoing thalidomide treatment. The packet contains an FDA-approved informed-consent form, an initial confidential patient survey, several patient surveys for use on subsequent visits, a form for referring patients for contraception counseling, a brochure on emergency contraception, a brochure on contraceptive choice, a brochure containing important information for the patient, a patient quiz, and a letter from the Thalidomide Victims Association of Canada. In addition, videotapes on the risks, precautions, and requirements associated with thalidomide for both men and women are distributed to each prescriber to help convey information on the risks and benefits.

Patient requirements. Patients must be active participants in the program. All patients receive prescriber-provided education on the risks and benefits of thalidomide and their responsibilities in taking the drug. They are then required to complete the informed-consent form and, for women of childbearing age, required to test negative for pregnancy before beginning drug therapy. Patients are eligible to continue to receive thalidomide if they agree to and meet the following requirements:

- For women of childbearing potential, use two reliable forms of contraception or continuous abstinence and have regular pregnancy tests as defined in the informed consent form and labeling.
- For men, use a latex condom every time they have sex with a woman.
- Not share thalidomide with anyone.
- Participate in a mandatory and confidential patient survey every 30 days (women) or every 90 days (men).

Pharmacy requirements. Pharmacies must register with Celgene and agree in writing to comply with the requirements of the program in order to receive thalidomide. Any pharmacy may register. As a condition of registration, pharmacies must provide specific discreet information, such as their National Association of Boards of Pharmacy (NABP) number, as part of the distribution control requirements. If the NABP number is not used, as is the case for federal facilities, the DEA number can be substituted. Pharmacies must agree in writing to

- Collect a signed informed consent form with the initial prescription.
- Register the patient with Celgene.
- Dispense a maximum of 28 days' supply with no refills.
- Dispense thalidomide in the manufacturer's intact blister pack.
- For subsequent prescriptions, verify that the patient is registered and seek authorization to dispense the prescription by online transmission, fax, or telephone.
- Not dispense thalidomide unless there are seven or fewer days of therapy remaining from the previous prescription.
- Accept and destroy, or return to Celgene, any unused thalidomide returned by patients.
- Inform all staff pharmacists of the dispensing procedures for thalidomide.

Dispensing process. *Initial prescriptions.* When a registered pharmacy receives the initial prescription for thalidomide, the patient must present the pharmacy copy of the signed informed-consent form. If the signed form is on file at another pharmacy, the pharmacist should contact that pharmacy to obtain a copy, unless other arrangements are made with Celgene. The signed form must be kept on file in the pharmacy, because it provides assurance that the patient has been educated on the risks and benefits of the drug. It also contains information that is required in the dispensing process.

The pharmacy is responsible for registering the patient with Celgene by one of three methods: online adjudication, submission of a manual patient registration form by fax (1 888 132 9325), or telephone (1 888 4CELGENE). This patient registration process is sepa-

1722 Am J Health-Syst Pharm Vol 56 Sep 1 1999

CFAD VI 1018-0002

- Submit completed informed-consent forms to SEU.

Source: Ex. 1018 (-01096); Paper 52 (-01096), Reply, at 23-24.

The Institution Decision - 01096

risk is acceptable, and controlling dispensation of the drug using an approval code) for their known purpose (control distribution of drug) to achieve a predictable result (avoid giving patients drugs that have an unacceptable risk of side effects).

Patent Owner contends that Thalomid PI does not disclose defining a set of information to be obtained from a patient, where the information is probative of risk of the adverse side effect. Prelim. Resp. 24–25. Patent Owner states that Celgene did not introduce a system to conduct a prospective risk analysis until after the '720 patent had been filed. *Id.* We disagree. Thalomid PI provides specific guideline on the information that is probative of the risk associated with taking thalidomide. Dr. Fudin testifies that one skilled in the art would recognize that Thalomid PI warns patients that serious birth defects can occur if taken during pregnancy, and that this defines a set of information to be obtained, namely, information related to pregnancy. Ex. 1021 ¶¶ 86–87. Further, Thalomid PI teaches that a patient survey is required prior to dispensing the product. Ex. 1006, 19. Based on the record presented, we credit Dr. Fudin's testimony and conclude that one skilled in the art seeking to dispense thalidomide would have defined a set of information, such as potential pregnancy, to be obtained from a patient that is probative of the risk of an adverse side effect, birth defects.

Patent Owner contends that Thalomid PI fails to disclose assigning patients to risk groups and entering the risk group assignment into a computer database. Prelim. Resp. 25–28. We disagree. The challenged claims are written in a Jepson format, where the admitted prior art recites filling prescriptions only after consulting a computer readable storage medium. Prior art Thalomid PI identifies different risk groups, including

survey is required prior to dispensing the product. Ex. 1006, 19. Based on the record presented, we credit Dr. Fudin's testimony and conclude that one skilled in the art seeking to dispense thalidomide would have defined a set of information, such as potential pregnancy, to be obtained from a patient that is probative of the risk of an adverse side effect, birth defects.

Source: Paper 21 (-01096), Institution Decision, at 17.

The Institution Decision - 01096

women of childbearing potential and sexually mature males. Ex. 1006, 3–4. The set of conditions for thalidomide treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention, computers were used by physicians and pharmacists to enter and track patient information for harmful and teratogenic drug prescriptions. Ex. 1021 ¶ 91. Dr. Fudin also testifies that one of ordinary skill in the art would have understood that patient risk group assignment would have been entered into a computer database before prescribing and filling prescriptions for thalidomide. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

Patent Owner contends that Thalomid PI does not disclose determining whether the risk that an adverse side effect is likely to occur is acceptable. Prelim. Resp. 28. We disagree. Thalomid PI states that a prescription for thalidomide for a woman of childbearing potential must not be issued until a written report of a negative pregnancy test has been obtained by the prescriber. Ex. 1006, 2. Accordingly, we find that Thalomid PI discloses determining that the risk is unacceptable for a positive pregnancy test.

Patent Owner contends that Thalomid PI does not describe generating an approval code. Prelim. Resp. 28–29. Patent Owner further contends that Petitioner has failed to provide a rationale to combine Thalomid PI and

thalidomide. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

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computer. According to Patent Owner, the cited prior art fails to disclose how, when, or by whom the informed consent and risk assignment would be verified. *Id.* at 48–49. Dr. Fudin testifies that one of ordinary skill in the art would have reason to have the prescriber verify both risk group assignment and informed consent at the time of computer entry to eliminate error and delay. Ex. 1021 ¶ 220. Based upon the evidence of record, we credit Dr. Fudin's testimony and hold that one skilled in the art seeking to reduce errors would have reason to enter the informed consent and risk assignment into a computer database at the same time.

Patent Owner also contends that Petitioner has failed to demonstrate that the use of a telephone survey using an integrated voice response system, such as recited in claim 17, would have been obvious to one skilled in the art. Prelim. Resp. 49–50. Petitioner contends that conducting telephone surveys was well known in the art. Pet. 59. Petitioner relies upon the teachings of Mundt, which states that use of interactive voice response systems can strengthen clinical practice, extend research methods, and enhance administrative support of service quality and value. *Id.* (citing Ex. 1024, 612). We hold that the evidence of record demonstrates that one skilled in the art had reason to use interactive voice response systems to conduct patient surveys.

a. Secondary Considerations

Patent Owner contends that secondary consideration evidence demonstrates that the challenged claims are nonobvious over the relied upon prior art. Prelim. Resp. 49–55. We have reviewed the alleged secondary consideration evidence, but are not persuaded that it is sufficient to show

verified. *Id.* at 48–49. Dr. Fudin testifies that one of ordinary skill in the art would have reason to have the prescriber verify both risk group assignment and informed consent at the time of computer entry to eliminate error and delay. Ex. 1021 ¶ 220. Based upon the evidence of record, we credit Dr. Fudin's testimony and hold that one skilled in the art seeking to reduce errors would have reason to enter the informed consent and risk assignment into a computer database at the same time.

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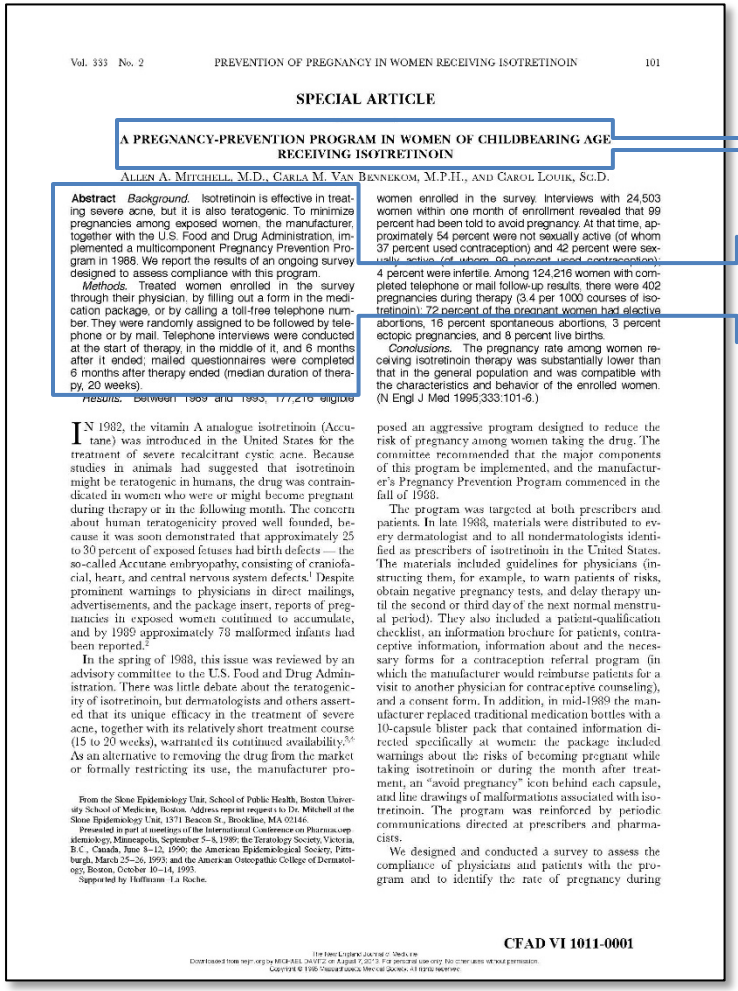

Vol. 333 No. 2 PREVENTION OF PREGNANCY IN WOMEN RECEIVING ISOTRETINOIN 101

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Methods. Treated women enrolled in the survey through their physician, by filling out a form in the medication package, or by calling a toll-free telephone number. They were randomly assigned to be followed by telephone or by mail. Telephone interviews were conducted at the start of therapy, in the middle of it, and 6 months after it ended; mailed questionnaires were completed 6 months after therapy ended (median duration of therapy, 20 weeks).

Results. Between 1989 and 1993, 177,216 eligible women enrolled in the survey. Interviews with 24,503 women within one month of enrollment revealed that 99 percent had been told to avoid pregnancy. At that time, approximately 54 percent were not sexually active (of whom 37 percent used contraception) and 42 percent were sexually active (of whom 99 percent used contraception); 4 percent were infertile. Among 124,216 women with completed telephone or mail follow-up results, there were 402 pregnancies during therapy (3.4 per 1000 courses of isotretinoin); 72 percent of the pregnant women had elective abortions, 16 percent spontaneous abortions, 3 percent ectopic pregnancies, and 8 percent live births.

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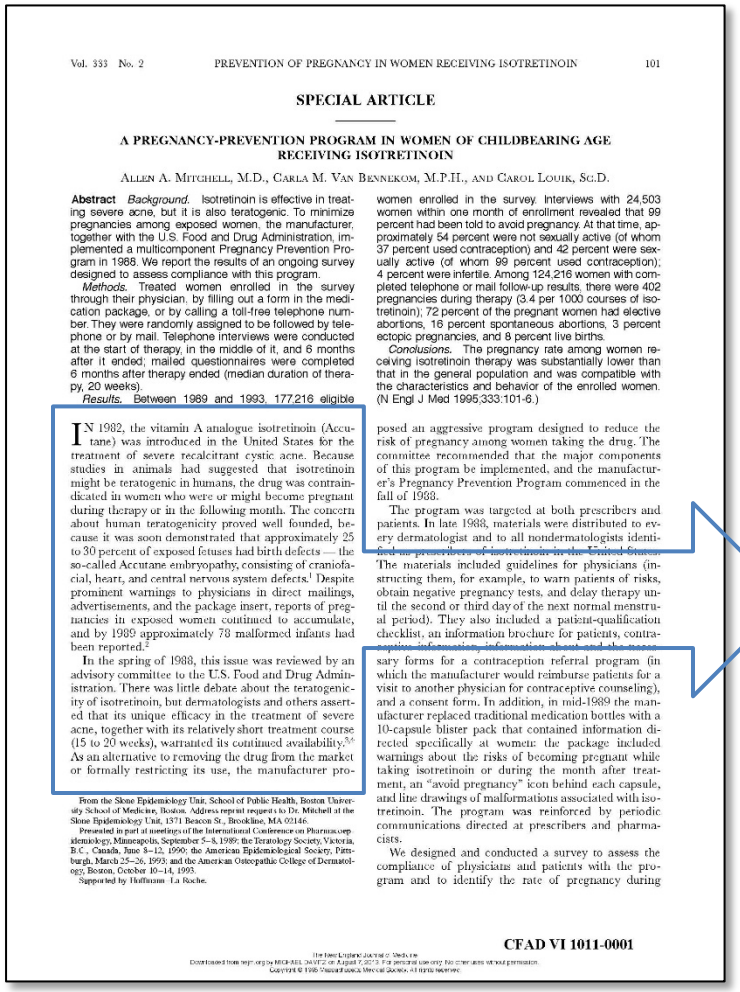

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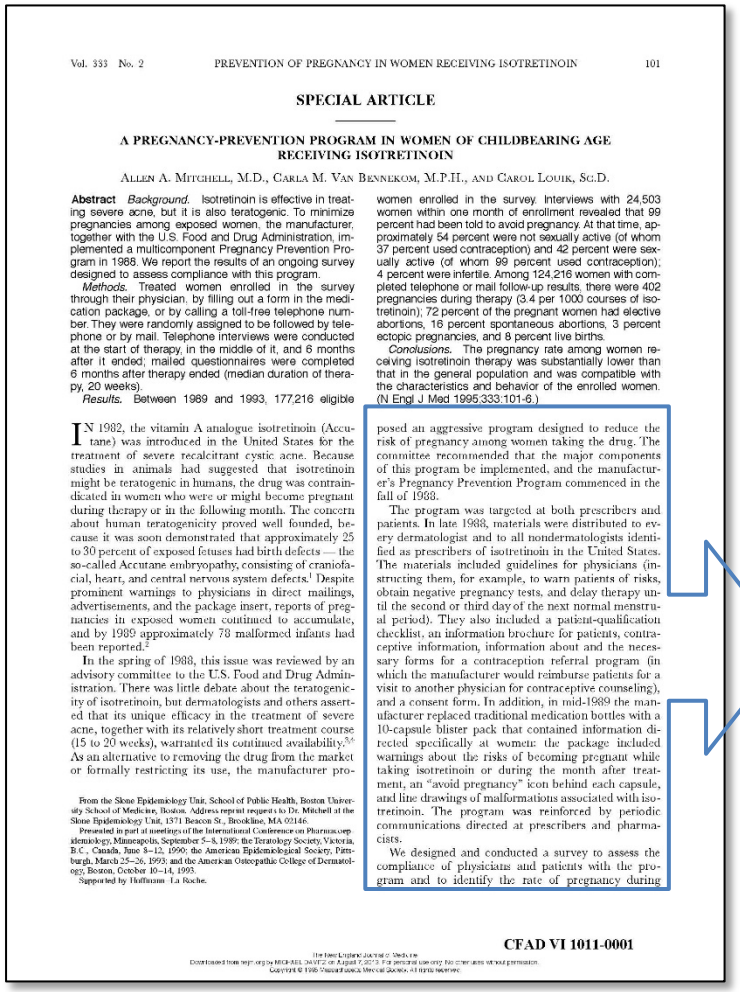

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Source: Paper 1 (-01103), Petition, at 26, 46, 49-50, 54-55, 58-59; Ex. 1010 (-01103) at 101.

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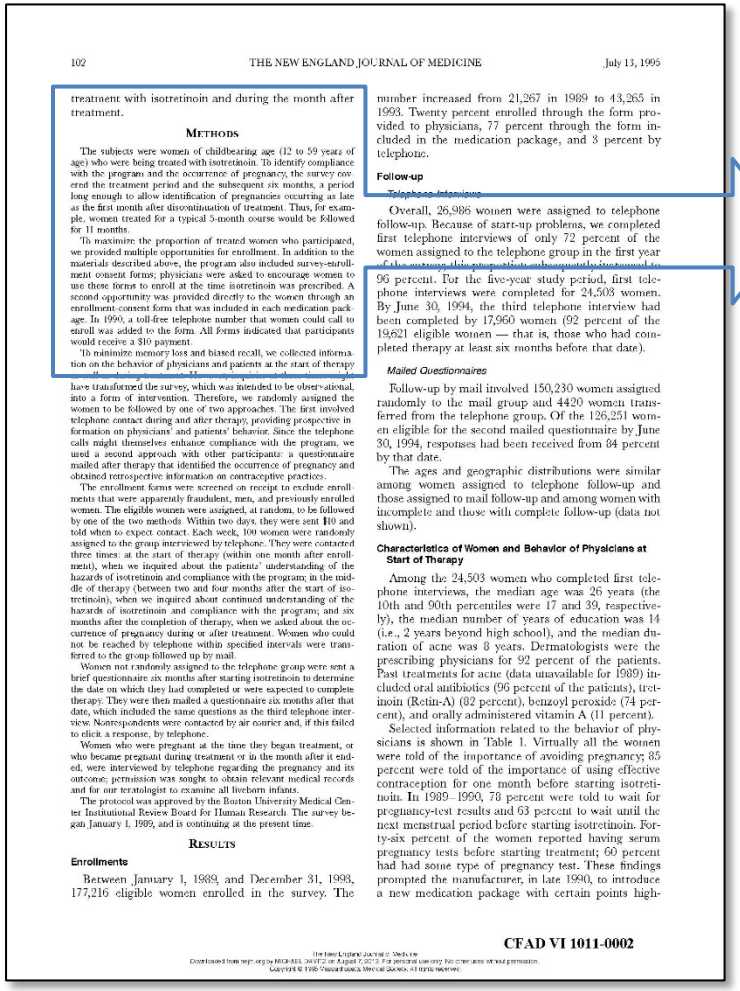

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The subjects were women of childbearing age (12 to 59 years of age) who were being treated with isotretinoin. To identify compliance with the program and the occurrence of pregnancy, the survey covered the treatment period and the subsequent six months, a period long enough to allow identification of pregnancies occurring as late as the first month after discontinuation of treatment. Thus, for example, women treated for a typical 5-month course would be followed for 11 months.

To maximize the proportion of treated women who participated, we provided multiple opportunities for enrollment. In addition to the materials described above, the program also included survey-enrollment consent forms; physicians were asked to encourage women to use these forms to enroll at the time isotretinoin was prescribed. A second opportunity was provided directly to the women through an enrollment-consent form that was included in each medication package. In 1990, a toll-free telephone number that women could call to enroll was added to the form. All forms indicated that participants would receive a $10 payment.

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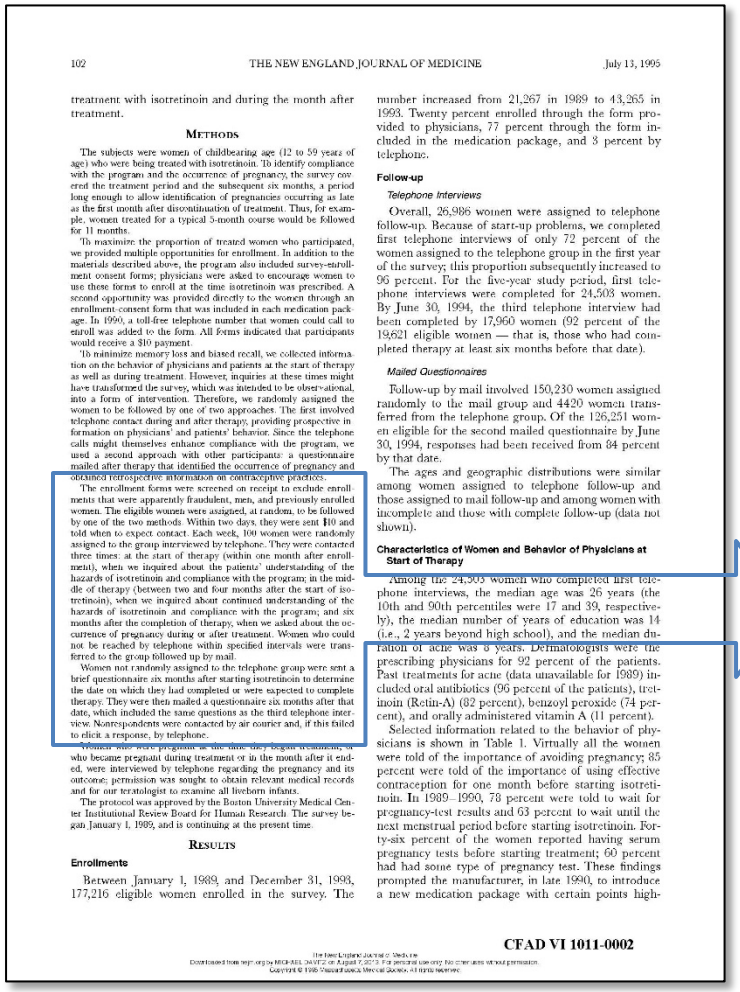

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To minimize memory loss and biased recall, we collected information on the behavior of physicians and patients at the start of therapy as well as during treatment. However, inquiries at these times might have transformed the survey, which was intended to be observational, into a form of intervention. Therefore, we randomly assigned the women to be followed by one of two approaches. The first involved telephone contact during and after therapy, providing prospective information on physicians' and patients' behavior. Since the telephone calls might themselves enhance compliance with the program, we used a second approach with other participants: a questionnaire mailed after therapy that identified the occurrence of pregnancy and obtained retrospective information on contraceptive practices.

The enrollment forms were screened on receipt to exclude enrollments that were apparently fraudulent, men, and previously enrolled women. The eligible women were assigned, at random, to be followed by one of the two methods. Within two days, they were sent $10 and told when to expect contact. Each week, 100 women were randomly assigned to the group interviewed by telephone. They were contacted three times: at the start of therapy (within one month after enrollment), when we inquired about the patients' understanding of the hazards of isotretinoin and compliance with the program; in the middle of therapy (between two and four months after the start of isotretinoin), when we inquired about continued understanding of the hazards of isotretinoin and compliance with the program; and six months after the completion of therapy, when we asked about the occurrence of pregnancy during or after treatment. Women who could not be reached by telephone within specified intervals were transferred to the group followed up by mail.

Women not randomly assigned to the telephone group were sent a brief questionnaire six months after starting isotretinoin to determine the date on which they had completed or were expected to complete therapy. They were then mailed a questionnaire six months after that date, which included the same questions as the third telephone interview. Nonrespondents were contacted by air courier and, if this failed to elicit a response, by telephone.

Women who were pregnant at the time they began treatment, or who became pregnant during treatment or in the month after it ended, were interviewed by telephone regarding the pregnancy and its outcome; permission was sought to obtain relevant medical records and for our teratologist to examine all liveborn infants.

The protocol was approved by the Boston University Medical Center Institutional Review Board for Human Research. The survey began January 1, 1989, and is continuing at the present time.

RESULTS

Enrollments

Between January 1, 1989, and December 31, 1993, 177,216 eligible women enrolled in the survey. The number increased from 21,267 in 1989 to 43,265 in 1993. Twenty percent enrolled through the form provided to physicians, 77 percent through the form included in the medication package, and 3 percent by telephone.

Follow-up

Telephone Interviews

Overall, 26,986 women were assigned to telephone follow-up. Because of start-up problems, we completed first telephone interviews of only 72 percent of the women assigned to the telephone group in the first year of the survey; this proportion subsequently increased to 96 percent. For the five-year study period, first telephone interviews were completed for 24,503 women. By June 30, 1994, the third telephone interview had been completed by 17,960 women (92 percent of the 19,621 eligible women — that is, those who had completed therapy at least six months before that date).

Mailed Questionnaires

Follow-up by mail involved 150,230 women assigned randomly to the mail group and 4420 women transferred from the telephone group. Of the 126,251 women eligible for the second mailed questionnaire by June 30, 1994, responses had been received from 84 percent by that date.

The ages and geographic distributions were similar among women assigned to telephone follow-up and those assigned to mail follow-up and among women with incomplete and those with complete follow-up (data not shown).

Characteristics of Women and Behavior of Physicians at Start of Therapy

Among the 24,503 women who completed first telephone interviews, the median age was 26 years (the 10th and 90th percentiles were 17 and 39, respectively), the median number of years of education was 14 (i.e., 2 years beyond high school), and the median duration of acne was 3 years. Dermatologists were the prescribing physicians for 92 percent of the patients. Past treatments for acne (data unavailable for 1989) included oral antibiotics (96 percent of the patients), tretinoin (Retin-A) (82 percent), benzoyl peroxide (74 percent), and orally administered vitamin A (11 percent).

Selected information related to the behavior of physicians is shown in Table 1. Virtually all the women were told of the importance of avoiding pregnancy; 85 percent were told of the importance of using effective contraception for one month before starting isotretinoin. In 1989–1990, 78 percent were told to wait for pregnancy-test results and 63 percent to wait until the next menstrual period before starting isotretinoin. Forty-six percent of the women reported having serum pregnancy tests before starting treatment; 60 percent had had some type of pregnancy test. These findings prompted the manufacturer, in late 1990, to introduce a new medication package with certain points high-

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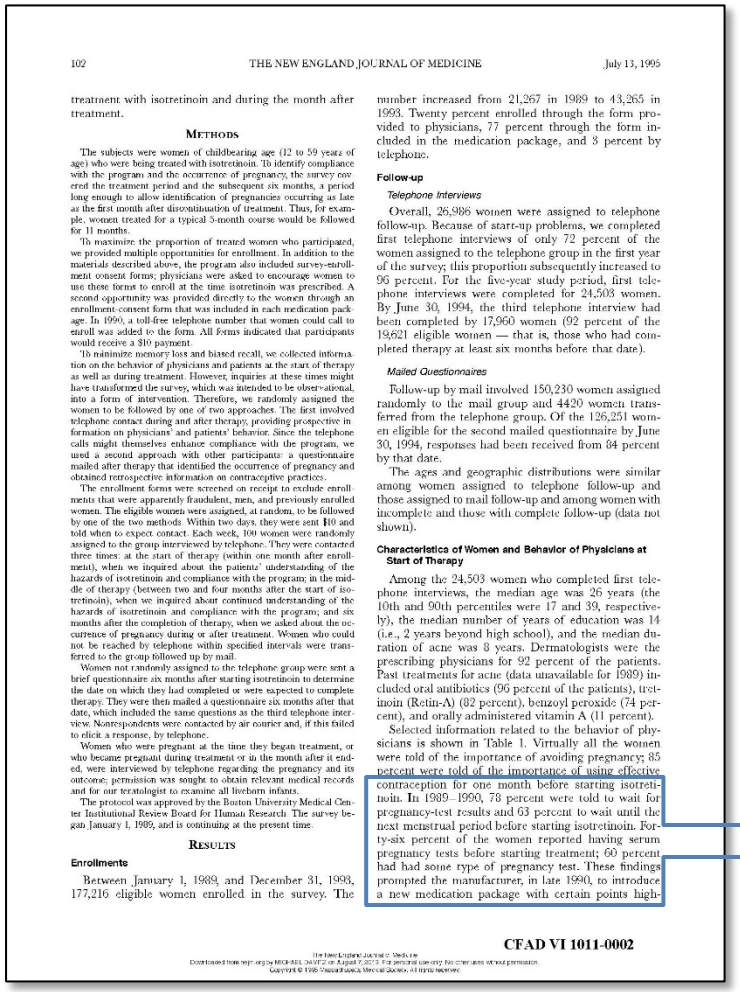
Women not randomly assigned to the telephone group were sent a brief questionnaire six months after starting isotretinoin to determine the date on which they had completed or were expected to complete therapy. They were then mailed a questionnaire six months after that date, which included the same questions as the third telephone interview. Nonrespondents were contacted by air courier and, if this failed to elicit a response, by telephone.

PRIOR ART

Mitchell



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treatment with isotretinoin and during the month after treatment.

METHODS

The subjects were women of childbearing age (12 to 59 years of age) who were being treated with isotretinoin. To identify compliance with the program and the occurrence of pregnancy, the survey covered the treatment period and the subsequent six months, a period long enough to allow identification of pregnancies occurring as late as the first month after discontinuation of treatment. Thus, for example, women treated for a typical 5-month course would be followed for 11 months.

To maximize the proportion of treated women who participated, we provided multiple opportunities for enrollment. In addition to the materials described above, the program also included survey-enrollment consent forms; physicians were asked to encourage women to use these forms to enroll at the time isotretinoin was prescribed. A second opportunity was provided directly to the women through an enrollment-consent form that was included in each medication package. In 1990, a toll-free telephone number that women could call to enroll was added to the form. All forms indicated that participants would receive a $10 payment.

To minimize memory loss and biased recall, we collected information on the behavior of physicians and patients at the start of therapy as well as during treatment. However, inquiries at these times might have transformed the survey, which was intended to be observational, into a form of intervention. Therefore, we randomly assigned the women to be followed by one of two approaches. The first involved telephone contact during and after therapy, providing prospective information on physicians' and patients' behavior. Since the telephone calls might themselves enhance compliance with the program, we used a second approach with other participants: a questionnaire mailed after therapy that identified the occurrence of pregnancy and obtained retrospective information on contraceptive practices.

The enrollment forms were screened on receipt to exclude enrollments that were apparently fraudulent, men, and previously enrolled women. The eligible women were assigned, at random, to be followed by one of the two methods. Within two days, they were sent $10 and told when to expect contact. Each week, 100 women were randomly assigned to the group interviewed by telephone. They were contacted three times: at the start of therapy (within one month after enrollment), when we inquired about the patients' understanding of the hazards of isotretinoin and compliance with the program; in the middle of therapy (between two and four months after the start of isotretinoin), when we inquired about continued understanding of the hazards of isotretinoin and compliance with the program; and six months after the completion of therapy, when we asked about the occurrence of pregnancy during or after treatment. Women who could not be reached by telephone within specified intervals were transferred to the group followed up by mail.

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Women who were pregnant at the time they began treatment, or who became pregnant during treatment or in the month after it ended, were interviewed by telephone regarding the pregnancy and its outcome; permission was sought to obtain relevant medical records and for our teratologist to examine all liveborn infants.

The protocol was approved by the Boston University Medical Center Institutional Review Board for Human Research. The survey began January 1, 1989, and is continuing at the present time.

RESULTS

Enrollments

Between January 1, 1989, and December 31, 1993, 177,216 eligible women enrolled in the survey. The number increased from 21,267 in 1989 to 43,265 in 1993. Twenty percent enrolled through the form provided to physicians, 77 percent through the form included in the medication package, and 3 percent by telephone.

Follow-up

Telephone Interviews

Overall, 26,986 women were assigned to telephone follow-up. Because of start-up problems, we completed first telephone interviews of only 72 percent of the women assigned to the telephone group in the first year of the survey; this proportion subsequently increased to 96 percent. For the five-year study period, first telephone interviews were completed for 24,503 women. By June 30, 1994, the third telephone interview had been completed by 17,960 women (92 percent of the 19,621 eligible women — that is, those who had completed therapy at least six months before that date).

Mailed Questionnaires

Follow-up by mail involved 150,230 women assigned randomly to the mail group and 4420 women transferred from the telephone group. Of the 126,251 women eligible for the second mailed questionnaire by June 30, 1994, responses had been received from 84 percent by that date.

The ages and geographic distributions were similar among women assigned to telephone follow-up and those assigned to mail follow-up and among women with incomplete and those with complete follow-up (data not shown).

Characteristics of Women and Behavior of Physicians at Start of Therapy

Among the 24,503 women who completed first telephone interviews, the median age was 26 years (the 10th and 90th percentiles were 17 and 39, respectively), the median number of years of education was 14 (i.e., 2 years beyond high school), and the median duration of acne was 8 years. Dermatologists were the prescribing physicians for 92 percent of the patients. Past treatments for acne (data unavailable for 1989) included oral antibiotics (96 percent of the patients), tretinoin (Retin-A) (82 percent), benzoyl peroxide (74 percent), and orally administered vitamin A (11 percent).

Selected information related to the behavior of physicians is shown in Table 1. Virtually all the women were told of the importance of avoiding pregnancy; 85 percent were told of the importance of using effective contraception for one month before starting isotretinoin. In 1989–1990, 78 percent were told to wait for pregnancy-test results and 63 percent to wait until the next menstrual period before starting isotretinoin. Forty-six percent of the women reported having serum pregnancy tests before starting treatment; 60 percent had had some type of pregnancy test. These findings prompted the manufacturer, in late 1990, to introduce a new medication package with certain points high-

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Source: Paper 1 (-01103), Petition, at 39, 51, 58-59; Ex. 1010 (-01103) at 102.

PRIOR ART

Mitchell

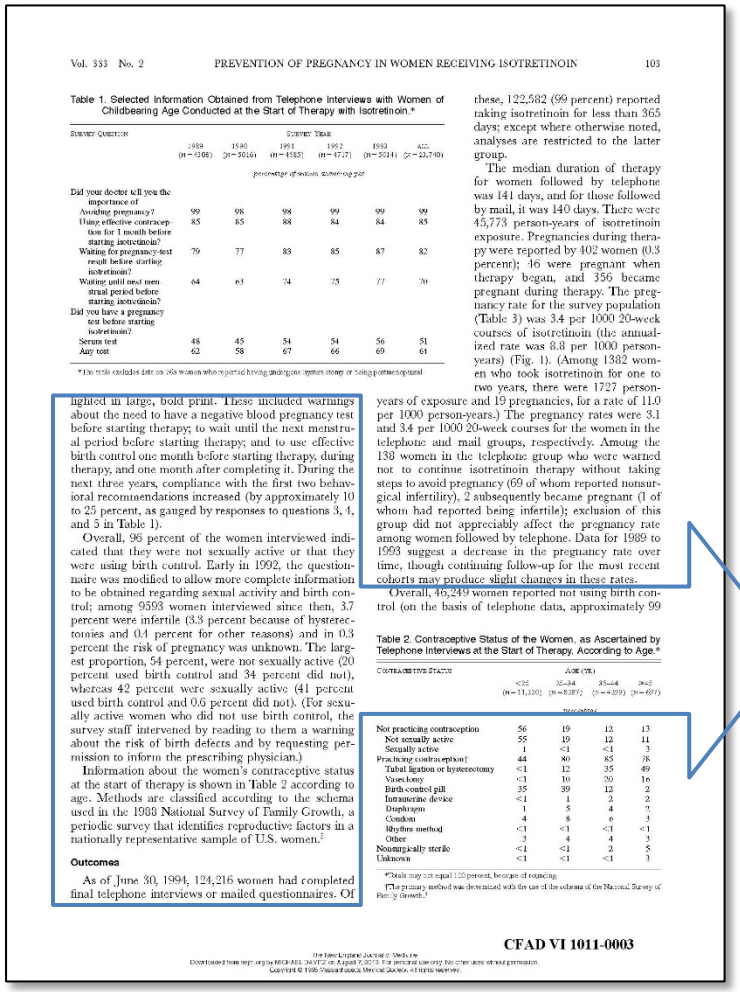

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Table 1. Selected Information Obtained from Telephone Interviews with Women of Childbearing Age Conducted at the Start of Therapy with Isotretinoin.*

Survey Question	Survey Year					
	1989 (n = 4208)	1990 (n = 5016)	1991 (n = 4585)	1992 (n = 4717)	1993 (n = 5014)	All (n = 23,740)
	percentage of women answering yes					
Did your doctor tell you the importance of						
Avoiding pregnancy?	99	98	98	99	99	99
Using effective contraception for 1 month before starting isotretinoin?	85	85	88	84	84	85
Waiting for pregnancy-test result before starting isotretinoin?	79	77	83	85	87	82
Waiting until next menstrual period before starting isotretinoin?	64	65	74	75	77	70
Did you have a pregnancy test before starting isotretinoin?						
Serum test	48	45	54	54	56	51
Any test	62	58	67	66	69	61

*The table excludes data on 368 women who reported having undergone hysterectomy or tubing postmenopausal.

lighted in large, bold print. These included warnings about the need to have a negative blood pregnancy test before starting therapy; to wait until the next menstrual period before starting therapy; and to use effective birth control one month before starting therapy, during therapy, and one month after completing it. During the next three years, compliance with the first two behavioral recommendations increased (by approximately 10 to 25 percent, as gauged by responses to questions 3, 4, and 5 in Table 1).

Overall, 96 percent of the women interviewed indicated that they were not sexually active or that they were using birth control. Early in 1992, the questionnaire was modified to allow more complete information to be obtained regarding sexual activity and birth control; among 9593 women interviewed since then, 3.7 percent were infertile (3.3 percent because of hysterectomies and 0.4 percent for other reasons) and in 0.3 percent the risk of pregnancy was unknown. The largest proportion, 54 percent, were not sexually active (20 percent used birth control and 34 percent did not), whereas 42 percent were sexually active (41 percent used birth control and 0.6 percent did not). (For sexually active women who did not use birth control, the survey staff intervened by reading to them a warning about the risk of birth defects and by requesting permission to inform the prescribing physician.)

Information about the women's contraceptive status at the start of therapy is shown in Table 2 according to age. Methods are classified according to the schema used in the 1988 National Survey of Family Growth, a periodic survey that identifies reproductive factors in a nationally representative sample of U.S. women.[5]

Outcomes

As of June 30, 1994, 124,216 women had completed final telephone interviews or mailed questionnaires. Of

these, 122,582 (99 percent) reported taking isotretinoin for less than 365 days; except where otherwise noted, analyses are restricted to the latter group.

The median duration of therapy for women followed by telephone was 141 days, and for those followed by mail, it was 140 days. There were 45,773 person-years of isotretinoin exposure. Pregnancies during therapy were reported by 402 women (0.3 percent); 46 were pregnant when therapy began, and 356 became pregnant during therapy. The pregnancy rate for the survey population (Table 3) was 3.4 per 1000 20-week courses of isotretinoin (the annualized rate was 8.8 per 1000 person-years) (Fig. 1). (Among 1382 women who took isotretinoin for one to two years, there were 1727 person-years of exposure and 19 pregnancies, for a rate of 11.0 per 1000 person-years.) The pregnancy rates were 3.1 and 3.4 per 1000 20-week courses for the women in the telephone and mail groups, respectively. Among the 138 women in the telephone group who were warned not to continue isotretinoin therapy without taking steps to avoid pregnancy (69 of whom reported nonsurgical infertility), 2 subsequently became pregnant (1 of whom had reported being infertile); exclusion of this group did not appreciably affect the pregnancy rate among women followed by telephone. Data for 1989 to 1993 suggest a decrease in the pregnancy rate over time, though continuing follow-up for the most recent cohorts may produce slight changes in these rates.

Overall, 46,249 women reported not using birth control (on the basis of telephone data, approximately 99

Table 2. Contraceptive Status of the Women, as Ascertained by Telephone Interviews at the Start of Therapy, According to Age.*

Contraceptive Status	Age (yr)			
	<25 (n = 11,130)	25–34 (n = 8387)	35–44 (n = 4393)	≥45 (n = 697)
	percentage			
Not practicing contraception	56	19	12	13
Not sexually active	55	19	12	11
Sexually active	1	<1	<1	3
Practicing contraception†	44	80	85	78
Tubal ligation or hysterectomy	<1	12	35	49
Vasectomy	<1	10	20	16
Birth-control pill	35	39	12	2
Intrauterine device	<1	1	2	2
Diaphragm	1	5	4	3
Condom	4	8	6	3
Rhythm method	<1	<1	<1	<1
Other	3	4	4	3
Nonsurgically sterile	<1	<1	2	5
Unknown	<1	<1	<1	3

*Totals may not equal 100 percent, because of rounding.
†The primary method was determined with the use of the schema of the National Survey of Family Growth.[5]

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lighted in large, bold print. These included warnings about the need to have a negative blood pregnancy test before starting therapy; to wait until the next menstrual period before starting therapy; and to use effective birth control one month before starting therapy, during therapy, and one month after completing it. During the next three years, compliance with the first two behavioral recommendations increased (by approximately 10 to 25 percent, as gauged by responses to questions 3, 4, and 5 in Table 1).

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Source: Paper 1 (-01103), Petition, at 15, 29, 34, 37, 39, 40, 42, 51, 55, 58, 59; Ex. 1010 (-01103) at 103.

PRIOR ART

Mitchell

percent were not sexually active at the beginning of therapy or during it). Eighty-eight became pregnant during treatment (1.9 per 1000 20-week courses). In comparison, among the 76,149 women who practiced contraception, 268 became pregnant (3.6 per 1000 20-week courses) (P<0.001).[2] On the basis of the primary contraceptive method being used at the start of treatment (reported in the third telephone interview or the second mailed questionnaire), we estimated method-specific pregnancy rates during therapy. Among women using nonsurgical means of contraception, rates for the most commonly used methods were 3.2 pregnancies per 1000 20-week courses for birth-control pills (39,053 women), 10.3 for condoms (7686 women), and 8.1 for diaphragms (3023 women). The rates among women who had had tubal ligations or whose male partners had had vasectomies were 0.4 (4 of 10,949 women) and 0.3 (2 of 7394 women), respectively.

There were 136 pregnancies that were conceived during the month after discontinuation of therapy, for a rate of 13.4 per 1000 person-years (Fig. 1). Pregnancy rates were also calculated for the next three months, when pregnancy was no longer discouraged by the program; these were 29.0, 37.1, and 43.2 per 1000 person-years, respectively.

Of the 402 women with pregnancies conceived during treatment with isotretinoin, 290 (72 percent) had elective terminations, 63 (16 percent) had spontaneous abortions, 13 (3 percent) had ectopic pregnancies, none had stillbirths, 32 (8 percent) had live births, and in 4 (1 percent) the outcome could not be determined. Among the 136 pregnancies occurring during the month after therapy, a smaller proportion (55 percent) were electively terminated and a larger proportion (28 percent) were carried to term or were continuing at the time of analysis. For pregnancies occurring in the subsequent three months, 23 percent were terminated and 61 percent were carried to term or were continuing.

Among the 32 liveborn infants, 13 had been examined by the survey teratologist by January 1995. Six had no defects, one had major anomalies (ear, eye, craniofacial, and brain), and six had minor anomalies (ear in two, ear and craniofacial in two, and hypoplastic scrotum and confluent eyebrows in one each). The examiner, who knew the exposure status of the mothers, did not consider the latter two defects to be associated with isotretinoin; thus, five infants (38 percent) were judged to have defects compatible with the isotretinoin embryopathy. Birth records available for four additional infants revealed no defects. Parental reports, available for 13 of the remaining 15, identified 1 infant as having cerebral palsy and developmental delay and 1 who died from defects involving the ear, eye, heart, kidney, and liver.

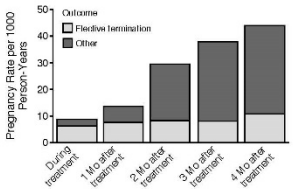

Figure 1. Pregnancy Rates and Outcomes during and after Therapy with Isotretinoin in 122,582 Women, 1989 to 1993.

Discussion

Among women enrolled in this survey, understanding of the teratogenic risks of isotretinoin and of the need to avoid pregnancy was virtually universal. Compliance with other aspects of the program was less complete, although in no case did compliance for any measure decline during the study period. Apart from ensuring that the program understood the risks, perhaps the most important aspect of the program was the recommendations that women ensure that pregnancy tests were negative, that they wait until menses had begun before initiating isotretinoin therapy, and that they use effective birth control preceding, during, and immediately after treatment. Information from the first months of the survey revealed incomplete compliance with these guidelines. As a result, the manufacturer reinforced physician education about these three recommendations and changed the medication package to highlight their importance. Within months after distribution of the new package, compliance with these recommendations, though still incomplete, improved.

Whatever attention is directed to the education and compliance of patients and physicians, the most relevant measure of the effectiveness of efforts to prevent pregnancies is the pregnancy rate. Among U.S. women 15 to 44 years of age, the pregnancy rate is approximately 109 per 1000 person-years.[7] For women in the same age group in the survey population, the rate during isotretinoin

Table 3. Pregnancy Rates during Isotretinoin Treatment, Based on Completed Follow-up by Telephone and Mail.*

Variable	1989	1990	1991	1992	1993	All
No. of women	18,075	28,757	29,649	30,048	16,053	122,582
Pregnancies reported†	73	102	91	90	46	402
Person-years of isotretinoin exposure	7,045	10,759	11,093	11,190	5,686	45,773
Rate per 1000 20-wk courses of isotretinoin	4.0	3.6	3.1	3.1	3.1	3.4

*The table excludes data on 1634 women who reported taking isotretinoin for one year or more and includes 78 reports of pregnancies awaiting confirmation.
†Values include 46 women who were pregnant at the time they began taking isotretinoin.

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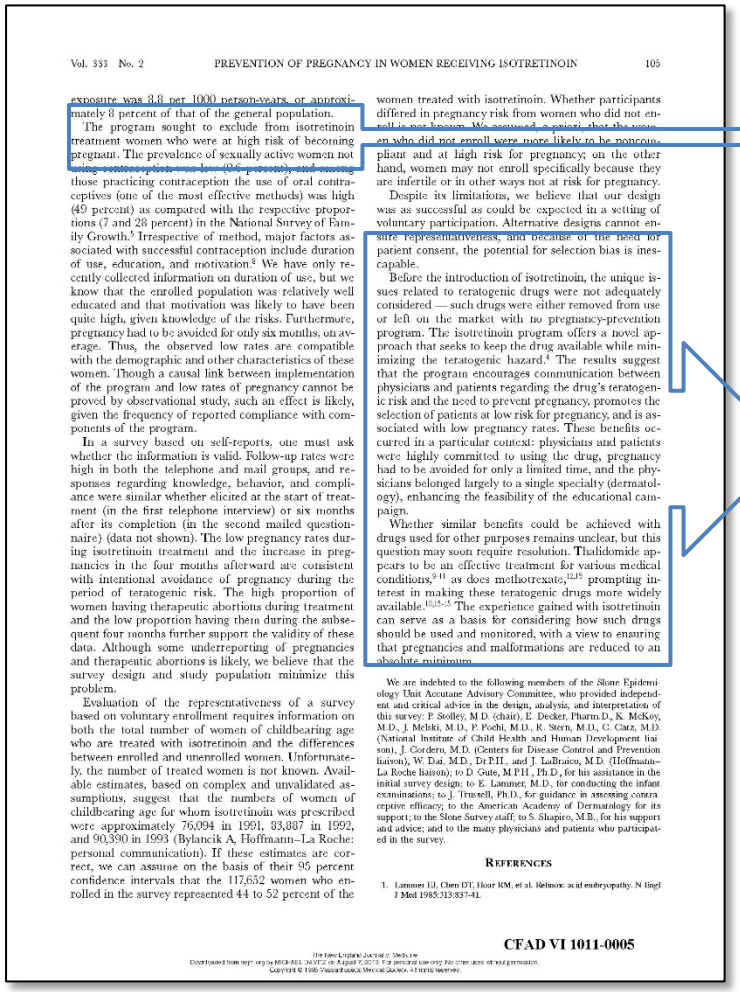
Source: Paper 1 (-01103), Petition, at 38, 52, 55, 57-58; Ex. 1010 (-01103) at 104.

PRIOR ART

Mitchell



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exposure was 8.8 per 1000 person-years, or approximately 8 percent of that of the general population.

The program sought to exclude from isotretinoin treatment women who were at high risk of becoming pregnant. The prevalence of sexually active women not using contraception was low (0.6 percent) and among those practicing contraception the use of oral contraceptives (one of the most effective methods) was high (49 percent) as compared with the respective proportions (7 and 28 percent) in the National Survey of Family Growth.[5] Irrespective of method, major factors associated with successful contraception include duration of use, education, and motivation.[6] We have only recently collected information on duration of use, but we know that the enrolled population was relatively well educated and that motivation was likely to have been quite high, given knowledge of the risks. Furthermore, pregnancy had to be avoided for only six months, on average. Thus, the observed low rates are compatible with the demographic and other characteristics of these women. Though a causal link between implementation of the program and low rates of pregnancy cannot be proved by observational study, such an effect is likely, given the frequency of reported compliance with components of the program.

In a survey based on self-reports, one must ask whether the information is valid. Follow-up rates were high in both the telephone and mail groups, and responses regarding knowledge, behavior, and compliance were similar whether elicited at the start of treatment (in the first telephone interview) or six months after its completion (in the second mailed questionnaire) (data not shown). The low pregnancy rates during isotretinoin treatment and the increase in pregnancies in the four months afterward are consistent with intentional avoidance of pregnancy during the period of teratogenic risk. The high proportion of women having therapeutic abortions during treatment and the low proportion having them during the subsequent four months further support the validity of these data. Although some underreporting of pregnancies and therapeutic abortions is likely, we believe that the survey design and study population minimize this problem.

Evaluation of the representativeness of a survey based on voluntary enrollment requires information on both the total number of women of childbearing age who are treated with isotretinoin and the differences between enrolled and unenrolled women. Unfortunately, the number of treated women is not known. Available estimates, based on complex and unvalidated assumptions, suggest that the numbers of women of childbearing age for whom isotretinoin was prescribed were approximately 76,094 in 1991, 83,887 in 1992, and 90,390 in 1993 (Bylancik A, Hoffmann–La Roche: personal communication). If these estimates are correct, we can assume on the basis of their 95 percent confidence intervals that the 117,632 women who enrolled in the survey represented 44 to 52 percent of the women treated with isotretinoin. Whether participants differed in pregnancy risk from women who did not enroll is not known. We assumed, a priori, that the women who did not enroll were more likely to be noncompliant and at high risk for pregnancy; on the other hand, women may not enroll specifically because they are infertile or in other ways not at risk for pregnancy.

Despite its limitations, we believe that our design was as successful as could be expected in a setting of voluntary participation. Alternative designs cannot ensure representativeness, and because of the need for patient consent, the potential for selection bias is inescapable.

Before the introduction of isotretinoin, the unique issues related to teratogenic drugs were not adequately considered — such drugs were either removed from use or left on the market with no pregnancy-prevention program. The isotretinoin program offers a novel approach that seeks to keep the drug available while minimizing the teratogenic hazard.[4] The results suggest that the program encourages communication between physicians and patients regarding the drug's teratogenic risk and the need to prevent pregnancy, promotes the selection of patients at low risk for pregnancy, and is associated with low pregnancy rates. These benefits occurred in a particular context: physicians and patients were highly committed to using the drug, pregnancy had to be avoided for only a limited time, and the physicians belonged largely to a single specialty (dermatology), enhancing the feasibility of the educational campaign.

Whether similar benefits could be achieved with drugs used for other purposes remains unclear, but this question may soon require resolution. Thalidomide appears to be an effective treatment for various medical conditions,[9-11] as does methotrexate,[12,13] prompting interest in making these teratogenic drugs more widely available.[10,13-15] The experience gained with isotretinoin can serve as a basis for considering how such drugs should be used and monitored, with a view to ensuring that pregnancies and malformations are reduced to an absolute minimum.

We are indebted to the following members of the Slone Epidemiology Unit Accutane Advisory Committee, who provided independent and critical advice in the design, analysis, and interpretation of this survey: P. Stolley, M.D. (chair), E. Decker, Pharm.D., K. McKoy, M.D., J. Melski, M.D., P. Pochi, M.D., K. Stern, M.D., C. Catz, M.D. (National Institute of Child Health and Human Development liaison), J. Cordero, M.D. (Centers for Disease Control and Prevention liaison), W. Dai, M.D., Dr.P.H., and J. LaBraico, M.D. (Hoffmann–La Roche liaison); to D. Gute, M.P.H., Ph.D., for his assistance in the initial survey design; to E. Lammer, M.D., for conducting the infant examinations; to J. Truscell, Ph.D., for guidance in assessing contraceptive efficacy; to the American Academy of Dermatology for its support; to the Slone Survey staff; to S. Shapiro, M.B., for his support and advice; and to the many physicians and patients who participated in the survey.

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1. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. N Engl J Med 1985;313:837-41.

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PRIOR ART

Institution Decision - 01103

computing station issues a pharmacy approval code. Ex. 1008, 11:6–8, 17–23. Dr. Fudin testifies that one skilled in the art would have implemented the methods disclosed in Dishman and Cunningham to limit the distribution of a drug. Ex. 1027 ¶¶ 98–100. Based upon the record presented, we conclude that Cunningham is directed to the same general endeavor as Mitchell and Dishman, controlling the distribution of pharmaceutical products.

Patent Owner contends that the Clozaril system of Dishman, as a whole, was a failure, and teaches away from the use of such a system. Prelim. Resp. 12–13, 30. Patent Owner relies upon an article by Dr. Honigfeld, which describes the effects of the National Clozapine Registry System on the incidence of deaths related to agranulocytosis. *Id.* (citing Ex. 2014). We note, however, that Honigfeld states that the actual number of cases of agranulocytosis and related deaths was lower than expected for the national registry maintained by the U.S. manufacturer of clozapine.

Ex. 2014, 52 (concluding the national registry "thought about lower than

Patent Owner states that Mitchell would have taught away from combining its pregnancy prevention program with any other prior art as Mitchell, like Dishman, is alleged to be a failure. Prelim. Resp. 31. Specifically, Patent Owner contends that Mitchell did not prevent all pregnancy. We are unpersuaded as, even if correct, Mitchell states that the

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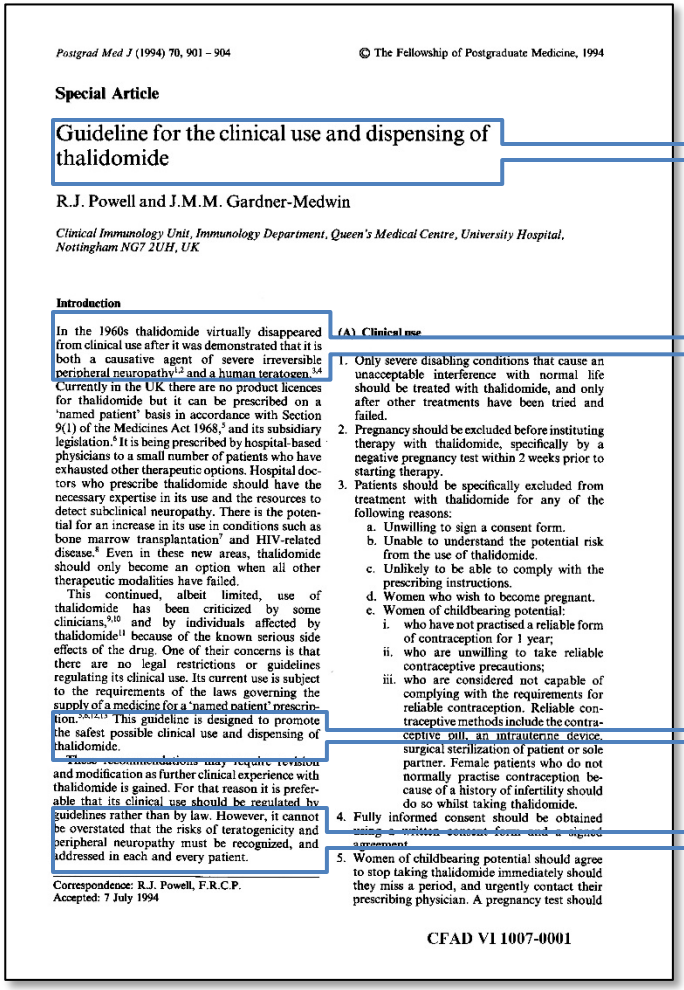
experience gained with the isotretinoin pregnancy prevention program can serve as a basis for considering how drugs, such as thalidomide, should be used and monitored, with a view to ensuring that adverse side effects are reduced to an absolute minimum. Ex. 1010, 105.

computer database. Prelim. Resp. 32–33. The challenged claims are written in a Jepson format, where the admitted prior art recites filling prescriptions only after consulting a computer readable storage medium. Mitchell identifies different risk groups, such as "women of childbearing age (12 to 59 years of age)" targeted for a pregnancy-prevention program. Ex. 1010, 101–102. Hence, we find that Mitchell discloses that the set of conditions for treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention, records would be kept relating to risk groups and that electronic records, such as patient risk group assignments, would be useful and easy to achieve through entry on a computer, and that a computerized system, such as that taught by Dishman, would help determine which prescriptions should be "locked out." Ex. 1027 ¶¶ 84–92. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing drugs, such as thalidomide, and filling such prescriptions to avoid the risk of harmful birth defects.

Source: Paper 22 (-01103), Institution Decision, at 18-19.

PRIOR ART

Powell



Postgrad Med J (1994) 70, 901 – 904 © The Fellowship of Postgraduate Medicine, 1994

Special Article

Guideline for the clinical use and dispensing of thalidomide

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Introduction

In the 1960s thalidomide virtually disappeared from clinical use after it was demonstrated that it is both a causative agent of severe irreversible peripheral neuropathy[1,2] and a human teratogen.[3,4] Currently in the UK there are no product licences for thalidomide but it can be prescribed on a 'named patient' basis in accordance with Section 9(1) of the Medicines Act 1968,[5] and its subsidiary legislation.[6] It is being prescribed by hospital-based physicians to a small number of patients who have exhausted other therapeutic options. Hospital doctors who prescribe thalidomide should have the necessary expertise in its use and the resources to detect subclinical neuropathy. There is the potential for an increase in its use in conditions such as bone marrow transplantation[7] and HIV-related disease.[8] Even in these new areas, thalidomide should only become an option when all other therapeutic modalities have failed.

This continued, albeit limited, use of thalidomide has been criticized by some clinicians,[9,10] and by individuals affected by thalidomide[11] because of the known serious side effects of the drug. One of their concerns is that there are no legal restrictions or guidelines regulating its clinical use. Its current use is subject to the requirements of the laws governing the supply of a medicine for a 'named patient' prescription.[5,6,12,13] This guideline is designed to promote the safest possible clinical use and dispensing of thalidomide.

These recommendations may require revision and modification as further clinical experience with thalidomide is gained. For that reason it is preferable that its clinical use should be regulated by guidelines rather than by law. However, it cannot be overstated that the risks of teratogenicity and peripheral neuropathy must be recognized, and addressed in each and every patient.

Correspondence: R.J. Powell, F.R.C.P.
Accepted: 7 July 1994

(A) Clinical use

1. Only severe disabling conditions that cause an unacceptable interference with normal life should be treated with thalidomide, and only after other treatments have been tried and failed.
2. Pregnancy should be excluded before instituting therapy with thalidomide, specifically by a negative pregnancy test within 2 weeks prior to starting therapy.
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.
4. Fully informed consent should be obtained using a written consent form and a signed agreement.
5. Women of childbearing potential should agree to stop taking thalidomide immediately should they miss a period, and urgently contact their prescribing physician. A pregnancy test should

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Guideline for the clinical use and dispensing of thalidomide

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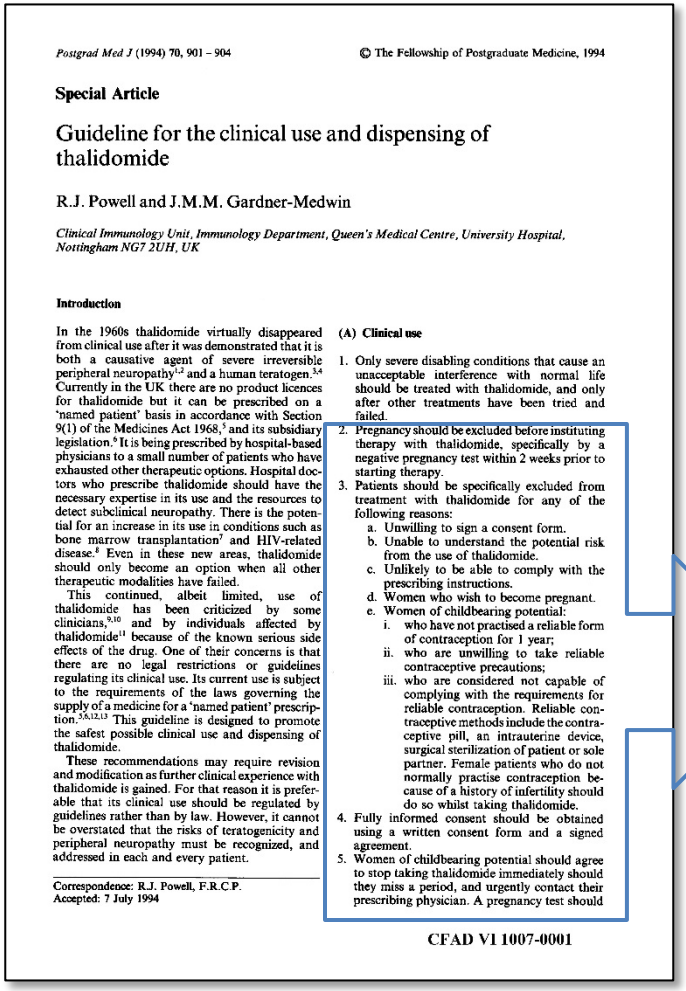

Postgrad Med J (1994) 70, 901 – 904 © The Fellowship of Postgraduate Medicine, 1994

Special Article

Guideline for the clinical use and dispensing of thalidomide

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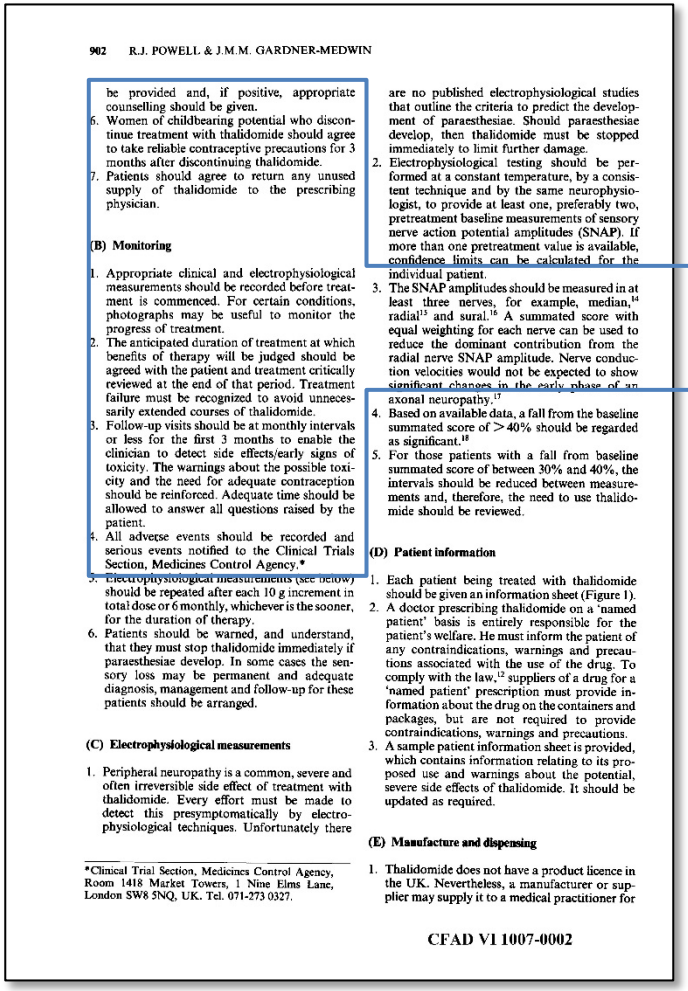

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6. Women of childbearing potential who discontinue treatment with thalidomide should agree to take reliable contraceptive precautions for 3 months after discontinuing thalidomide.
7. Patients should agree to return any unused supply of thalidomide to the prescribing physician.

(B) Monitoring

1. Appropriate clinical and electrophysiological measurements should be recorded before treatment is commenced. For certain conditions, photographs may be useful to monitor the progress of treatment.
2. The anticipated duration of treatment at which benefits of therapy will be judged should be agreed with the patient and treatment critically reviewed at the end of that period. Treatment failure must be recognized to avoid unnecessarily extended courses of thalidomide.
3. 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. The warnings about the possible toxicity and the need for adequate contraception should be reinforced. Adequate time should be allowed to answer all questions raised by the patient.
4. All adverse events should be recorded and serious events notified to the Clinical Trials Section, Medicines Control Agency.*
5. Electrophysiological measurements (see below) should be repeated after each 10 g increment in total dose or 6 monthly, whichever is the sooner, for the duration of therapy.
6. Patients should be warned, and understand, that they must stop thalidomide immediately if paraesthesiae develop. In some cases the sensory loss may be permanent and adequate diagnosis, management and follow-up for these patients should be arranged.

(C) Electrophysiological measurements

1. Peripheral neuropathy is a common, severe and often irreversible side effect of treatment with thalidomide. Every effort must be made to detect this presymptomatically by electrophysiological techniques. Unfortunately there are no published electrophysiological studies that outline the criteria to predict the development of paraesthesiae. Should paraesthesiae develop, then thalidomide must be stopped immediately to limit further damage.
2. Electrophysiological testing should be performed at a constant temperature, by a consistent technique and by the same neurophysiologist, to provide at least one, preferably two, pretreatment baseline measurements of sensory nerve action potential amplitudes (SNAP). If more than one pretreatment value is available, confidence limits can be calculated for the individual patient.
3. The SNAP amplitudes should be measured in at least three nerves, for example, median,[14] radial[15] and sural.[16] A summated score with equal weighting for each nerve can be used to reduce the dominant contribution from the radial nerve SNAP amplitude. Nerve conduction velocities would not be expected to show significant changes in the early phase of an axonal neuropathy.[17]
4. Based on available data, a fall from the baseline summated score of >40% should be regarded as significant.[18]
5. For those patients with a fall from baseline summated score of between 30% and 40%, the intervals should be reduced between measurements and, therefore, the need to use thalidomide should be reviewed.

(D) Patient information

1. Each patient being treated with thalidomide should be given an information sheet (Figure 1).
2. A doctor prescribing thalidomide on a 'named patient' basis is entirely responsible for the patient's welfare. He must inform the patient of any contraindications, warnings and precautions associated with the use of the drug. To comply with the law,[12] suppliers of a drug for a 'named patient' prescription must provide information about the drug on the containers and packages, but are not required to provide contraindications, warnings and precautions.
3. 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.

(E) Manufacture and dispensing

1. Thalidomide does not have a product licence in the UK. Nevertheless, a manufacturer or supplier may supply it to a medical practitioner for

*Clinical Trial Section, Medicines Control Agency, Room 1418 Market Towers, 1 Nine Elms Lane, London SW8 5NQ, UK. Tel. 071-273 0327.

CFAD VI 1007-0002

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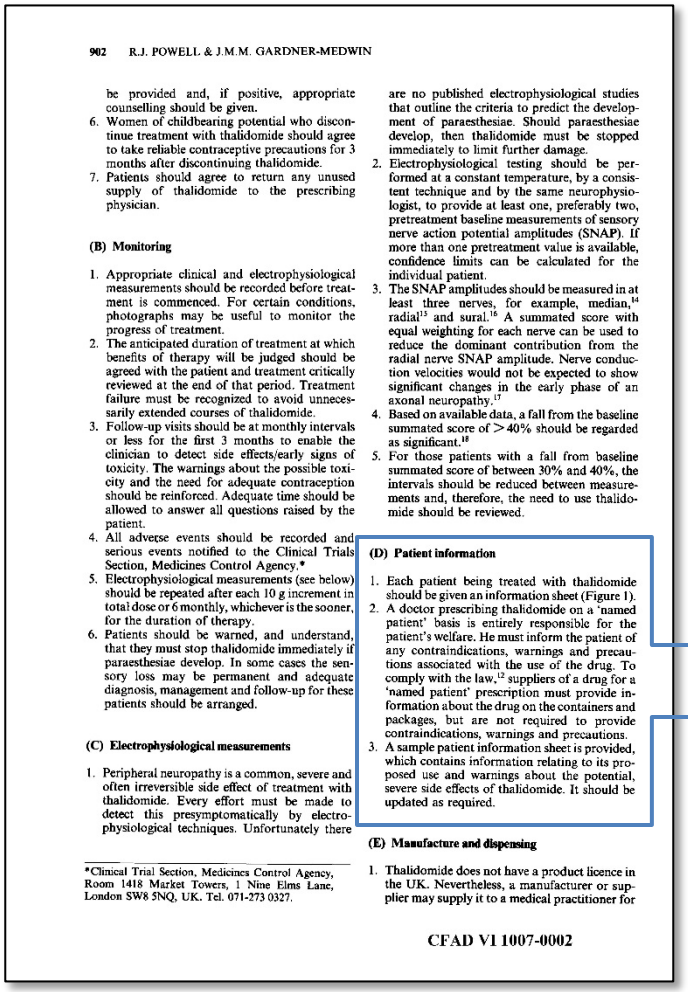

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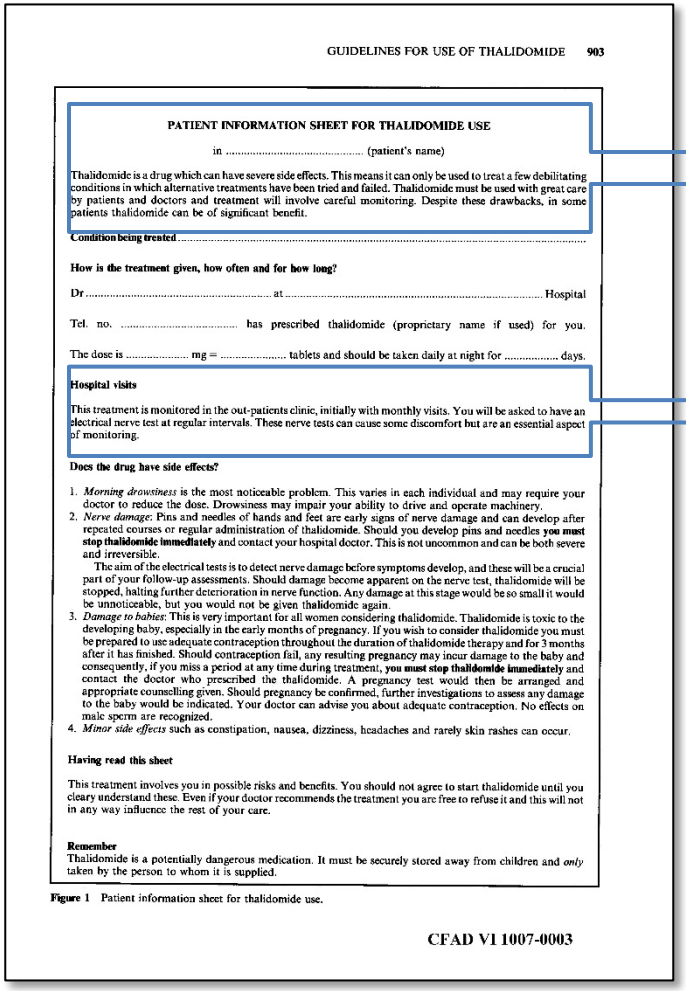

GUIDELINES FOR USE OF THALIDOMIDE 903

PATIENT INFORMATION SHEET FOR THALIDOMIDE USE

in ..... (patient's name)

Thalidomide is a drug which can have severe side effects. This means it can only be used to treat a few debilitating conditions in which alternative treatments have been tried and failed. Thalidomide must be used with great care by patients and doctors and treatment will involve careful monitoring. Despite these drawbacks, in some patients thalidomide can be of significant benefit.

Condition being treated .....

How is the treatment given, how often and for how long?

Dr ..... at ..... Hospital

Tel. no. ..... has prescribed thalidomide (proprietary name if used) for you.

The dose is ..... mg = ... tablets and should be taken daily at night for ..... days.

Hospital visits

This treatment is monitored in the out-patients clinic, initially with monthly visits. You will be asked to have an electrical nerve test at regular intervals. These nerve tests can cause some discomfort but are an essential aspect of monitoring.

Does the drug have side effects?

1. *Morning drowsiness* is the most noticeable problem. This varies in each individual and may require your doctor to reduce the dose. Drowsiness may impair your ability to drive and operate machinery.
2. *Nerve damage*: Pins and needles of hands and feet are early signs of nerve damage and can develop after repeated courses or regular administration of thalidomide. Should you develop pins and needles **you must stop thalidomide immediately** and contact your hospital doctor. This is not uncommon and can be both severe and irreversible.
   The aim of the electrical tests is to detect nerve damage before symptoms develop, and these will be a crucial part of your follow-up assessments. Should damage become apparent on the nerve test, thalidomide will be stopped, halting further deterioration in nerve function. Any damage at this stage would be so small it would be unnoticeable, but you would not be given thalidomide again.
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. 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. Should contraception fail, any resulting pregnancy may incur damage to the baby and consequently, if you miss a period at any time during treatment, **you must stop thalidomide immediately** and contact the doctor who prescribed the thalidomide. A pregnancy test would then be arranged and appropriate counselling given. Should pregnancy be confirmed, further investigations to assess any damage to the baby would be indicated. Your doctor can advise you about adequate contraception. No effects on male sperm are recognized.
4. *Minor side effects* such as constipation, nausea, dizziness, headaches and rarely skin rashes can occur.

Having read this sheet

This treatment involves you in possible risks and benefits. You should not agree to start thalidomide until you clearly understand these. Even if your doctor recommends the treatment you are free to refuse it and this will not in any way influence the rest of your care.

Remember

Thalidomide is a potentially dangerous medication. It must be securely stored away from children and *only* taken by the person to whom it is supplied.

Figure 1 Patient information sheet for thalidomide use.

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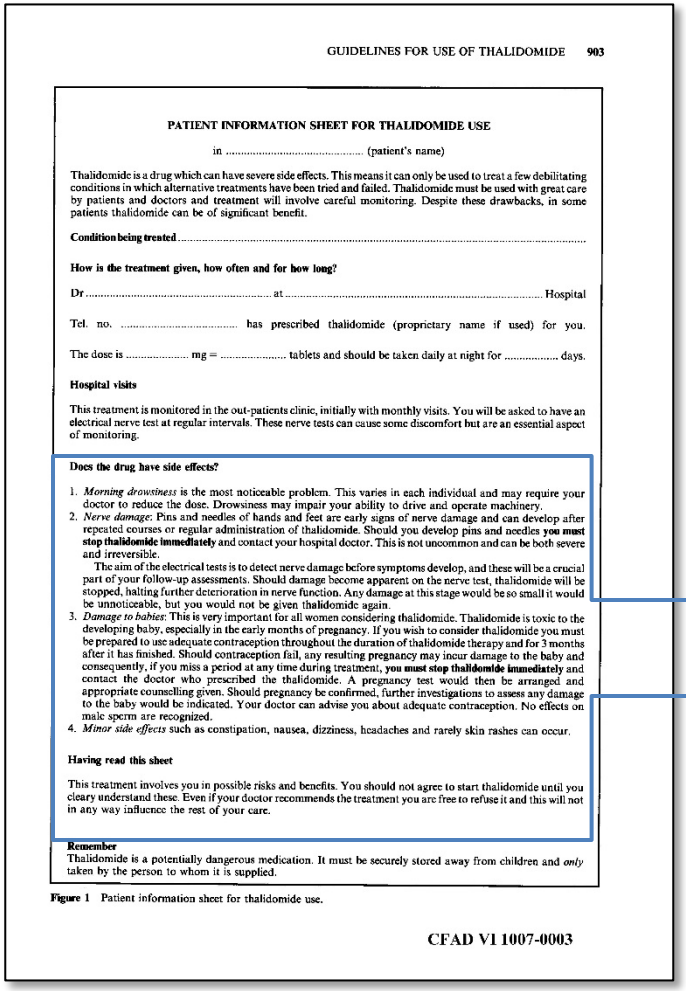

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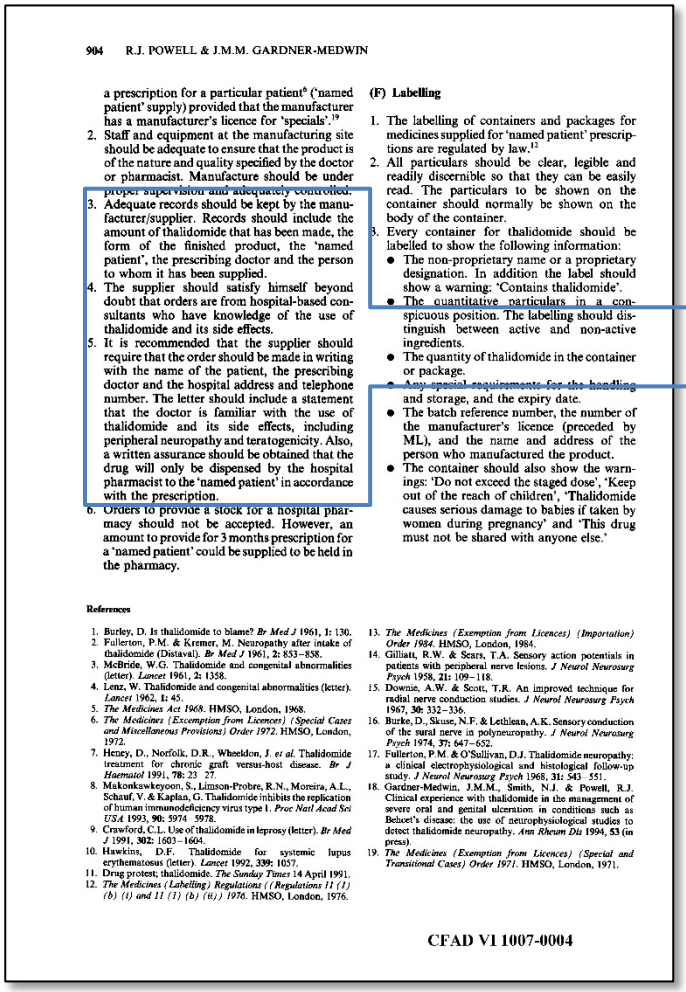

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a prescription for a particular patient[6] ('named patient' supply) provided that the manufacturer has a manufacturer's licence for 'specials'.[19]
2. Staff and equipment at the manufacturing site should be adequate to ensure that the product is of the nature and quality specified by the doctor or pharmacist. Manufacture should be under proper supervision and adequately controlled.
3. Adequate records should be kept by the manufacturer/supplier. 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.
4. The supplier should satisfy himself beyond doubt that orders are from hospital-based consultants who have knowledge of the use of thalidomide and its side effects.
5. It is recommended that the supplier should require that the order 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.
6. 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.

(F) Labelling

1. The labelling of containers and packages for medicines supplied for 'named patient' prescriptions are regulated by law.[12]
2. All particulars should be clear, legible and readily discernible so that they can be easily read. The particulars to be shown on the container should normally be shown on the body of the container.
3. Every container for thalidomide should be labelled to show the following information:
   - The non-proprietary name or a proprietary designation. In addition the label should show a warning: 'Contains thalidomide'.
   - The quantitative particulars in a conspicuous position. The labelling should distinguish between active and non-active ingredients.
   - The quantity of thalidomide in the container or package.
   - Any special requirements for the handling and storage, and the expiry date.
   - The batch reference number, the number of the manufacturer's licence (preceded by ML), and the name and address of the person who manufactured the product.
   - The container should also show the warnings: 'Do not exceed the staged dose', 'Keep out of the reach of children', 'Thalidomide causes serious damage to babies if taken by women during pregnancy' and 'This drug must not be shared with anyone else.'

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3. Adequate records should be kept by the manufacturer/supplier. 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.
4. The supplier should satisfy himself beyond doubt that orders are from hospital-based consultants who have knowledge of the use of thalidomide and its side effects.
5. It is recommended that the supplier should require that the order 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.

Institution Decision - 01102

IPR2015-01102
Patent 6,315,720 B1

Patent Owner contends that the Clozaril system of Dishman, as a whole, was a failure, and teaches away from the use of such a system. Prelim. Resp. 12–13, 29. Patent Owner relies upon an article by Dr. Honigfeld, which describes the effects of the National Clozapine Registry System on the incidence of deaths related to agranulocytosis. *Id.* (citing Ex. 2014). We note, however, that Honigfeld states that the actual number of cases of agranulocytosis and related deaths was lower than expected for the national registry maintained by the U.S. manufacturer of clozapine. Ex. 2014, 52 (concluding the national registry "brought about lower than expected rates of agranulocytosis and associated deaths"). We hold that Patent Owner has failed to identify sufficient and credible evidence that the specific computerized system described by Dishman, which was approved by the U.S. manufacturer of clozapine, was considered by one of ordinary skill in the art to be a failure.

According to Patent Owner, Powell fails to disclose assigning patients to risk groups and entering the risk group assignment into a computer database. Prelim. Resp. 32–33. We disagree. The challenged claims are written in a Jepson format, where the admitted prior art recites filling prescriptions only after consulting a computer readable storage medium. Powell identifies different risk groups, including patients that should be excluded such as women who wish to become pregnant and women of childbearing potential who have not practiced a reliable form of contraception for 1 year. Ex. 1006, 901. Hence, we find that Powell discloses that the set of conditions for thalidomide treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention, records would be kept relating to risk groups and that electronic records,

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contraception for 1 year. Ex. 1006, 901. Hence, we find that Powell discloses that the set of conditions for thalidomide treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention,

Source: Paper 21 (-01102), Institution Decision, at 18.

Institution Decision - 01102

and other drug in combination, and that the diagnostic testing test for evidence of the use and adverse effect of the other drug.

As to the dependent claims, claims 2–27 and 29–32, Petitioner provides detailed claim charts identifying where the additional limitations are taught in the prior art. Pet. 48–60. For example, as to claim 4, which requires filling a prescription only after informed consent, Petitioner identifies how Powell teaches that thalidomide should only be prescribed after fully informed consent has been obtained using a written consent form. Pet. 49; Ex. 1006, 901. Additionally, Petitioner relies upon the Declaration of Dr. Fudin to demonstrate that the one of ordinary skill in the art would understand that the prior art teaches each and every requirement of the challenged dependent claims, and that one would have had reason to employ the additional requirements in combination with the subject matter of the independent claims. Ex. 1027 ¶¶ 107–202.

Patent Owner contends that Petitioner has failed to meet its burden of showing that dependent claim 5 would have been obvious. Prelim. Resp. 38–39. Dependent claim 5 requires the prescriber verify risk group

verifying informed consent and risk assignment. *Id.* Dr. Fudin testifies that one of ordinary skill in the art would have reason to have the prescriber verify both risk group assignment and informed consent at the time of computer entry as Powell teaches that a physician is responsible for the patient's welfare and also in view of Dishman's teaching that candidates are to be screened by reviewing the patient file and interviewing the patients. Ex. 1027 ¶¶ 116–118. Based upon the evidence of record, we credit Dr.

Fudin's testimony and hold that one skilled in the art would have reason to enter the informed consent and risk assignment into a computer database at the same time to ensure that errors are avoided.

that the use of a telephone survey using an integrated voice response system, such as recited in claim 17, would have been obvious to one skilled in the art. Prelim. Resp. 43–44. Petitioner contends that conducting telephone surveys was well known in the art. Pet. 37. Petitioner relies upon the teachings of Mundt, which states that use of interactive voice response systems can strengthen clinical practice, extend research methods, and enhance administrative support of service quality and value. Ex. 1017, 612. We hold that the evidence of record demonstrates that one skilled in the art had reason to use interactive voice response systems to conduct patient surveys.

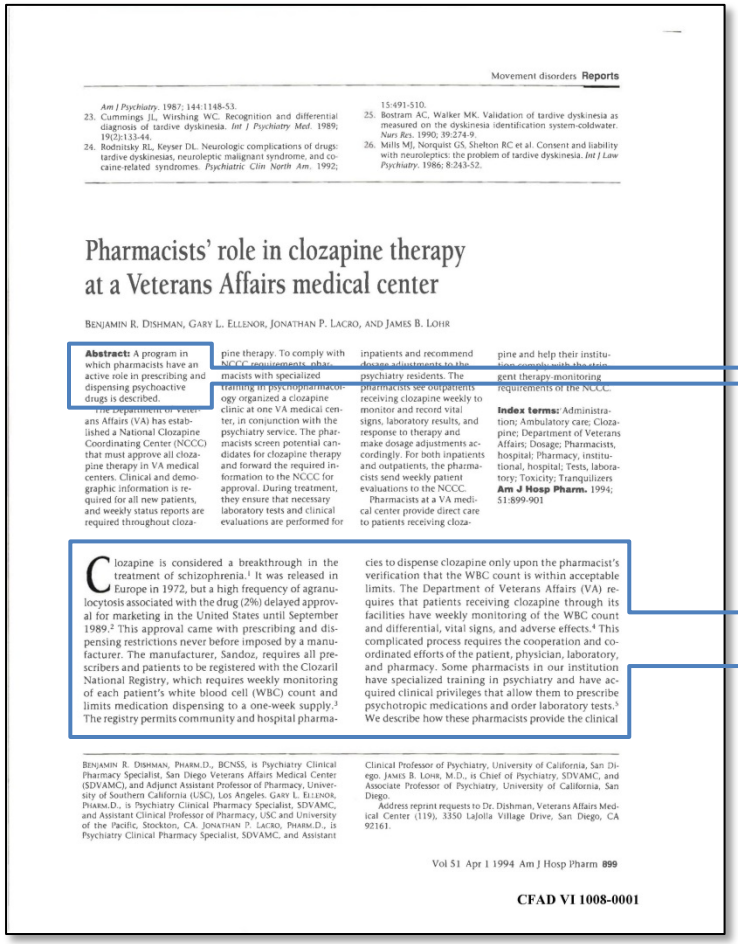
b. Secondary Considerations

Patent Owner contends that secondary consideration evidence demonstrates that the challenged claims are nonobvious over the relied upon prior art. Prelim. Resp. 48–54. We have reviewed the alleged secondary consideration evidence, but are not persuaded that it is sufficient to show that the claimed improvement is nonobvious over the prior art. For example, Patent Owner contends that the challenged '720 patent claims provide unexpected results. Specifically, Patent Owner states that the method of the '720 patent claims, as evidenced by the Enhanced S.T.E.P.S. program, has achieved a 100% prevention of birth defects of the type associated with thalidomide. *Id.* at 1. Yet, Patent Owner states that the admitted prior art

Source: Paper 21 (-01102), Institution Decision, at 21-22.

PRIOR ART

Dishman



Movement disorders **Reports**

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Pharmacists' role in clozapine therapy at a Veterans Affairs medical center

BENJAMIN R. DISHMAN, GARY L. ELLENOR, JONATHAN P. LACRO, AND JAMES B. LOHR

Abstract: A program in which pharmacists have an active role in prescribing and dispensing psychoactive drugs is described.

The Department of Veterans Affairs (VA) has established a National Clozapine Coordinating Center (NCCC) that must approve all clozapine therapy in VA medical centers. Clinical and demographic information is required for all new patients, and weekly status reports are required throughout clozapine therapy. To comply with NCCC requirements, pharmacists with specialized training in psychopharmacology organized a clozapine clinic at one VA medical center, in conjunction with the psychiatry service. The pharmacists screen potential candidates for clozapine therapy and forward the required information to the NCCC for approval. During treatment, they ensure that necessary laboratory tests and clinical evaluations are performed for inpatients and recommend dosage adjustments to the psychiatry residents. The pharmacists see outpatients receiving clozapine weekly to monitor and record vital signs, laboratory results, and response to therapy and make dosage adjustments accordingly. For both inpatients and outpatients, the pharmacists send weekly patient evaluations to the NCCC.

Pharmacists at a VA medical center provide direct care to patients receiving clozapine and help their institution comply with the stringent therapy-monitoring requirements of the NCCC.

Index terms: Administration; Ambulatory care; Clozapine; Department of Veterans Affairs; Dosage; Pharmacists, hospital; Pharmacy, institutional, hospital; Tests, laboratory; Toxicity; Tranquilizers
Am J Hosp Pharm. 1994; 51:899-901

Clozapine is considered a breakthrough in the treatment of schizophrenia.[1] It was released in Europe in 1972, but a high frequency of agranulocytosis associated with the drug (2%) delayed approval for marketing in the United States until September 1989.[2] This approval came with prescribing and dispensing restrictions never before imposed by a manufacturer. 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.[3] The registry permits community and hospital pharmacies to dispense clozapine only upon the pharmacist's verification that the WBC count is within acceptable limits. The Department of Veterans Affairs (VA) requires that patients receiving clozapine through its facilities have weekly monitoring of the WBC count and differential, vital signs, and adverse effects.[4] This complicated process requires the cooperation and coordinated efforts of the patient, physician, laboratory, and pharmacy. 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.[5] We describe how these pharmacists provide the clinical

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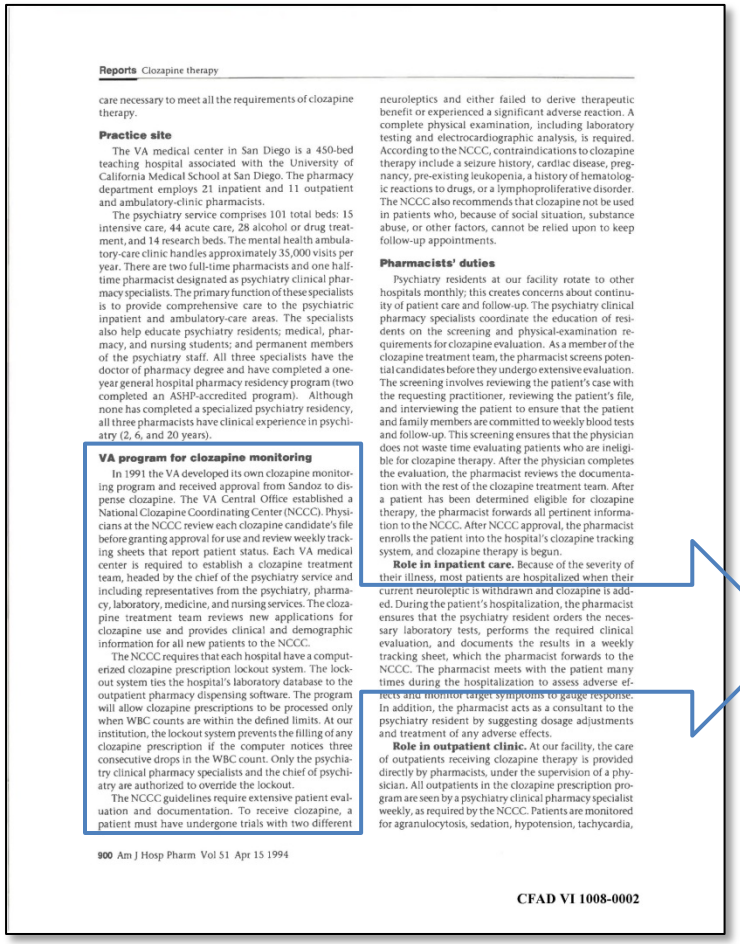

care necessary to meet all the requirements of clozapine therapy.

Practice site

The VA medical center in San Diego is a 450-bed teaching hospital associated with the University of California Medical School at San Diego. The pharmacy department employs 21 inpatient and 11 outpatient and ambulatory-clinic pharmacists.

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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. Only the psychiatry clinical pharmacy specialists and the chief of psychiatry are authorized to override the lockout.

The NCCC guidelines require extensive patient evaluation and documentation. To receive clozapine, a patient must have undergone trials with two different neuroleptics and either failed to derive therapeutic benefit or experienced a significant adverse reaction. A complete physical examination, including laboratory testing and electrocardiographic analysis, is required. According to the NCCC, contraindications to clozapine therapy include a seizure history, cardiac disease, pregnancy, pre-existing leukopenia, a history of hematologic reactions to drugs, or a lymphoproliferative disorder. The NCCC also recommends that clozapine not be used in patients who, because of social situation, substance abuse, or other factors, cannot be relied upon to keep follow-up appointments.

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Source: Paper 1 (-01102), Petition, at 15-16, 21-22, 28, 35-36, 41, 45, 47, 51, 54, 59; Ex. 1007 (-01102) at 900.

PRIOR ART

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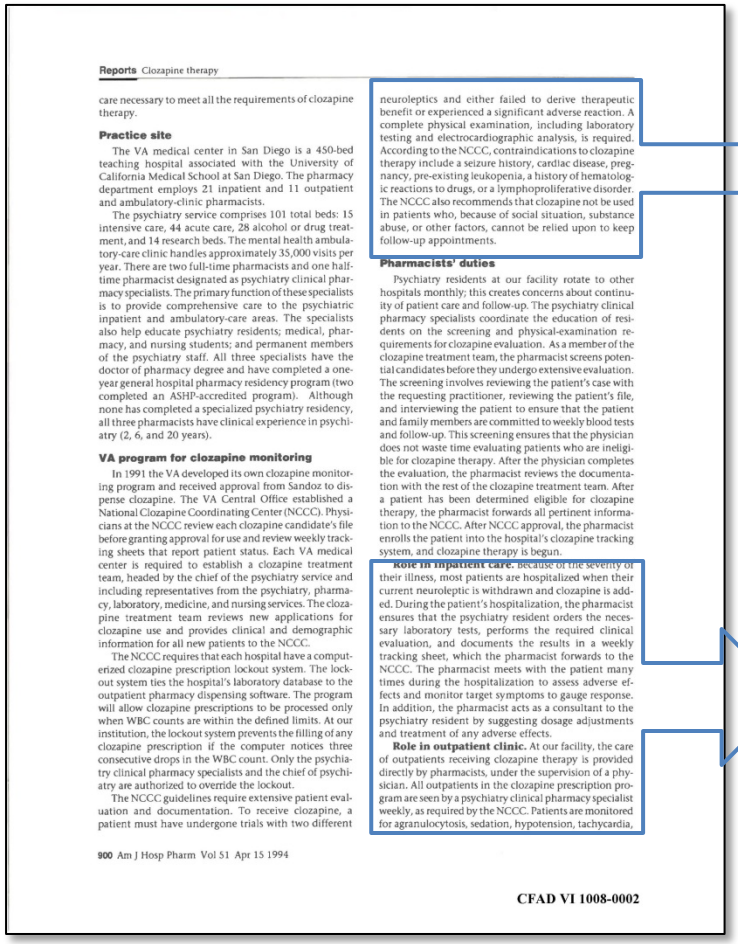

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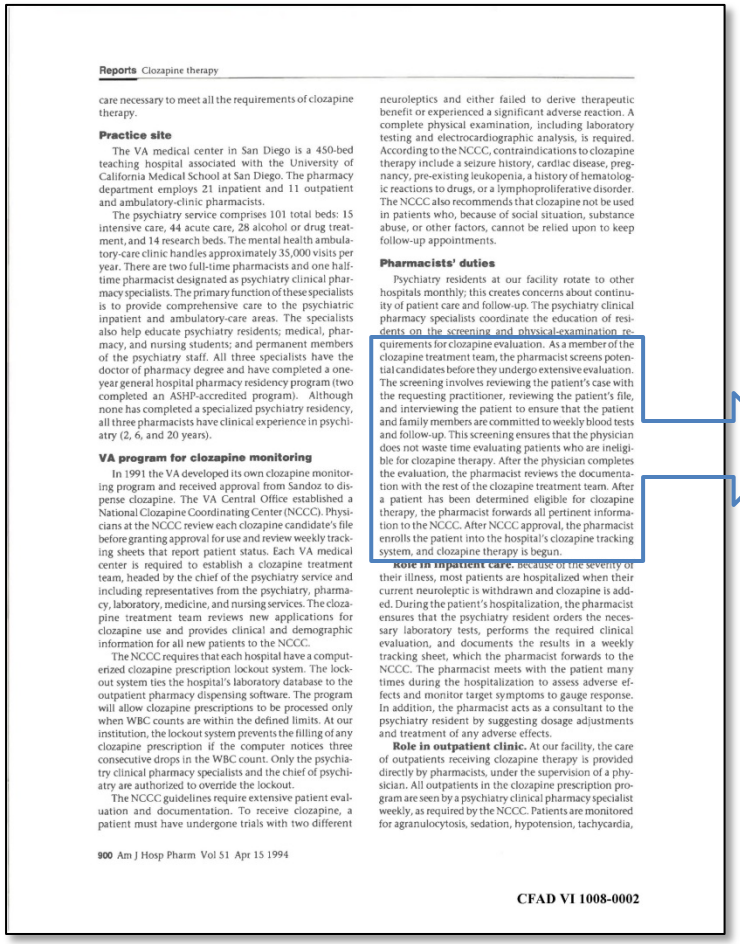
PRIOR ART

Dishman



Reports Clozapine therapy

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Pharmacists' duties

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Role in inpatient care. Because of the severity of their illness, most patients are hospitalized when their current neuroleptic is withdrawn and clozapine is added. During the patient's hospitalization, the pharmacist ensures that the psychiatry resident orders the necessary laboratory tests, performs the required clinical evaluation, and documents the results in a weekly tracking sheet, which the pharmacist forwards to the NCCC. The pharmacist meets with the patient many times during the hospitalization to assess adverse effects and monitor target symptoms to gauge response. In addition, the pharmacist acts as a consultant to the psychiatry resident by suggesting dosage adjustments and treatment of any adverse effects.

Role in outpatient clinic. At our facility, the care of outpatients receiving clozapine therapy is provided directly by pharmacists, under the supervision of a physician. All outpatients in the clozapine prescription program are seen by a psychiatry clinical pharmacy specialist weekly, as required by the NCCC. Patients are monitored for agranulocytosis, sedation, hypotension, tachycardia,

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quirements for clozapine evaluation. As a member of the clozapine treatment team, the pharmacist screens potential candidates before they undergo extensive evaluation. The screening involves reviewing the patient's case with the requesting practitioner, reviewing the patient's file, and interviewing the patient to ensure that the patient and family members are committed to weekly blood tests and follow-up. This screening ensures that the physician does not waste time evaluating patients who are ineligible for clozapine therapy. After the physician completes the evaluation, the pharmacist reviews the documentation with the rest of the clozapine treatment team. After a patient has been determined eligible for clozapine therapy, the pharmacist forwards all pertinent information to the NCCC. After NCCC approval, the pharmacist enrolls the patient into the hospital's clozapine tracking system, and clozapine therapy is begun.

Source: Paper 1 (-01102), Petition, at 26-27, 36, 47, 50, 53-55; Ex. 1007 (-01102) at 900.

PRIOR ART

Dishman

Clozapine therapy **Reports**

sialorrhea, seizures, constipation, hyperthermia, weight gain, and other adverse effects. In addition, the pharmacist monitors and records vital signs, psychiatric target symptoms, laboratory results, and response to therapy. The pharmacist adjusts the clozapine dosage as necessary and treats serious adverse effects after consulting with a psychiatrist. Once the pharmacist and psychiatrist have selected a drug regimen for treating the adverse effects, the pharmacist makes routine dosage adjustments. After each weekly follow-up appointment, the pharmacist faxes a tracking sheet containing an evaluation of the patient to the NCCC and places the original document in the patient's medical record.

Conclusion

Pharmacists working with patients receiving clozapine at a VA medical center provide direct patient care and help the institution comply with the stringent therapy-monitoring requirements of the NCCC.

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Stability of aztreonam and ampicillin sodium–sulbactam sodium in 0.9% sodium chloride injection

PAUL P. BELLIVEAU, CHARLES H. NIGHTINGALE, AND RICHARD QUINTILIANI

Abstract: The stability of aztreonam, ampicillin sodium, and sulbactam sodium admixed in 0.9% sodium chloride injection and stored at room temperature and under refrigeration was studied.

Each of the following admixtures was prepared in 0.9% sodium chloride injection: (1) aztreonam 10 mg/mL; (2) ampicillin 20 mg/mL (as the sodium salt) and sulbactam 10 mg/mL (as the sodium salt); and (3) aztreonam 10 mg/mL, ampicillin 20 mg/mL, and sulbactam 10 mg/mL. Three minibags of each admixture were stored at room temperature and three were refrigerated. Every 12 hours, up to 96 hours, the admixtures were visually inspected and 5-mL samples were withdrawn for high-performance liquid chromatography and pH testing.

No color change or precipitation was observed in any sample. In admixtures containing ampicillin, ampicillin was the first or only drug to lose more than 10% of initial concentration. In the ampicillin–sulbactam admixture, ampicillin was stable for 32 hours at room temperature and 68 hours refrigerated. In the aztreonam–ampicillin–sulbactam admixture, ampicillin was stable for 30 hours at room temperature and 94 hours refrigerated.

Aztreonam 10 mg/mL, ampicillin 20 mg/mL (as the sodium salt), and sulbactam 10 mg/mL (as the sodium salt) in 0.9% sodium chloride injection were stable in combination for up to 30 hours at room temperature and 94 hours under refrigeration.

Index terms: Additives; Ampicillin sodium; Antibiotics; Aztreonam; Dosage forms; Incompatibilities; Penicillins; Sodium chloride; Stability; Storage; Sulbactam sodium; Temperature; Vehicles

Am J Hosp Pharm. 1994; 51:901-4

Aztreonam, a monocyclic β-lactam antibiotic, is active against aerobic gram-negative organisms but inactive against anaerobic and gram-positive organisms.[1] It is not appropriate monotherapy for intra-abdominal infections, because both aztreonam-sensitive (enteric gram-negative rods) and aztreonam-resistant (*Bacteroides fragilis*) organisms are encountered.[2] In such situations, an antimicrobial (such as ampicillin–sulbactam) must be added to provide coverage against anaerobic organisms.[3]

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Supported by a grant from E. R. Squibb & Sons, Inc., Princeton, NJ.

The technical assistance of Qiang Fu is acknowledged.

Presented at the 28th Annual Midyear Clinical Meeting, Atlanta, GA, December 9, 1993.

CFAD VI 1008-0003

psychiatrist. Once the pharmacist and psychiatrist have selected a drug regimen for treating the adverse effects, the pharmacist makes routine dosage adjustments. After each weekly follow-up appointment, the pharmacist faxes a tracking sheet containing an evaluation of the patient to the NCCC and places the original document in the patient's medical record.

Source: Paper 1 (-01102), Petition, at 27, 50, 54-55; Ex. 1007 (-01102) at 901.

PRIOR ART

Institution Decision – 01102 (and – 01103)

such as patient risk group assignments, would be useful and easy to achieve through entry on a computer, and that a computerized system, such as that taught by Dishman, would help determine which prescriptions should be "locked out." Ex. 1027, 89–94. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

Patent Owner states that Dishman does not describe risk group assignments or determining whether the risk that an adverse effect is likely to occur is acceptable. According to Patent Owner, locking out a prescription when a patient has three consecutive drops in the white blood count has "nothing to do with risk group assignments." Prelim. Resp. 34. We disagree. Dishman teaches that clozapine prescriptions are only to be dispensed upon a pharmacist's verification that the white blood cell count is within acceptable limits. Ex. 1007, 899. In other words, Dishman discloses that patients having three consecutive drops in the white blood count are assigned to such a risk group.

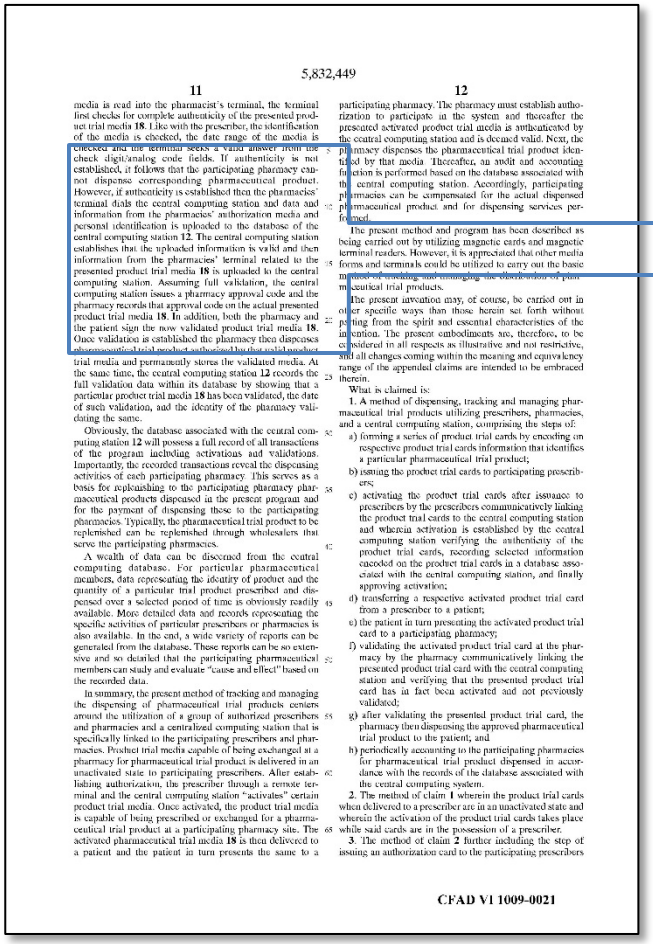
Patent Owner takes the position that Dishman does not describe generating an approval code. Prelim. Resp. 35–37. Patent Owner further contends that Petitioner has failed to provide a rationale to combine Dishman and Cunningham to arrive at the claimed invention. *Id.* We disagree. On this record, we are persuaded that, as recognized by Dr. Fudin, one skilled in the art seeking to control the distribution of thalidomide would

We disagree. Dishman teaches that clozapine prescriptions are only to be dispensed upon a pharmacist's verification that the white blood cell count is within acceptable limits. Ex. 1007, 899. In other words, Dishman discloses that patients having three consecutive drops in the white blood count are assigned to such a risk group.

Source: Paper 21 (-01102), Institution Decision, at 19; Paper 22 (-01103), Institution Decision, at 20.

PRIOR ART

Cunningham



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media is read into the pharmacist's terminal, the terminal first checks for complete authenticity of the presented product trial media **18**. Like with the prescriber, the identification of the media is checked, the date range of the media is checked and the terminal seeks a valid answer from the check digit/analog code fields. If authenticity is not established, it follows that the participating pharmacy cannot dispense corresponding pharmaceutical product. However, if authenticity is established then the pharmacies' terminal dials the central computing station and data and information from the pharmacies' authorization media and personal identification is uploaded to the database of the central computing station **12**. The central computing station establishes that the uploaded information is valid and then information from the pharmacies' terminal related to the presented product trial media **18** is uploaded to the central computing station. Assuming full validation, the central computing station issues a pharmacy approval code and the pharmacy records that approval code on the actual presented product trial media **18**. In addition, both the pharmacy and the patient sign the now validated product trial media **18**. Once validation is established the pharmacy then dispenses pharmaceutical trial product authorized by that valid product trial media and permanently stores the validated media. At the same time, the central computing station **12** records the full validation data within its database by showing that a particular product trial media **18** has been validated, the date of such validation, and the identity of the pharmacy validating the same.

Obviously, the database associated with the central computing station **12** will possess a full record of all transactions of the program including activations and validations. Importantly, the recorded transactions reveal the dispensing activities of each participating pharmacy. This serves as a basis for replenishing to the participating pharmacy pharmaceutical products dispensed in the present program and for the payment of dispensing these to the participating pharmacies. Typically, the pharmaceutical trial product to be replenished can be replenished through wholesalers that serve the participating pharmacies.

A wealth of data can be discerned from the central computing database. For particular pharmaceutical members, data representing the identity of product and the quantity of a particular trial product prescribed and dispensed over a selected period of time is obviously readily available. More detailed data and records representing the specific activities of particular prescribers or pharmacies is also available. In the end, a wide variety of reports can be generated from the database. Those reports can be so extensive and so detailed that the participating pharmaceutical members can study and evaluate "cause and effect" based on the recorded data.

In summary, the present method of tracking and managing the dispensing of pharmaceutical trial products centers around the utilization of a group of authorized prescribers and pharmacies and a centralized computing station that is specifically linked to the participating prescribers and pharmacies. Product trial media capable of being exchanged at a pharmacy for pharmaceutical trial product is delivered in an unactivated state to participating prescribers. After establishing authorization, the prescriber through a remote terminal and the central computing station "activates" certain product trial media. Once activated, the product trial media is capable of being prescribed or exchanged for a pharmaceutical trial product at a participating pharmacy site. The activated pharmaceutical trial media **18** is then delivered to a patient and the patient in turn presents the same to a participating pharmacy. The pharmacy must establish authorization to participate in the system and thereafter the presented activated product trial media is authenticated by the central computing station and is deemed valid. Next, the pharmacy dispenses the pharmaceutical trial product identified by that media. Thereafter, an audit and accounting function is performed based on the database associated with the central computing station. Accordingly, participating pharmacies can be compensated for the actual dispensed pharmaceutical product and for dispensing services performed.

The present method and program has been described as being carried out by utilizing magnetic cards and magnetic terminal readers. However, it is appreciated that other media forms and terminals could be utilized to carry out the basic method of tracking and managing the distribution of pharmaceutical trial products.

The present invention may, of course, be carried out in other specific ways than those herein set forth without departing from the spirit and essential characteristics of the invention. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive, and all changes coming within the meaning and equivalency range of the appended claims are intended to be embraced therein.

What is claimed is:

1. A method of dispensing, tracking and managing pharmaceutical trial products utilizing prescribers, pharmacies, and a central computing station, comprising the steps of:

a) forming a series of product trial cards by encoding on respective product trial cards information that identifies a particular pharmaceutical trial product;

b) issuing the product trial cards to participating prescribers;

c) activating the product trial cards after issuance to prescribers by the prescribers communicatively linking the product trial cards to the central computing station and wherein activation is established by the central computing station verifying the authenticity of the product trial cards, recording selected information encoded on the product trial cards in a database associated with the central computing station, and finally approving activation;

d) transferring a respective activated product trial card from a prescriber to a patient;

e) the patient in turn presenting the activated product trial card to a participating pharmacy;

f) validating the activated product trial card at the pharmacy by the pharmacy communicatively linking the presented product trial card with the central computing station and verifying that the presented product trial card has in fact been activated and not previously validated;

g) after validating the presented product trial card, the pharmacy then dispensing the approved pharmaceutical trial product to the patient; and

h) periodically accounting to the participating pharmacies for pharmaceutical trial product dispensed in accordance with the records of the database associated with the central computing system.

2. The method of claim **1** wherein the product trial cards when delivered to a prescriber are in an unactivated state and wherein the activation of the product trial cards takes place while said cards are in the possession of a prescriber.

3. The method of claim **2** further including the step of issuing an authorization card to the participating prescribers

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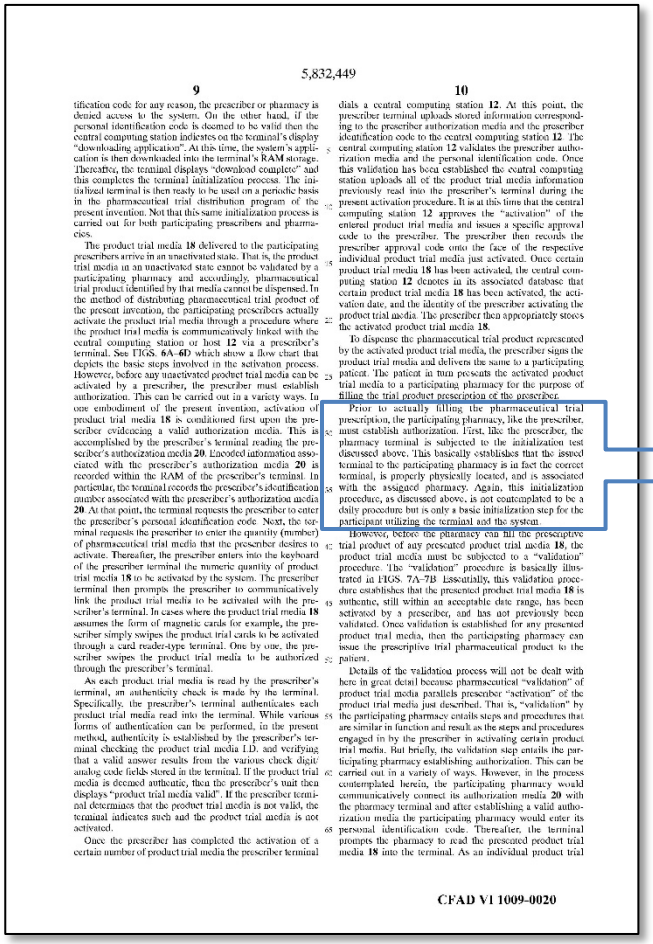
check digit/analog code fields. If authenticity is not established, it follows that the participating pharmacy cannot dispense corresponding pharmaceutical product. However, if authenticity is established then the pharmacies' terminal dials the central computing station and data and information from the pharmacies' authorization media and personal identification is uploaded to the database of the central computing station **12**. The central computing station establishes that the uploaded information is valid and then information from the pharmacies' terminal related to the presented product trial media **18** is uploaded to the central computing station. Assuming full validation, the central computing station issues a pharmacy approval code and the pharmacy records that approval code on the actual presented product trial media **18**. In addition, both the pharmacy and the patient sign the now validated product trial media **18**. Once validation is established the pharmacy then dispenses pharmaceutical trial product authorized by that valid product

PRIOR ART

Cunningham



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tification code for any reason, the prescriber or pharmacy is denied access to the system. On the other hand, if the personal identification code is deemed to be valid then the central computing station indicates on the terminal's display "downloading application". At this time, the system's application is then downloaded into the terminal's RAM storage. Thereafter, the terminal displays "download completed" and this completes the terminal initialization process. The initialized terminal is then ready to be used on a periodic basis in the pharmaceutical trial distribution program of the present invention. Not that this same initialization process is carried out for both participating prescribers and pharmacies.

The product trial media **18** delivered to the participating prescribers arrive in an unactivated state. That is, the product trial media in an unactivated state cannot be validated by a participating pharmacy and accordingly, pharmaceutical trial product identified by that media cannot be dispensed. In the method of distributing pharmaceutical trial product of the present invention, the participating prescribers actually activate the product trial media through a procedure where the product trial media is communicatively linked with the central computing station or host **12** via a prescriber's terminal. See FIGS. **6A–6D** which show a flow chart that depicts the basic steps involved in the activation process. However, before any unactivated product trial media can be activated by a prescriber, the prescriber must establish authorization. This can be carried out in a variety ways. In one embodiment of the present invention, activation of product trial media **18** is conditioned first upon the prescriber evidencing a valid authorization media. This is accomplished by the prescriber's terminal reading the prescriber's authorization media **20**. Encoded information associated with the prescriber's authorization media **20** is recorded within the RAM of the prescriber's terminal. In particular, the terminal records the prescriber's identification number associated with the prescriber's authorization media **20**. At that point, the terminal requests the prescriber to enter the prescriber's personal identification code. Next, the terminal requests the prescriber to enter the quantity (number) of pharmaceutical trial media that the prescriber desires to activate. Thereafter, the prescriber enters into the keyboard of the prescriber terminal the numeric quantity of product trial media **18** to be activated by the system. The prescriber terminal then prompts the prescriber to communicatively link the product trial media to be activated with the prescriber's terminal. In cases where the product trial media **18** assumes the form of magnetic cards for example, the prescriber simply swipes the product trial cards to be activated through a card reader-type terminal. One by one, the prescriber swipes the product trial media to be authorized through the prescriber's terminal.

As each product trial media is read by the prescriber's terminal, an authenticity check is made by the terminal. Specifically, the prescriber's terminal authenticates each product trial media read into the terminal. While various forms of authentication can be performed, in the present method, authenticity is established by the prescriber's terminal checking the product trial media I.D. and verifying that a valid answer results from the various check digit/analog code fields stored in the terminal. If the product trial media is deemed authentic, then the prescriber's unit then displays "product trial media valid". If the prescriber terminal determines that the product trial media is not valid, the terminal indicates such and the product trial media is not activated.

Once the prescriber has completed the activation of a certain number of product trial media the prescriber terminal dials a central computing station **12**. At this point, the prescriber terminal uploads stored information corresponding to the prescriber authorization media and the prescriber identification code to the central computing station **12**. The central computing station **12** validates the prescriber authorization media and the personal identification code. Once this validation has been established the central computing station uploads all of the product trial media information previously read into the prescriber's terminal during the present activation procedure. It is at this time that the central computing station **12** approves the "activation" of the entered product trial media and issues a specific approval code to the prescriber. The prescriber then records the prescriber approval code onto the face of the respective individual product trial media just activated. Once certain product trial media **18** has been activated, the central computing station **12** denotes in its associated database that certain product trial media **18** has been activated, the activation date, and the identity of the prescriber activating the product trial media. The prescriber then appropriately stows the activated product trial media **18**.

To dispense the pharmaceutical trial product represented by the activated product trial media, the prescriber signs the product trial media and delivers the same to a participating patient. The patient in turn presents the activated product trial media to a participating pharmacy for the purpose of filling the trial product prescription of the prescriber.

Prior to actually filling the pharmaceutical trial prescription, the participating pharmacy, like the prescriber, must establish authorization. First, like the prescriber, the pharmacy terminal is subjected to the initialization test discussed above. This basically establishes that the issued terminal to the participating pharmacy is in fact the correct terminal, is properly physically located, and is associated with the assigned pharmacy. Again, this initialization procedure, as discussed above, is not contemplated to be a daily procedure but is only a basic initialization step for the participant utilizing the terminal and the system.

However, before the pharmacy can fill the prescriptive trial product of any presented product trial media **18**, the product trial media must be subjected to a "validation" procedure. The "validation" procedure is basically illustrated in FIGS. 7A–7B. Essentially, this validation procedure establishes that the presented product trial media **18** is authentic, still within an acceptable date range, has been activated by a prescriber, and has not previously been validated. Once validation is established for any presented product trial media, then the participating pharmacy can issue the prescriptive trial pharmaceutical product to the patient.

Details of the validation process will not be dealt with here in great detail because pharmaceutical "validation" of product trial media parallels prescriber "activation" of the product trial media just described. That is, "validation" by the participating pharmacy entails steps and procedures that are similar in function and result as the steps and procedures engaged in by the prescriber in activating certain product trial media. But briefly, the validation step entails the participating pharmacy establishing authorization. This can be carried out in a variety of ways. However, in the process contemplated herein, the participating pharmacy would communicatively connect its authorization media **20** with the pharmacy terminal and after establishing a valid authorization media the participating pharmacy would enter its personal identification code. Thereafter, the terminal prompts the pharmacy to read the presented product trial media **18** into the terminal. As an individual product trial

CFAD VI 1009-0020

Prior to actually filling the pharmaceutical trial prescription, the participating pharmacy, like the prescriber, must establish authorization. First, like the prescriber, the pharmacy terminal is subjected to the initialization test discussed above. This basically establishes that the issued terminal to the participating pharmacy is in fact the correct terminal, is properly physically located, and is associated with the assigned pharmacy. Again, this initialization procedure, as discussed above, is not contemplated to be a daily procedure but is only a basic initialization step for the participant utilizing the terminal and the system.

PRIOR ART

Institution Decision – 01096 (- 1102, - 1103)

Cunningham to arrive at the claimed invention. *Id.* at 43–47. We disagree. On this record, we are persuaded that, as recognized by Dr. Fudin, one skilled in the art seeking to control the distribution of thalidomide would have looked to the approval code of Cunningham to limit dispensation of a drug with known severe adverse side effects to certain risk groups, *i.e.*, further control distribution in order to avoid severe birth defects associated with distributing thalidomide to pregnant women. Ex. 1021 ¶¶ 215–216. Dr. Fudin's testimony is consistent with the prior art, e.g., Cunningham's teaching that an approval code validation aids in the controlled distribution of a pharmaceutical product. Ex. 1009, 11:6–23; Ex. 1015, 1.

As to the dependent claims, claims 2–27 and 29–32, Petitioner provides detailed claim charts identifying where the additional limitations are taught in the prior art. Pet. 41–51. For example, Petitioner identifies how Keravich teaches that one using the S.T.E.P.S. program would understand that patients can be registered via fax (claim 6) and how Thalomid PI discloses that information obtained from a patient can include results of a pregnancy test (claim 26). Additionally, Petitioner relies upon the Declaration of Dr. Fudin to demonstrate that the one of ordinary skill in the art would understand that the prior art teaches each and every requirement of the challenged dependent claims, and that one would have had a reason to employ the additional requirements in combination with the subject matter of the independent claims. Ex. 1021 ¶¶ 107–212, 217–223.

Patent Owner contends that Petitioner has failed to meet its burden of showing that dependent claim 5 would have been obvious. Prelim. Resp. 47–49. Dependent claim 5 requires the prescriber to verify risk group assignment and informed consent at the time the patient is registered in a

On this record, we are persuaded that, as recognized by Dr. Fudin, one skilled in the art seeking to control the distribution of thalidomide would have looked to the approval code of Cunningham to limit dispensation of a drug with known severe adverse side effects to certain risk groups, *i.e.*, further control distribution in order to avoid severe birth defects associated with distributing thalidomide to pregnant women. Ex. 1021 ¶¶ 215–216. Dr. Fudin's testimony is consistent with the prior art, e.g., Cunningham's teaching that an approval code validation aids in the controlled distribution of a pharmaceutical product. Ex. 1009, 11:6–23; Ex. 1015, 1.

Source: Paper 21 (-01096), Institution Decision, at 19; Paper 21 (-01102), Institution Decision, at 19-20; Paper 22 (-01103), Institution Decision, at 20.

PRIOR ART

Institution Decision – 01096 (- 1102, - 1103)

such as patient risk group assignments, would be useful and easy to achieve through entry on a computer, and that a computerized system, such as that taught by Dishman, would help determine which prescriptions should be "locked out." Ex. 1027, 89–94. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

Patent Owner states that Dishman does not describe risk group assignments or determining whether the risk that an adverse effect is likely to occur is acceptable. According to Patent Owner, locking out a prescription when a patient has three consecutive drops in the white blood count has "nothing to do with risk group assignments." Prelim. Resp. 34. We disagree. Dishman teaches that clozapine prescriptions are only to be dispensed upon a pharmacist's verification that the white blood cell count is within acceptable limits. Ex. 1007, 899. In other words, Dishman discloses that patients having three consecutive drops in the white blood count are assigned to such a risk group.

Patent Owner takes the position that Dishman does not describe generating an approval code. Prelim. Resp. 35–37. Patent Owner further

disagree. On this record, we are persuaded that, as recognized by Dr. Fudin, one skilled in the art seeking to control the distribution of thalidomide would

have looked to the approval code of Cunningham to limit dispensation of a drug with known severe adverse side effects to certain risk groups, i.e., further control distribution in order to avoid severe birth defects associated with distributing thalidomide to pregnant women. Ex. 1027 ¶¶ 102–105. Dr. Fudin's testimony is consistent with the prior art, e.g., Cunningham's teaching that an approval code validation aids in the controlled distribution of a pharmaceutical product. Ex. 1008, 11:6–23.

the patient. Dependent claims 5 and 6 require that the informed consent is verified by the prescriber at the time the patient is registered in a computer, and consent is transmitted via facsimile and interpreted by optical character recognition software. Dependent claims 7–10 require information be obtained from the patient prior to treatment, including the results of diagnostic testing, which can comprise genetic testing. Dependent claims 11–14 and 20–25 further require additional features, such as a teratogenic effect being otherwise likely to arise in the patient, arise in a fetus carried by the patient, and that the drug is thalidomide. Dependent claims 15–19, 26, and 27 require defining a second set of information to be collected from the patient on a periodic basis, which can comprise a telephonic survey regarding the results of pregnancy testing, and where the adverse side effect of the drug can be a teratogenic effect. Dependent claims 29–32 each depend from independent claim 28, and further require that the information collected be probative of the likelihood that the patient may take the drug

Source: Paper 21 (-01096), Institution Decision, at 19; Paper 21 (-01102), Institution Decision, at 19-20; Paper 22 (-01103), Institution Decision, at 20.

Dr. Frau's Admissions

15	Q. So the record is clear, my question is
16	you agree that Claim 13 mentions a pharmacy
17	approval code on the presented product trial card
18	as a part of the validation procedure; right?
19	A. It states -- those are the words on
20	this page, yes.

Source: Ex. 1075 (-01096) at 319:15-20.

PRIOR ART

Dr. DiPiro's Admissions

Q. Looking further down column 10 around line 28, in Cunningham it says, "Prior to actually filling the pharmaceutical trial prescription, the participating pharmacy, like the prescriber, must establish authorization."

Do you see that?

A. I do.

Q. And the next paragraph in the same column says, "However, before the pharmacy can fill the prescriptive trial product of any presented product trial media, the product trial media must be subjected to a validation procedure."

Do you see that?

A. I do.

Source: Ex. 1074 (-01096) at 268:3-18.

PRIOR ART

Mundt

Clinical Computing

Interactive Voice Response Systems in Clinical Research and Treatment

James C. Mundt, Ph.D.

From Bell's first cry to Watson for assistance to the many crisis help-lines currently available, telephones have been serving people in need. Interactive voice response (IVR) systems, a rapidly expanding technology for automated acquisition and dispersal of information, represent the convergence of computer-automated interviewing with touch-tone telephone service. IVR applications for routing telephone calls or accessing banking services are now commonplace.

Potential benefits of IVR systems for clinical research and treatment have recently begun to be explored and realized. As budgets for research and treatment delivery continue to require greater efficiency without sacrificing quality, use of IVR applications will continue to expand. This column describes the use of IVR technology in research and treatment of psychiatric and substance use disorders.

Use of IVR systems for data collection

IVR systems for obtaining and managing data are a major advance over previous methods. Touch-tone telephones permit 24-hour data collection, removing previous limitations related to distance or temporal availability of study staff. Automatic data collection by computers eliminates errors due to transcription or interviewer mistakes and facilitates optimal data management procedures.

Dr. Mundt is a research scientist at the Dean Foundation for Health, Research, and Education, 2711 Allen Boulevard, Middleton, Wisconsin 53562 (e-mail, Mundt_James_C@ssmhcr.com). John H. Greist, M.D., is editor of this column.

More detailed discussions of IVR applications in research have appeared elsewhere (1,2).

An IVR program for obtaining daily self-reports of alcohol consumption has been demonstrated to provide valid data, permitting analyses of alcohol use patterns that differentiate dependent from nondependent drinkers otherwise matched on quantity-frequency measures of use (3,4). Data collection using IVR systems is beginning to be used for investigating other conditions, such as eating disorders and impaired psychomotor and cognitive performance (5).

Assessment and diagnosis using IVR applications

Computers can reliably assess clinical symptoms and provide valid diagnoses (6). Several computerized assessments, including the Hamilton Anxiety Scale, the Hamilton Depression Scale, the Yale-Brown Obsessive Compulsive Scale, and the Liebowitz Social Anxiety Scale, have been reviewed recently (7) and are being incorporated into clinical drug trials (8). IVR implementations of these instruments are being used to monitor patients and provide feedback to clinicians (9).

Computerized interviews, such as PRIME-MD (10) and Symptom-Driven Diagnostic System for Primary Care (11), have been developed to diagnose *DSM-IV* axis I disorders commonly found in primary care patients and have been implemented as IVR applications. A study of 200 patients using PRIME-MD, implemented via IVR technology, found a high correspondence between the PRIME-MD diagnoses made with the IVR system and those obtained using the Structured Clinical Interview for DSM-IV (kappa=.67, $p<.001$). These data contribute to other findings supporting the use of computers to assess psychiatric symptoms. Such computerized diagnostic interviews are now available for touch-tone telephone administration.

IVR applications for treatment

Accessible around the clock, IVR programs can provide patient-specific information, self-help treatment, encouragement, reinforcement, and support on request. With confidentiality protected by unique personal identification numbers and passwords, patients interacting with IVR systems provide information that is used to tailor current and future interactions. As goals are achieved or setbacks encountered, context-relevant messages are provided. This type of interaction may be most beneficial in treating frequently occurring behaviors that intrude on daily life, such as smoking, drinking, obsessive-compulsive behaviors, or depression.

A voluntary smoking cessation program using an IVR system advertised through work site health promotions, print media, and radio found that of 571 smokers, 35 percent quit smoking while using the program, and 14 percent remained abstinent six months after their initial call (12). For smokers who called the system five or more times, these percentages increased substantially (68 percent and 22 percent, respectively), suggesting that patients' willingness to use such systems is a strong predictor of IVR treatment effectiveness.

An IVR application for treating patients with obsessive-compulsive disorder allows patients to develop and implement a treatment plan by guid-

More detailed discussions of IVR applications in research have appeared elsewhere (1,2).

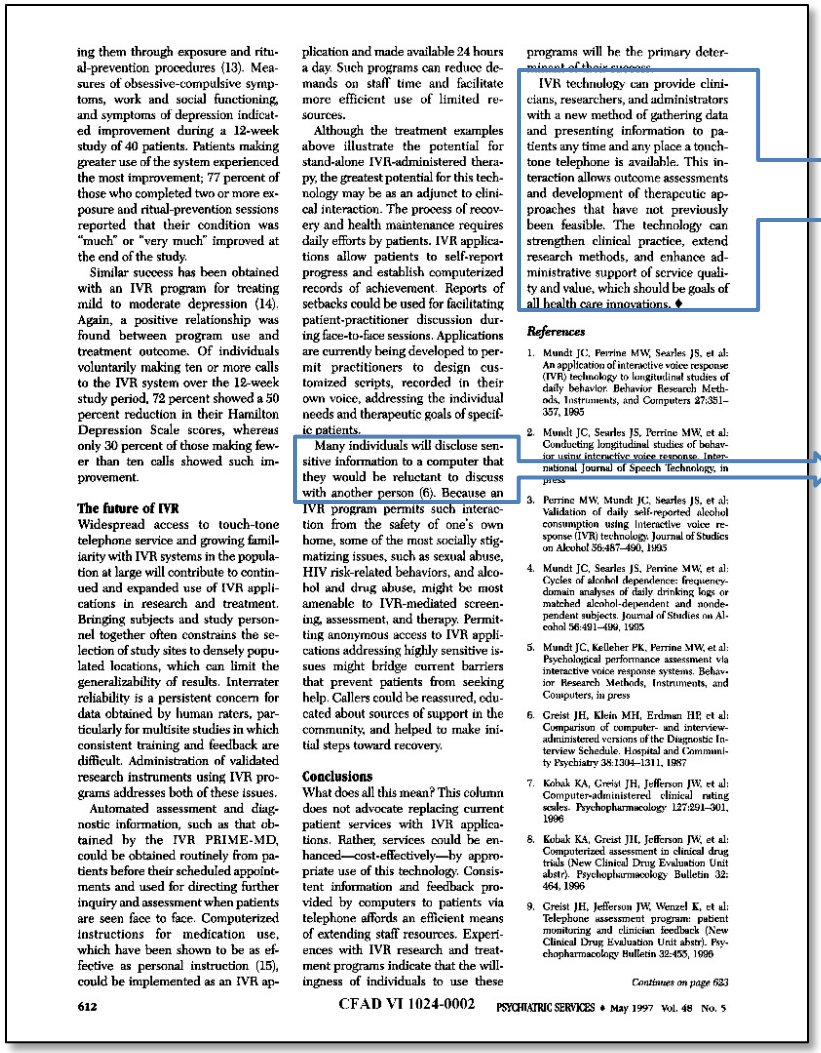
An IVR program for obtaining daily self-reports of alcohol consumption has been demonstrated to provide valid data, permitting analyses of alcohol use patterns that differentiate dependent from nondependent drinkers otherwise matched on quantity-frequency measures of use (3,4). Data collection using IVR systems is beginning to be used for investigating other conditions, such as eating disorders and impaired psychomotor and cognitive performance (5).

Use of IVR systems for data collection

IVR systems for obtaining and managing data are a major advance over previous methods. Touch-tone telephones permit 24-hour data collection, removing previous limitations related to distance or temporal availability of study staff. Automatic data collection by computers eliminates errors due to transcription or interviewer mistakes and facilitates optimal data management procedures.

PRIOR ART

Mundt



ing them through exposure and ritual-prevention procedures (13). Measures of obsessive-compulsive symptoms, work and social functioning, and symptoms of depression indicated improvement during a 12-week study of 40 patients. Patients making greater use of the system experienced the most improvement; 77 percent of those who completed two or more exposure and ritual-prevention sessions reported that their condition was "much" or "very much" improved at the end of the study.

Similar success has been obtained with an IVR program for treating mild to moderate depression (14). Again, a positive relationship was found between program use and treatment outcome. Of individuals voluntarily making ten or more calls to the IVR system over the 12-week study period, 72 percent showed a 50 percent reduction in their Hamilton Depression Scale scores, whereas only 30 percent of those making fewer than ten calls showed such improvement.

The future of IVR

Widespread access to touch-tone telephone service and growing familiarity with IVR systems in the population at large will contribute to continued and expanded use of IVR applications in research and treatment. Bringing subjects and study personnel together often constrains the selection of study sites to densely populated locations, which can limit the generalizability of results. Interrater reliability is a persistent concern for data obtained by human raters, particularly for multisite studies in which consistent training and feedback are difficult. Administration of validated research instruments using IVR programs addresses both of these issues.

Automated assessment and diagnostic information, such as that obtained by the IVR PRIME-MD, could be obtained routinely from patients before their scheduled appointments and used for directing further inquiry and assessment when patients are seen face to face. Computerized instructions for medication use, which have been shown to be as effective as personal instruction (15), could be implemented as an IVR application and made available 24 hours a day. Such programs can reduce demands on staff time and facilitate more efficient use of limited resources.

Although the treatment examples above illustrate the potential for stand-alone IVR-administered therapy, the greatest potential for this technology may be as an adjunct to clinical interaction. The process of recovery and health maintenance requires daily efforts by patients. IVR applications allow patients to self-report progress and establish computerized records of achievement. Reports of setbacks could be used for facilitating patient-practitioner discussion during face-to-face sessions. Applications are currently being developed to permit practitioners to design customized scripts, recorded in their own voice, addressing the individual needs and therapeutic goals of specific patients.

Many individuals will disclose sensitive information to a computer that they would be reluctant to discuss with another person (6). Because an IVR program permits such interaction from the safety of one's own home, some of the most socially stigmatizing issues, such as sexual abuse, HIV risk-related behaviors, and alcohol and drug abuse, might be most amenable to IVR-mediated screening, assessment, and therapy. Permitting anonymous access to IVR applications addressing highly sensitive issues might bridge current barriers that prevent patients from seeking help. Callers could be reassured, educated about sources of support in the community, and helped to make initial steps toward recovery.

Conclusions

What does all this mean? This column does not advocate replacing current patient services with IVR applications. Rather, services could be enhanced—cost-effectively—by appropriate use of this technology. Consistent information and feedback provided by computers to patients via telephone affords an efficient means of extending staff resources. Experiences with IVR research and treatment programs indicate that the willingness of individuals to use these programs will be the primary determinant of their success.

IVR technology can provide clinicians, researchers, and administrators with a new method of gathering data and presenting information to patients any time and any place a touch-tone telephone is available. This interaction allows outcome assessments and development of therapeutic approaches that have not previously been feasible. The technology can strengthen clinical practice, extend research methods, and enhance administrative support of service quality and value, which should be goals of all health care innovations. ♦

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Continues on page 623

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Many individuals will disclose sensitive information to a computer that they would be reluctant to discuss with another person (6). Because an

Source: Ex. 1024 (-01096) at 612; Paper 52 (-01096), Petitioner's Reply, at 26-27.

PRIOR ART

Dr. Fudin's Testimony

233. Because one method of conducting surveys well known to POSAs at the time of the '720 Patent was via the telephone, using an integrated voice response system—which was well known to POSAs at the time—as required by Claim 17, would have been obvious to a POSA. (*See, e.g.*, Ex. 1024 at 611–12, 623.)

Source: Ex. 1021 (-01096) ¶ 233; Paper 52 (-01096), Petitioner's Reply, at 27.

PRIOR ART

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computer. According to Patent Owner, the cited prior art fails to disclose how, when, or by whom the informed consent and risk assignment would be verified. *Id.* at 48–49. Dr. Fudin testifies that one of ordinary skill in the art would have reason to have the prescriber verify both risk group assignment and informed consent at the time of computer entry to eliminate error and delay. Ex. 1021 ¶ 220. Based upon the evidence of record, we credit Dr. Fudin's testimony and hold that one skilled in the art seeking to reduce errors would have reason to enter the informed consent and risk assignment into a computer database at the same time.

Patent Owner also contends that Petitioner has failed to demonstrate that the use of a telephone survey using an integrated voice response system, such as recited in claim 17, would have been obvious to one skilled in the art. Prelim. Resp. 49–50. Petitioner contends that conducting telephone surveys was well known in the art. Pet. 59. Petitioner relies upon the teachings of Mundt, which states that use of interactive voice response systems can strengthen clinical practice, extend research methods, and enhance administrative support of service quality and value. *Id.* (citing Ex. 1024, 612). We hold that the evidence of record demonstrates that one skilled in the art had reason to use interactive voice response systems to conduct patient surveys.

a. Secondary Considerations

Patent Owner contends that secondary consideration evidence demonstrates that the challenged claims are nonobvious over the relied upon prior art. Prelim. Resp. 49–55. We have reviewed the alleged secondary consideration evidence, but are not persuaded that it is sufficient to show

1024, 612). We hold that the evidence of record demonstrates that one skilled in the art had reason to use interactive voice response systems to conduct patient surveys.

Source: Paper 21 (-01096), Institution Decision, at 20; Paper 21 (-01102), Institution Decision, at 22; Paper 22 (-01103), Institution Decision, at 23.

PRIOR ART

FDA Meeting - Genetics

days and see if we come close. We'll try.

Is Dr. Holmes present?

Dr. Holmes is representing the American College of Medical Genetics and the Teratology Society.

DR. HOLMES: Mr. Chairman, could I just sort of make the point that each wants to make separately, back to back, because each submitted a separated statement?

DR. McGUIRE: Okay. He is representing them sequentially. It took me a while to catch on to that.

Thank you.

DR. HOLMES: Okay. First, my comments are reflected in a one-page memo that was just handed out to all the members of the committee after lunch, the American College of Medical Genetics.

It may seem strange to you that a genetics society would be standing here, commenting on potential environmental exposures with awful fetal effects, but many clinical geneticists around the country are expected to provide counseling to pregnant women about exposures in pregnancies, so the geneticists, in fact, are often the clinical teratologists. And I am speaking myself as an active clinical teratologist in the Boston area.

We have several recommendations that are listed, and we are particularly concerned that the committee hear from us what they have obviously heard now

It may seem strange to you that a genetics society would be standing here, commenting on potential environmental exposures with awful fetal effects, but many clinical geneticists around the country are expected to provide counseling to pregnant women about exposures in pregnancies, so the geneticists, in fact, are often the clinical teratologists. And I am speaking myself as an active clinical teratologist in the Boston area.

Source: Ex. 1013 (-01096) at 137; Paper 52 (-01096), Petitioner's Reply, at 25.

PRIOR ART

Dr. Fudin's Testimony

141. *Thalomid PI* does not explicitly disclose genetic testing. However, a POSA would have recognized the need for genetic testing, given the history of a teratogenic drug, particularly thalidomide, which was known to halt a pregnancy or produce a congenital malformation (a birth defect). Also, it was common practice at the time of the invention to conduct genetic testing at the same as the pregnancy testing taught in *Thalomid PI*.

Source: Ex. 1021 (-01096) ¶ 141; Paper 52 (-01096), Petitioner's Reply, at 25.

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taken off of most markets by 1962. (Ex. 1001 at 1:44–45.) Due to thalidomide's therapeutic effects, the drug was reintroduced in the United States in the 1990s with the understanding that it could be marketed only with strict controls, and gained FDA approval for treatment of ENL in 1998. (*See* Ex. 1007 at 901; Ex. 1012 at 320.)

Doctors and pharmacists interested in bringing thalidomide to the market with restrictions to protect from its teratogenic effects considered the Accutane PPP, with its focus on counseling, as a starting point. (Ex. 1013 at 110–11; *see* Ex. 1015 at 1.) They also considered modeling a thalidomide program on experiences with other hazardous drugs, including clozapine (trade name Clozaril®). (Ex. 1013 at 111–12.) As early as 1997, medical professionals observed that the prescription control methods for clozapine, an anti-depressant with potential adverse effects indicated by white blood cell counts ("WBCs"), could be copied for thalidomide. (Ex. 1013 at 112.) In particular, these prescription control methods included keeping records of patients taking the drug, as well as physicians and pharmacists pre-approved to prescribe and dispense the drug. (Ex. 1008 at 899–900; *see* Ex. 1013 at 115–19; Ex. 1015 at 9, 24.) The clozapine patients were also required to submit to weekly WBC testing and could only have a prescription for clozapine filled if the test results fell within a pre-designated range. (Ex. 1008 at 899; *see* Ex. 1013 at 112; Ex. 1015 at 8.)

"It was also well known in the art prior to 2000 to keep prescription records in a computerized system." (*See, e.g.*, Ex. 1016 at 174; Ex. 1017 at 56, 60–63, 68; Ex. 1021 ¶ 56.) Such records would include information such as the patient's sex, allergies,

Doctors and pharmacists interested in bringing thalidomide to the market with restrictions to protect from its teratogenic effects considered the Accutane PPP, with its focus on counseling, as a starting point. (Ex. 1013 at 110–11; *see* Ex. 1015 at 1.) They also considered modeling a thalidomide program on experiences with other hazardous drugs, including clozapine (trade name Clozaril®). (Ex. 1013 at 111–12.) As early as 1997, medical professionals observed that the prescription control methods for clozapine, an anti-depressant with potential adverse effects indicated by white blood cell counts ("WBCs"), could be copied for thalidomide. (Ex. 1013 at 112.) In particular, these prescription control methods included keeping records of patients taking the drug, as well as physicians and pharmacists pre-approved to prescribe and dispense the drug. (Ex. 1008 at 899–900; *see* Ex. 1013 at 115–19; Ex. 1015 at 9, 24.) The clozapine patients were also required to submit to weekly WBC testing and could only have a prescription for clozapine filled if the test results fell within a pre-designated range. (Ex. 1008 at 899; *see* Ex. 1013 at 112; Ex. 1015 at 8.)

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height, weight, and other health-related measures. (*See* Ex. 1017 at 59; Ex. 1021 ¶ 56.) Physicians and pharmacists had used computerized systems to track their patients since at least 1975. (*See, e.g.*, Ex. 1017 at 53; Ex. 1016 at 174, 182–83.) Practitioners then used this data to determine (1) whether to prescribe a drug to a patient, and (2) the duration of the prescription. (*See* Ex. 1017 at 53, 63–67.)

Thus, in the case of thalidomide or any other teratogenic drug, those of ordinary skill in the art would have been—**and indeed were**—motivated to combine the method for avoiding pregnancy with a computerized tracking system that only permits filling prescriptions for the drug when certain conditions (*e.g.*, non-pregnancy) are met. (*See* Ex.1013 at 111–12; Ex. 1021, ¶ 59.) An example of this combination, discussed in detail below, is the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)—"a comprehensive program to control prescribing, dispensing, and use of" thalidomide to ensure that fetal exposure to thalidomide does not occur. (Ex. 1006 at 1, 2, 3; Ex. 1012 at Abstract; *see* Ex. 1021 ¶ 59.)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: THALOMID™ (thalidomide) Capsules Revised Package Insert anticipates Claims 1–32 of U.S. Patent No. 6,315,720 under 35 U.S.C. § 102(b).

The '720 Patent's method for delivering a drug to a patient while avoiding the occurrence of an adverse side effect was known before October 23, 2000—the earliest possible priority date for the '720 Patent—as evidenced by the THALOMID™ (thalidomide) Capsules Revised Package Insert (15 July 1998) ("*Thalomid PI*"). (*See*

Thus, in the case of thalidomide or any other teratogenic drug, those of ordinary skill in the art would have been—**and indeed were**—motivated to combine the method for avoiding pregnancy with a computerized tracking system that only permits filling prescriptions for the drug when certain conditions (*e.g.*, non-pregnancy) are met. (*See* Ex.1013 at 111–12; Ex. 1021, ¶ 59.) An example of this combination,

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perform and yields no more than one would expect from such an arrangement, the combination is obvious.") (internal quotations and citations omitted).

"In view of the guidelines for the avoidance of treating pregnant patients with thalidomide taught by *Thalomid PI*, it would have been obvious to a" person of ordinary skill in the art "to implement the methods disclosed in *Cunningham* to limit dispensation of a drug associated with adverse effects to certain risk groups." (Ex. 1021 ¶ 215.) *See Abbott Labs v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006) (finding substantial question of invalidity because the combination of references for "the reduction of systemic side effects would not be surprising and would not be unexpected."). Therefore, an ordinarily skilled artisan "treating a patient with a teratogenic or other risk-laden drug in accordance with *Thalomid PI's* guidelines would look to the approval code system taught by *Cunningham*—and would view Claims 1 and 28 of the '720 Patent obvious in view of these references." (Ex. 1021 ¶ 216.) *See Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) ("The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.").

2. **Claims 5 and 6 are obvious over *Thalomid PI* in view of the knowledge of one of ordinary skill in the art.**

Claim 5 requires that "said risk group assignment and informed consent is verified by said prescriber at the time that said patient is registered in said computer

"In view of the guidelines for the avoidance of treating pregnant patients with thalidomide taught by *Thalomid PI*, it would have been obvious to a" person of ordinary skill in the art "to implement the methods disclosed in *Cunningham* to limit dispensation of a drug associated with adverse effects to certain risk groups." (Ex. 1021 ¶ 215.) *See Abbott Labs v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir.

unexpected."). Therefore, an ordinarily skilled artisan "treating a patient with a teratogenic or other risk-laden drug in accordance with *Thalomid PI's* guidelines would look to the approval code system taught by *Cunningham*—and would view Claims 1 and 28 of the '720 Patent obvious in view of these references." (Ex. 1021 ¶ 216.) *See*

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Dishman system "to further implement a computerized registry for 'delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug.'" (Ex. 1001 at 18:16–18; Ex. 1027 ¶ 91.) *See Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 977 (Fed. Cir. 2014) ("When a claimed invention involves a combination of elements, however, any need or problem known in the relevant field of endeavor at the time of invention can provide a reason to combine."). Indeed, those of ordinary skill in the art *did* look to the clozapine system described in *Dishman* when developing a thalidomide system like that disclosed in *Powell*. (Ex. 1012 at 111–12.) *See Rogers v. Desa Int'l, Inc.*, 198 Fed. Appx. 918, 922 (Fed. Cir. 2006) ("Evidence that those of ordinary skill in the art in fact combined the prior art teachings as claimed is certainly evidence that they were motivated to do so. Such evidence shows the knowledge of the skilled artisan at the time of the invention, which can provide the basis for a motivation to combine.").

With respect to the second portion of **Claim 1(c)**—"entering said risk group in said medium"—*Dishman* discloses the storage of the patient's "clinical and demographic information" on a computer readable storage medium. (Ex. 1007 at 899.) For example, *Dishman* teaches that 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.) "A POSA would have understood from the *Dishman* reference that this computerized system must include the patient's risk group assignment data in order to

invention can provide a reason to combine."). Indeed, those of ordinary skill in the art *did* look to the clozapine system described in *Dishman* when developing a thalidomide system like that disclosed in *Powell*. (Ex. 1012 at 111–12.) *See Rogers v. Desa Int'l, Inc.*,

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Dr. Fudin's Testimony (-01096)

52. As a result, 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® PPP as well as the clozapine restricted distribution program. (Ex. 1013 at 110–11; *see* Ex. 1015 at 1.)

59. Thus, in the case of thalidomide or any other teratogenic drug, a POSA 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 condition (*e.g.*, non-pregnancy) are met.

Source: Ex. 1002 (-01096) ¶¶ 52, 59.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony (-01102)

59. Thus, in the case of thalidomide or any other teratogenic drug, a POSA 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 condition (*e.g.*, non–pregnancy) are met.

91. A POSA would have been motivated to look to the system disclosed in *Dishman* to further implement a computerized registry for "delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug." (Ex. 1001 at col. 18:34–36.)

Source: Ex. 1027 (-01102) ¶¶ 59, 91.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony (-01103)

60. Indeed, those of ordinary skill in the art *were* motivated to combine the method for avoiding pregnancy with a computerized tracking system that only permits filling prescriptions for the drug when certain conditions (*e.g.*, non-pregnancy) are met. (*See* Ex. 1033 at 1136 ("Celgene has drafted a plan that it hopes will prevent fetal exposure to the drug. … The plan is built on experience with restrictions on such other drugs with severe adverse effects as Accutane … , used to treat severe acne, and Clozaril … , used to treat schizophrenia … [and] a tracking system would be in place to ensure compliance."); Ex.1012 at 111–12.)

Source: Ex. 1027 (-01103) ¶ 60.

MOTIVATION TO COMBINE

Zeldis

require that patients, prescribers, and pharmacists be re-educated if they do not demonstrate an understanding of their responsibilities in the S.T.E.P.S.™ program. The committee also reserves the right, in cases of serious or repeated noncompliance, to revoke a prescriber's, pharmacist's, or patient's registration. Without registration, the individual cannot prescribe, distribute, or receive thalidomide. As necessary, the committee may recommend changes in the S.T.E.P.S.™ program to the FDA. These recommendations may be part of or in addition to the quarterly monitoring reports submitted to the agency as part of the normal drug-licensing process. Any possible fetal exposure is reported to the FDA as a serious adverse event.

Despite all the checks and balances in the S.T.E.P.S.™ program, the system will work only if it makes intuitive sense to its participants and they adhere to program requirements. Before finalizing the design of the program, Celgene conducted market research in groups of physicians who were likely to prescribe thalidomide, patients who were likely to use the drug, and pharmacists. Discussion groups were conducted in several regions of the United States. When given a description of thalidomide's properties without being told the name of the drug, every group stated that the drug being described was similar to thalidomide. When asked to take 10 minutes to discuss and design a system for safe distribution of the drug to those who would benefit from it, every group outlined a plan similar to the S.T.E.P.S.™ program. Finally, after being presented the rudiments of the S.T.E.P.S.™ program, every group agreed that the program was acceptable as presented.

On the basis of this experience and comments received subsequently from various patient advocacy groups, public health officials, and professional groups, we believe that the S.T.E.P.S.™ program makes sense and thus participants will accept and follow it. Every person who comes in contact with a lawfully prescribed formulation of thalidomide will understand the drug's risks and should behave in a manner that will ensure prevention of fetal exposure.

CONCLUSIONS

Thalidomide carries a unique risk along with its important benefits, and a unique approach to managing this risk is necessary. Successful programs previously developed for isotretinoin and clozapine provided guides. However, the S.T.E.P.S.™ program has a greater scope, combining intensive, continuing patient and professional education with restricted distribution and pregnancy testing. It also provides mechanisms for close, constant monitoring to quickly identify noncompliance or other problems. Celgene is committed to making the S.T.E.P.S.™ program succeed and will make any modifications to the program that are necessary to ensure its effectiveness.

Future cases are certain to arise in which a drug offers compelling clinical benefits, but unrestricted distribution poses profound risks to patients or society. It is hoped that the S.T.E.P.S.™ program will provide a model for resolving this recurring dilemma.

Address correspondence to: Jerome B. Zeldis, MD, PhD, Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059.

Future cases are certain to arise in which a drug offers compelling clinical benefits, but unrestricted distribution poses profound risks to patients or society. It is hoped that the S.T.E.P.S.™ program will provide a model for resolving this recurring dilemma.

Source: Ex. 1012 (-01096) at 329; Ex. 2061 (-01096) at 565:10-567:16.

MOTIVATION TO COMBINE

FDA Meeting

contraception, birth control, counseling, and a voluntary registry to track compliance with the program and outcomes to the program.

The program also included a repackaging of Roche's product, from available in bottles to available in a carded blister, where the card provided a lot of opportunity for reminders of the relevant warnings and instructions to patients to be intimately associated with the product.

All of this seemed good, but there were several elements that we questioned whether they were sufficient for the challenge that we saw with thalidomide. Firstly, the surveillance registry was not mandatory, and therefore it's not really clear what the effectiveness of the Accutane program is in the real world. It's not even clear what proportion of patients who take Accutane in fact are participating in the registry survey, although estimates of that have been made.

Secondly, there is no mechanism to ensure that when a prescription shows up in a pharmacy, that the patient has in fact participated in all of the support programs that have been provided by Roche to the dermatology community.

That caused us to look at other programs. Novartis, previously Sandoz, introduced

for the challenge that we saw with thalidomide. Firstly, the surveillance registry was not mandatory, and therefore it's not really clear what the effectiveness of the Accutane program is in the real world. It's not even clear what proportion of patients who take Accutane in fact are participating in the registry survey, although estimates of that have been made.

Secondly, there is no mechanism to ensure that when a prescription shows up in a pharmacy, that the patient has in fact participated in all of the support programs that have been provided by Roche to the dermatology community.

Source: Ex. 1013 (-01096) at 111.

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FDA Meeting

Clozaril, an anti-schizophrenic drug, some years ago as a significant improvement, from an efficacy perspective, over available therapies for many patients. However, it had a life-threatening side effect of agranulocytosis that occurred in a small proportion of the patients.

Sandoz developed a program that, from a practical perspective, ensures that patients have had their white blood counts taken prior to the dispensing of their next prescription, and that those white blood count numbers are in the appropriate range.

In looking at how Sandoz structured this system, we began to see that by taking elements from the Roche program, elements from the Clozaril program and other unique elements, we could create a system that really would be state-of-the-art, represent a significant step, we believe, forward in the ability to make drugs like thalidomide available to patients who need it, while at the same time providing a very high margin for protection.

Components of the program would include education -- not only patient education, but also education aimed at health care professionals from a CE and CME perspective included.

Counseling, with a referral option. If a prescribing physician does not feel capable, competent or willing to provide adequate contraceptive counseling,

In looking at how Sandoz structured this system, we began to see that by taking elements from the Roche program, elements from the Clozaril program and other unique elements, we could create a system that really would be state-of-the-art, represent a significant step, we believe, forward in the ability to make drugs like thalidomide available to patients who need it, while at the same time providing a very high margin for protection.

Source: Ex. 1013 (-01096) at 112.

MOTIVATION TO COMBINE

Institution Decision – 01096 (- 1102, - 1103)

women of childbearing potential and sexually mature males. Ex. 1006, 3–4. The set of conditions for thalidomide treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention, computers were used by physicians and pharmacists to enter and track patient information for harmful and teratogenic drug prescriptions. Ex. 1021 ¶ 91. Dr. Fudin also testifies that one of ordinary skill in the art would have understood that patient risk group assignment would have been entered into a computer database before prescribing and filling prescriptions for thalidomide. We credit Dr. Fudin's testimony, as it is consistent with the admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

Patent Owner contends that Thalomid PI does not disclose determining whether the risk that an adverse side effect is likely to occur is acceptable. Prelim. Resp. 28. We disagree. Thalomid PI states that a prescription for thalidomide for a woman of childbearing potential must not be issued until a written report of a negative pregnancy test has been obtained by the prescriber. Ex. 1006, 2. Accordingly, we find that Thalomid PI discloses determining that the risk is unacceptable for a positive pregnancy test.

Patent Owner contends that Thalomid PI does not describe generating an approval code. Prelim. Resp. 28–29. Patent Owner further contends that Petitioner has failed to provide a rationale to combine Thalomid PI and

admitted prior art and prior art of record. Based on the record presented, we conclude that one of ordinary skill in the art would have assigned risk groups, and entered that information into a computer database, to ensure that physicians and pharmacists had access to the information when prescribing thalidomide and filling such prescriptions to avoid the risk of harmful birth defects.

Source: Paper 21 (-01096), Institution Decision, at 18; Paper 21 (-01102), Institution Decision, at 19; Paper 22 (-01103), Institution Decision, at 19.

MOTIVATION TO COMBINE

Institution Decision – 01102 (and – 01103)

IPR2015-01102
Patent 6,315,720 B1

required different management, than distribution to a small group of individuals at the Department of Veterans Affairs. *Id.* Dr. Fudin testifies that Powell seeks to promote the safest possible clinical use and dispensing of thalidomide, due to the adverse side effect of teratogenicity, and that Dishman describes a computerized program for tightly controlling the dispensing of an antipsychotic drug, known to cause agranulocytosis.

Ex. 1027 ¶¶ 78, 92–94. Dr. Fudin concludes that one skilled in the art would have been guided to use the computer system of Dishman with the written records of Powell, as both references seek to provide a means to monitor and authorize distribution of contraindicated drugs. *Id.* ¶¶ 104, 108. We credit Dr. Fudin's testimony, as it is consistent with the teachings of the prior art, and hold that Powell and Dishman are directed towards similar endeavors, controlling the distribution of a drug having known adverse side effects.

Patent Owner argues that Cunningham is directed to a different endeavor than Powell and Dishman, and that one skilled in the art would not have looked to the teachings of Cunningham for a method of restricting distribution of pharmaceutical drugs. Prelim. Resp. 30. Cunningham describes a system where a pharmacy cannot dispense a pharmaceutical product until authenticity is established and a central computing station issues a pharmacy approval code. Ex. 1008, 11:6–8, 17–23. Dr. Fudin testifies that one skilled in the art would have implemented the methods disclosed in Dishman and Cunningham to limit the distribution of a drug. Ex. 1027 ¶ 104. Based upon the record presented, we conclude that Cunningham is directed to the same general endeavor as Powell and Dishman, controlling the distribution of pharmaceutical products.

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Ex. 1027 ¶¶ 78, 92–94. Dr. Fudin concludes that one skilled in the art would have been guided to use the computer system of Dishman with the written records of Powell, as both references seek to provide a means to monitor and authorize distribution of contraindicated drugs. *Id.* ¶¶ 104, 108. We credit Dr. Fudin's testimony, as it is consistent with the teachings of the prior art, and hold that Powell and Dishman are directed towards similar endeavors, controlling the distribution of a drug having known adverse side effects.

issues a pharmacy approval code. Ex. 1008, 11:6–8, 17–23. Dr. Fudin testifies that one skilled in the art would have implemented the methods disclosed in Dishman and Cunningham to limit the distribution of a drug. Ex. 1027 ¶ 104. Based upon the record presented, we conclude that Cunningham is directed to the same general endeavor as Powell and Dishman, controlling the distribution of pharmaceutical products.

Source: Paper 21 (-01102), Institution Decision, at 17; Paper 22 (-01103), Institution Decision, at 17-18.

MOTIVATION TO COMBINE

Institution Decision – 01102 (and – 01103)

IPR2015-01102
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Patent Owner contends that the Clozaril system of Dishman, as a whole, was a failure, and teaches away from the use of such a system. Prelim. Resp. 12–13, 29. Patent Owner relies upon an article by Dr. Honigfeld, which describes the effects of the National Clozapine Registry System on the incidence of deaths related to agranulocytosis. *Id.* (citing Ex. 2014). We note, however, that Honigfeld states that the actual number of cases of agranulocytosis and related deaths was lower than expected for the national registry maintained by the U.S. manufacturer of clozapine. Ex. 2014, 52 (concluding the national registry "brought about lower than expected rates of agranulocytosis and associated deaths"). We hold that Patent Owner has failed to identify sufficient and credible evidence that the specific computerized system described by Dishman, which was approved by the U.S. manufacturer of clozapine, was considered by one of ordinary skill in the art to be a failure.

According to Patent Owner, Powell fails to disclose assigning patients to risk groups and entering the risk group assignment into a computer database. Prelim. Resp. 32–33. We disagree. The challenged claims are written in a Jepson format, where the admitted prior art recites filling prescriptions only after consulting a computer readable storage medium. Powell identifies different risk groups, including patients that should be excluded such as women who wish to become pregnant and women of childbearing potential who have not practiced a reliable form of contraception for 1 year. Ex. 1006, 901. Hence, we find that Powell discloses that the set of conditions for thalidomide treatment differs based on the risk group assigned. Dr. Fudin testifies that, at the time of the invention, records would be kept relating to risk groups and that electronic records,

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expected rates of agranulocytosis and associated deaths"). We hold that Patent Owner has failed to identify sufficient and credible evidence that the specific computerized system described by Dishman, which was approved by the U.S. manufacturer of clozapine, was considered by one of ordinary skill in the art to be a failure.

Source: Paper 21 (-01102), Institution Decision, at 18; Paper 22 (-01103), Institution Decision, at 18.

MOTIVATION TO COMBINE

Institution Decision - 01103

achieve a predictable result (avoid giving patients drugs that have an unacceptable risk of side effects).

Patent Owner contends that one skilled in the art would not have combined Mitchell and Dishman as they are not directed towards the same endeavor. Prelim. Resp. 29. According to Patent Owner, the commercial pharmacy distribution of a teratogenic drug is far more complex, and required different management, than Dishman's distribution to a small group of individuals at the Department of Veterans Affairs. *Id.* We disagree. Dr. Fudin testifies that Mitchell seeks to avoid treating pregnant patients with isotretinoin, due to the adverse side effect of teratogenicity, and that Dishman describes a computerized program for tightly controlling the dispensing of an antipsychotic drug, known to cause agranulocytosis. Ex. 1027 ¶¶ 61, 63, 66, 99. Dr. Fudin concludes that one skilled in the art would have been guided to use the computer system of Dishman with the written records of Mitchell, as both references seek to provide a means to limit distribution of drugs associated with adverse effects to certain risk groups. *Id.* ¶¶ 99–100. We credit Dr. Fudin's testimony, as it is consistent with the teachings of the prior art, and hold that Mitchell and Dishman are directed towards similar endeavors, controlling the distribution of a drug having known adverse side effects.

Patent Owner argues that Cunningham is directed to a different endeavor than Mitchell and Dishman, and that one skilled in the art would not have looked to the teachings of Cunningham for a method of restricting distribution of pharmaceutical drugs. Prelim. Resp. 30. We disagree. Cunningham describes a system where a pharmacy cannot dispense a pharmaceutical product until authenticity is established and a central

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MOTIVATION TO COMBINE

Patent Owner's Response

PROTECTIVE ORDER MATERIAL

2060 ¶19), was launched with Thalomid® in July 1998. Ex. 1025 at 0002-3; Ex. 2061 at 70:20-71:1. Enhanced S.T.E.P.S.®, which was not launched until September of 2001, is claimed in the '720 patent. Ex. 2008; Ex. 2009; Ex. 2061 at 377:19-378:1; Ex. 2059 ¶22; Ex. 2060 ¶21. CFAD's description of the '720 patent's conception is therefore incorrect.

Dr. Fudin could not think of any reason why, other than the '720 patent itself, a change was needed from S.T.E.P.S.® to Enhanced S.T.E.P.S.® Ex. 2061 at 71:21-72:5. That is because there was no problem to be solved. Dr. Fudin's lack of support for any motivation to arrive at the claimed methods, especially those directed to teratogens and, in particular, thalidomide, is consistent with the prior art. Indeed, S.T.E.P.S.® was 100% successful in preventing the predicted second thalidomide tragedy. Thus, nothing in the prior art that would have motivated a POSA to arrive at the '720 patent's inventions. Ex. 2059 ¶21-22; Ex. 2060 ¶20-21.

Instead, the inventors of the '720 patent—both Celgene employees—conceived of the claimed improved methods using their confidential, nonpublic knowledge regarding Celgene's experience with S.T.E.P.S.®, including confidential feedback from Celgene's vendors pertaining to how S.T.E.P.S.® had functioned behind the scenes. *See generally, e.g.*, Ex. 2007 (discussing Celgene's proposal for Enhanced S.T.E.P.S.®). While S.T.E.P.S.® was 100% successful in preventing fetal exposure to thalidomide, the inventors saw room for significant

thalidomide tragedy. Thus, nothing in the prior art that would have motivated a POSA to arrive at the '720 patent's inventions. Ex. 2059 ¶21-22; Ex. 2060 ¶20-21.

Instead, the inventors of the '720 patent—both Celgene employees—conceived of the claimed improved methods using their confidential, nonpublic knowledge regarding Celgene's experience with S.T.E.P.S.®, including confidential feedback from Celgene's vendors pertaining to how S.T.E.P.S.® had functioned behind the scenes. *See generally, e.g.*, Ex. 2007 (discussing Celgene's proposal for Enhanced S.T.E.P.S.®). While S.T.E.P.S.® was 100% successful in

Source: Paper 40 (-01096), Patent Owner Response, at 6.

MOTIVATION TO COMBINE

Zeldis

require that patients, prescribers, and pharmacists be re-educated if they do not demonstrate an understanding of their responsibilities in the S.T.E.P.S.™ program. The committee also reserves the right, in cases of serious or repeated noncompliance, to revoke a prescriber's, pharmacist's, or patient's registration. Without registration, the individual cannot prescribe, distribute, or receive thalidomide. As necessary, the committee may recommend changes in the S.T.E.P.S.™ program to the FDA. These recommendations may be part of or in addition to the quarterly monitoring reports submitted to the agency as part of the normal drug-licensing process. Any possible fetal exposure is reported to the FDA as a serious adverse event.

Despite all the checks and balances in the S.T.E.P.S.™ program, the system will work only if it makes intuitive sense to its participants and they adhere to program requirements. Before finalizing the design of the program, Celgene conducted market research in groups of physicians who were likely to prescribe thalidomide, patients who were likely to use the drug, and pharmacists. Discussion groups were conducted in several regions of the United States. When given a description of thalidomide's properties without being told the name of the drug, every group stated that the drug being described was similar to thalidomide. When asked to take 10 minutes to discuss and design a system for safe distribution of the drug to those who would benefit from it, every group outlined a plan similar to the S.T.E.P.S.™ program. Finally, after being presented the rudiments of the S.T.E.P.S.™ program, every group agreed that the program was acceptable as presented.

On the basis of this experience and comments received subsequently from various patient advocacy groups, public health officials, and professional groups, we believe that the S.T.E.P.S.™ program makes sense and thus participants will accept and follow it. Every person who comes in contact with a lawfully prescribed formulation of thalidomide will understand the drug's risks and should behave in a manner that will ensure prevention of fetal exposure.

CONCLUSIONS

Thalidomide carries a unique risk along with its important benefits, and a unique approach to managing this risk is necessary. Successful programs previously developed for isotretinoin and clozapine provided guides. However, the S.T.E.P.S.™ program has a greater scope, combining intensive, continuing patient and professional education with restricted distribution and pregnancy testing. It also provides mechanisms for close, constant monitoring to quickly identify noncompliance or other problems. Celgene is committed to making the S.T.E.P.S.™ program succeed and will make any modifications to the program that are necessary to ensure its effectiveness.

Future cases are certain to arise in which a drug offers compelling clinical benefits, but unrestricted distribution poses profound risks to patients or society. It is hoped that the S.T.E.P.S.™ program will provide a model for resolving this recurring dilemma.

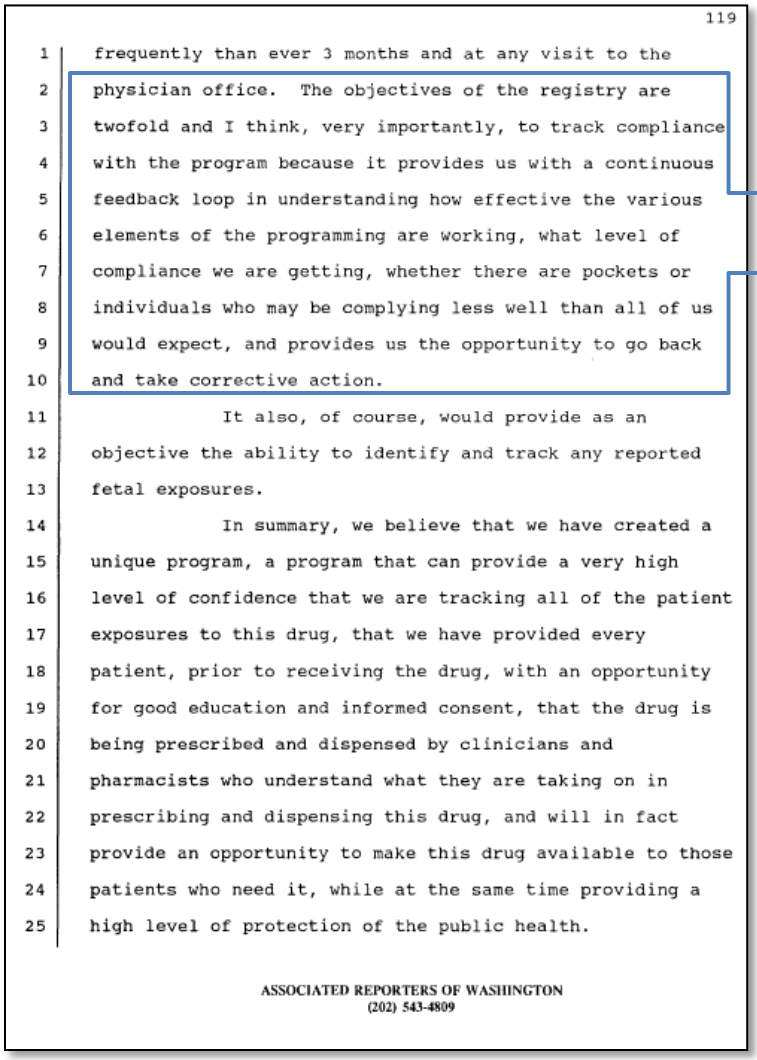
Address correspondence to: Jerome B. Zeldis, MD, PhD, Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059.

pliance or other problems. Celgene is committed to making the S.T.E.P.S.™ program succeed and will make any modifications to the program that are necessary to ensure its effectiveness.

Source: Ex. 1012 (-01096) at 329.

MOTIVATION TO COMBINE

FDA Meeting



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frequently than ever 3 months and at any visit to the physician office. The objectives of the registry are twofold and I think, very importantly, to track compliance with the program because it provides us with a continuous feedback loop in understanding how effective the various elements of the programming are working, what level of compliance we are getting, whether there are pockets or individuals who may be complying less well than all of us would expect, and provides us the opportunity to go back and take corrective action.

It also, of course, would provide as an objective the ability to identify and track any reported fetal exposures.

In summary, we believe that we have created a unique program, a program that can provide a very high level of confidence that we are tracking all of the patient exposures to this drug, that we have provided every patient, prior to receiving the drug, with an opportunity for good education and informed consent, that the drug is being prescribed and dispensed by clinicians and pharmacists who understand what they are taking on in prescribing and dispensing this drug, and will in fact provide an opportunity to make this drug available to those patients who need it, while at the same time providing a high level of protection of the public health.

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physician office. The objectives of the registry are twofold and I think, very importantly, to track compliance with the program because it provides us with a continuous feedback loop in understanding how effective the various elements of the programming are working, what level of compliance we are getting, whether there are pockets or individuals who may be complying less well than all of us would expect, and provides us the opportunity to go back and take corrective action.

Source: Ex. 1013 (-01096) at 119.

MOTIVATION TO COMBINE

Dr. DiPiro's Admission

Is it your testimony that these programs are then relevant to thalidomide?

MS. SHIH: Objection.

A. I believe that my prior discussion about that -- and we noted in some of the literature where isotretinoin and Clozapine systems were discussed by Celgene employees, that the results from these systems could guide an individual in either direction, as a way to do it or as a way not to do it. So in that sense they are relevant.

Source: Ex. 1074 (-01096) at 326:20-327:5

MOTIVATION TO COMBINE

Petitioner's Reply

PROTECTIVE ORDER MATERIAL

time S.T.E.P.S. was launched is of no consequence – Celgene does not dispute that the program had been designed by the time of the FDA meeting, since much of the presentation at the meeting related to the details of the program. *See generally id.*

Celgene and its experts claim that "Celgene conceived of Enhanced S.T.E.P.S. based on confidential, nonpublic information." (POR at 5.) But the POR does not specify what this purported confidential information was, except to call it "confidential feedback from Celgene's vendors." (*See* POR at 5–7.) Nor were Celgene's experts able to testify as to any confidential information that would have prompted a POSA to explore improvements to S.T.E.P.S. in a manner distinct from the actions such a POSA would take *without* the alleged confidential information. While Celgene's experts claim that Exhibit 2007 contains the confidential information that supposedly motivated the inventors, they are unable to (1) identify what that information is, (2) explain how any of it would *not* be known to participants of the S.T.E.P.S. program, or (3) explain how it related to the methods of the '720 patent. For instance, Dr. Frau testified that the confidential information in Exhibit 2007 would be in the "attachments," but she admitted that she had only reviewed Attachment 7, and was unable to point to any specific confidential information in that attachment:

Q. And what in these documents informed the inventors focused on implementing changes based on confidential information?

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S.T.E.P.S. based on confidential, nonpublic information." (POR at 5.) But the POR does not specify what this purported confidential information was, except to call it "confidential feedback from Celgene's vendors." (*See* POR at 5–7.) Nor were Celgene's experts able to testify as to any confidential information that would have prompted a POSA to explore improvements to S.T.E.P.S. in a manner distinct from the actions such a POSA would take *without* the alleged confidential information. While Celgene's experts claim that Exhibit 2007 contains the confidential information that supposedly motivated the inventors, they are unable to (1) identify what that information is, (2) explain how any of it would *not* be known to participants of the S.T.E.P.S. program, or (3) explain how it related to the methods of the '720 patent. For instance, Dr. Frau testified that the confidential information

Source: Paper 52 (-01096), Petitioner's Reply, at 14-15; Paper 24 (-01102), Petitioner's Reply, at 12; Paper 55 (-01103), Petitioner's Reply, at 12.

MOTIVATION TO COMBINE

Dr. Frau's Admissions

Q. What is the confidential information to which you refer in this paragraph?

A. The information between Celgene and the FDA.

Q. And what was that information, in the context of this paragraph?

A. Confidential information that was obtained by Celgene and discussed with the FDA.

Q. And what was that information? What were the contents of that information?

A. Can I have Exhibit 2007?

Q. So what specific information were you referring to in your paragraph 22?

A. All the attachments -- all the attachments mentioned: The S.T.E.P.S. update report immediately follows this cover letter. The attachments to the report contain the following information, and the list of attachments are given.

Q. And what in these documents informed the inventors focused on implementing changes based on confidential information?

A. All the information that they had submitted to the agency concerning Attachments 1 through 6 plus Attachment 7.

Q. Can you point me to specific information within those documents that they used?

A. I don't have those attachments.

Q. So you never reviewed those?

A. I didn't review the contents of those attachments, no.

Source: Ex. 1075 (-01096) at 323:24-324:10; 324:18-325:13.

MOTIVATION TO COMBINE

Dr. DiPiro's Admissions

So what does this particular confidential information have to do with the methods claimed in the '720 patent?

A. It's not possible for me to say. Clearly -- well, I assume they found some advantage in having historical data now being loaded into their database and analyzed.

Q. Is that part of what's claimed in the '720 patent?

A. My understanding of the patent claims, that that would not lay out the whole process.

first page. Could you please explain how the historical data being loaded into the database and analyzed relates to the claims of the '720 patent?

A. I mean in the sense that in my statement that these are methods relating to the '720 patent that are based on confidential information as part of the development of enhanced STEPS.

Q. Which specific method does that relate to?

A. I can't be sure about what specific method. I think it's the claimed methods overall, the claims overall and how they are implemented.

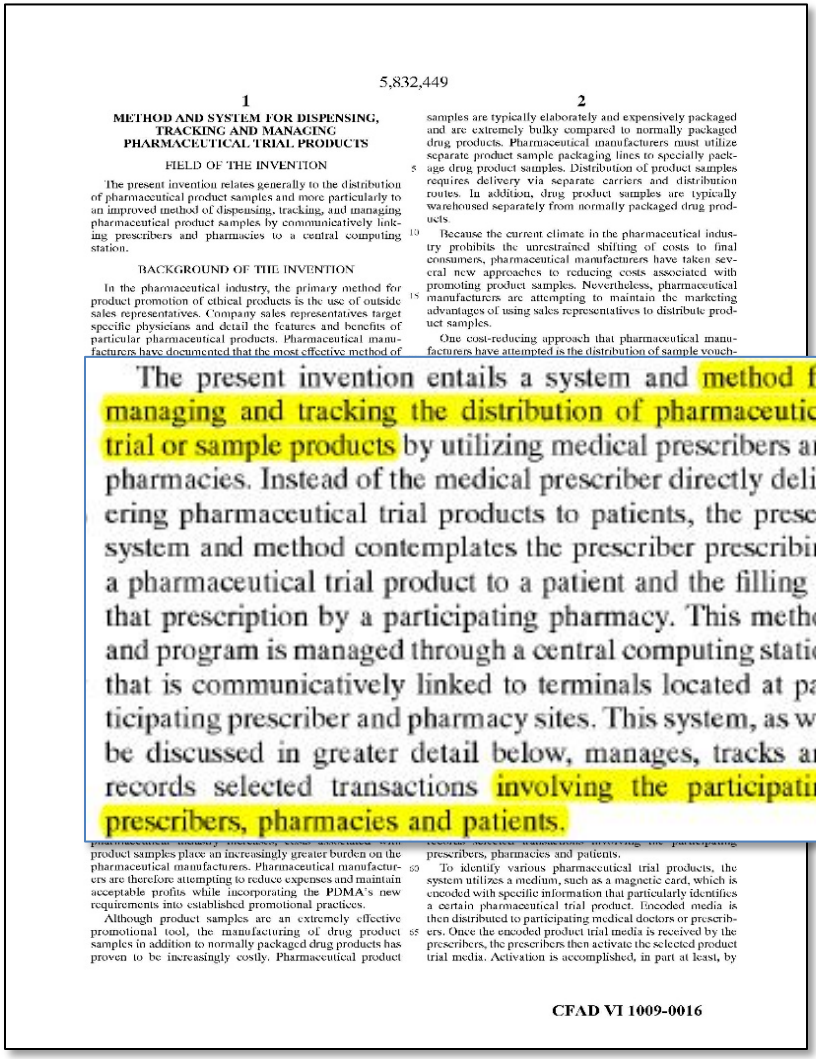
Q. So you can't point to any specific method or claim element of the '720 patent that this particular statement relates to?

A. No.

Source: Ex. 1074 (-01096) at 216:22-217:8; 218:18-219:11.

MOTIVATION TO COMBINE

Cunningham



5,832,449

1

METHOD AND SYSTEM FOR DISPENSING, TRACKING AND MANAGING PHARMACEUTICAL TRIAL PRODUCTS

FIELD OF THE INVENTION

The present invention relates generally to the distribution of pharmaceutical product samples and more particularly to an improved method of dispensing, tracking, and managing pharmaceutical product samples by communicatively linking prescribers and pharmacies to a central computing station.

BACKGROUND OF THE INVENTION

In the pharmaceutical industry, the primary method for product promotion of ethical products is the use of outside sales representatives. Company sales representatives target specific physicians and detail the features and benefits of particular pharmaceutical products. Pharmaceutical manufacturers have documented that the most effective method of

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samples are typically elaborately and expensively packaged and are extremely bulky compared to normally packaged drug products. Pharmaceutical manufacturers must utilize separate product sample packaging lines to specially package drug product samples. Distribution of product samples requires delivery via separate carriers and distribution routes. In addition, drug product samples are typically warehoused separately from normally packaged drug products.

Because the current climate in the pharmaceutical industry prohibits the unrestrained shifting of costs to final consumers, pharmaceutical manufacturers have taken several new approaches to reducing costs associated with promoting product samples. Nevertheless, pharmaceutical manufacturers are attempting to maintain the marketing advantages of using sales representatives to distribute product samples.

One cost-reducing approach that pharmaceutical manufacturers have attempted is the distribution of sample vouch-

product samples place an increasingly greater burden on the pharmaceutical manufacturers. Pharmaceutical manufacturers are therefore attempting to reduce expenses and maintain acceptable profits while incorporating the PDMA's new requirements into established promotional practices.

Although product samples are an extremely effective promotional tool, the manufacturing of drug product samples in addition to normally packaged drug products has proven to be increasingly costly. Pharmaceutical product

prescribers, pharmacies and patients.

To identify various pharmaceutical trial products, the system utilizes a medium, such as a magnetic card, which is encoded with specific information that particularly identifies a certain pharmaceutical trial product. Encoded media is then distributed to participating medical doctors or prescribers. Once the encoded product trial media is received by the prescribers, the prescribers then activate the selected product trial media. Activation is accomplished, in part at least, by

CFAD VI 1009-0016

The present invention entails a system and method for managing and tracking the distribution of pharmaceutical trial or sample products by utilizing medical prescribers and pharmacies. Instead of the medical prescriber directly delivering pharmaceutical trial products to patients, the present system and method contemplates the prescriber prescribing a pharmaceutical trial product to a patient and the filling of that prescription by a participating pharmacy. This method and program is managed through a central computing station that is communicatively linked to terminals located at participating prescriber and pharmacy sites. This system, as will be discussed in greater detail below, manages, tracks and records selected transactions involving the participating prescribers, pharmacies and patients.

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utilizing a prescriber terminal to communicatively link the selected product trial media with the central computing station or host. Once the product trial media has been activated, the prescriber then transfers the activated product trial media to patients. The patients then present the activated product trial media to participating pharmacies. Prior to filling the prescriptive pharmaceutical trial product identified by the media, the pharmacy engages in a procedure designed to validate the patient-presented pharmaceutical trial media. To validate the presented product trial media, the pharmacy communicatively links the presented media to the central computing station via the pharmacy terminal. After making selected verifications, the central computing station validates the presented product trial media. Validation results in the pharmacy dispensing the pharmaceutical trial product identified by the presented media.

Prior to activation and validation, the system and method of the present invention requires that the participating pharmacies and prescribers establish "authorization", that is that they are in fact authorized participants in the pharmaceutical trial product distribution program.

After validation and dispensing, a database associated with the central computing station will have recorded the activation and validation transactions and other data related thereto. Based on the recorded data, audit and accounting procedures can follow. Particularly, dispensed pharmaceutical trial products can now be replaced at the pharmacy level, via wholesalers, by simply replenishing quantities of pharmaceutical products dispensed by the participating pharmacies. Replenishment of the pharmaceutical trial product can be carried out and managed in accordance with the records of the database. Moreover, it is contemplated that participating pharmacies will be remunerated with a dispensing fee that can be determined based on the records of the database associated with the central computing station.

It is therefore an object of the present invention to provide a more effective and efficient process for managing the distribution of pharmaceutical trial products.

Another object of the present invention is to provide a system and process for the distribution of pharmaceutical trial products that inherently includes "checks and balances" and which in the end is designed to ensure integrity and accountability throughout the entire process.

It is also an object of the present invention to provide a system and process for distributing pharmaceutical trial products that is more cost effective than conventional processes, especially processes that require special trial or sample packaging.

It is also an object of the present invention to provide a

Other objects and advantages of the present invention will become apparent and obvious from a study of the following

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description and the accompanying drawings, which are merely illustrative of such invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic illustration of the system of the present invention for managing the distribution of pharmaceutical trial products.

FIG. **2**A is a front side view of the pharmaceutical trial product media that forms a part of the present invention.

FIG. **2**B is a back side view of the pharmaceutical trial media.

FIG. **3**A is a front side view of the authorization media that forms a part of the present invention.

FIG. **3**B is a back side view of the authorization media.

FIGS. **4**A–**4**B depicts a flow chart that shows the basic steps entailed in distributing, tracking and managing pharmaceutical trial product distributed in accordance with the present invention.

FIG. **5** is a flow chart that depicts the basic steps entailed in terminal initialization, whether it be at the prescriber or pharmacy level.

FIGS. **6**A–**6**D depicts a flow chart that shows the basic steps involved in the prescribers activating pharmaceutical trial media.

FIGS. **7**A–**7**E depicts a flow chart that shows the basic steps involved in validating activated product trial media and dispensing pharmaceutical trial products in response to the validation of product trial media.

DETAILED DESCRIPTION OF THE INVENTION

With further reference to the drawings and particularly to FIG. **1**, the system utilized for carrying out the present invention is shown therein and indicated generally by the numeral **10**. System **10** includes a central computing station **12** that has associated therewith a database for storing data and information communicated to the central computing station **12** during various steps or phases of the pharmaceutical trial product distribution process. As will be appreciated from subsequent portions of this disclosure, the present invention contemplates the utilization of participating medical doctors or prescribers and pharmacies to effectuate the distribution of pharmaceutical trial products. In order to communicate with the central computing station **12**, each participating prescriber and pharmacy is provided with a terminal communicatively linked with the central computing station **12**. Therefore, it is appreciated that the system **10** of the present invention will include prescriber terminals **14**

pharmaceutical product trial media that in FIG. 1 is indicated by the numeral **18**. As will be appreciated from subsequent

CFAD VI 1009-0017

Another object of the present invention is to provide a system and process for the distribution of pharmaceutical trial products that inherently includes "checks and balances" and which in the end is designed to ensure integrity and accountability throughout the entire process.

MOTIVATION TO COMBINE

Dr. DiPiro's Admissions

Q. Looking further down column 10 around line 28, in Cunningham it says, "Prior to actually filling the pharmaceutical trial prescription, the participating pharmacy, like the prescriber, must establish authorization."

Do you see that?

A. I do.

Q. And the next paragraph in the same column says, "However, before the pharmacy can fill the prescriptive trial product of any presented product trial media, the product trial media must be subjected to a validation procedure."

Do you see that?

A. I do.

Source: Ex. 1074 (-01096) 268:3-18.

MOTIVATION TO COMBINE

Dr. Frau's Admissions

Q. Going to now Column 3, which is on page 17, looking down at line 39, here Cunningham states, Another object of the present invention is to provide a system and process for the distribution of pharmaceutical trial products that inherently includes checks and balances and which in the end is designed to ensure integrity and accountability throughout the entire process.

Do you see that?

A. That's what it says in that paragraph.

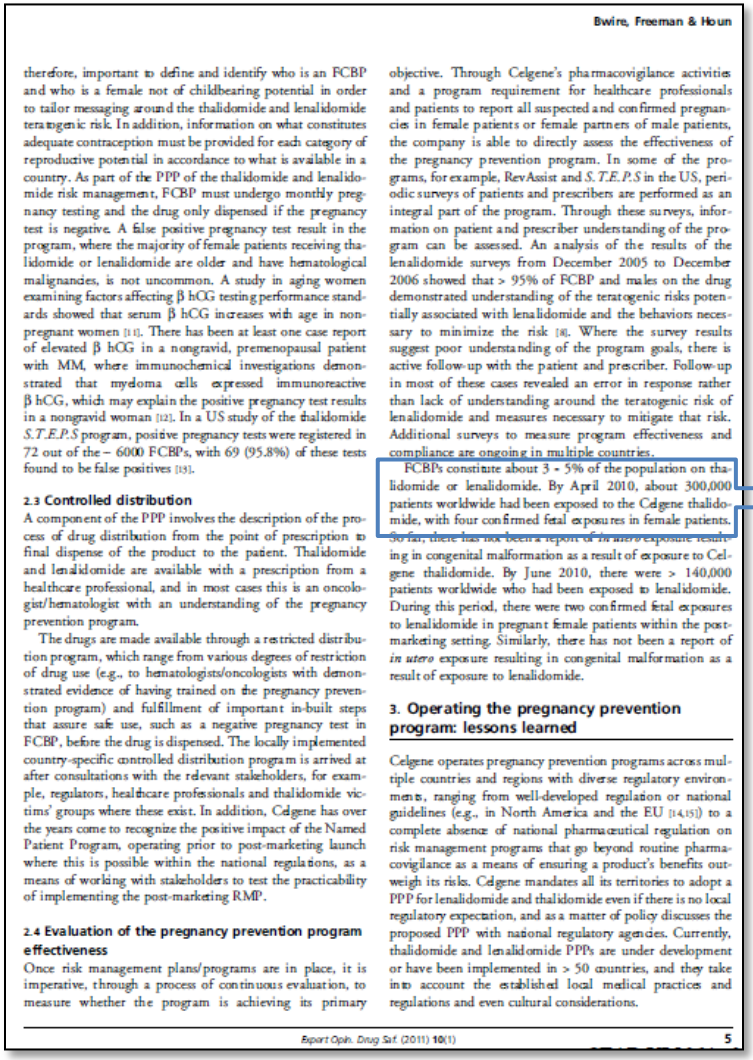
Q. And that's what Cunningham is describing as one of the objects of the present invention; correct?

A. That is what is stated on the page.

Source: Ex. 1075 (-01096) at 320:8-21.

MOTIVATION TO COMBINE

Bwire Publication



Bwire, Freeman & Houn

therefore, important to define and identify who is an FCBP and who is a female not of childbearing potential in order to tailor messaging around the thalidomide and lenalidomide teratogenic risk. In addition, information on what constitutes adequate contraception must be provided for each category of reproductive potential in accordance to what is available in a country. As part of the PPP of the thalidomide and lenalidomide risk management, FCBP must undergo monthly pregnancy testing and the drug only dispensed if the pregnancy test is negative. A false positive pregnancy test result in the program, where the majority of female patients receiving thalidomide or lenalidomide are older and have hematological malignancies, is not uncommon. A study in aging women examining factors affecting β hCG testing performance standards showed that serum β hCG increases with age in non-pregnant women [11]. There has been at least one case report of elevated β hCG in a nongravid, premenopausal patient with MM, where immunochemical investigations demonstrated that myeloma cells expressed immunoreactive β hCG, which may explain the positive pregnancy test results in a nongravid woman [12]. In a US study of the thalidomide *S.T.E.P.S* program, positive pregnancy tests were registered in 72 out of the ~ 6000 FCBPs, with 69 (95.8%) of these tests found to be false positives [13].

2.3 Controlled distribution

A component of the PPP involves the description of the process of drug distribution from the point of prescription to final dispense of the product to the patient. Thalidomide and lenalidomide are available with a prescription from a healthcare professional, and in most cases this is an oncologist/hematologist with an understanding of the pregnancy prevention program.

The drugs are made available through a restricted distribution program, which range from various degrees of restriction of drug use (e.g., to hematologists/oncologists with demonstrated evidence of having trained on the pregnancy prevention program) and fulfillment of important in-built steps that assure safe use, such as a negative pregnancy test in FCBP, before the drug is dispensed. The locally implemented country-specific controlled distribution program is arrived at after consultations with the relevant stakeholders, for example, regulators, healthcare professionals and thalidomide victims' groups where these exist. In addition, Celgene has over the years come to recognize the positive impact of the Named Patient Program, operating prior to post-marketing launch where this is possible within the national regulations, as a means of working with stakeholders to test the practicability of implementing the post-marketing RMP.

2.4 Evaluation of the pregnancy prevention program effectiveness

Once risk management plans/programs are in place, it is imperative, through a process of continuous evaluation, to measure whether the program is achieving its primary objective. Through Celgene's pharmacovigilance activities and a program requirement for healthcare professionals and patients to report all suspected and confirmed pregnancies in female patients or female partners of male patients, the company is able to directly assess the effectiveness of the pregnancy prevention program. In some of the programs, for example, RevAssist and *S.T.E.P.S* in the US, periodic surveys of patients and prescribers are performed as an integral part of the program. Through these surveys, information on patient and prescriber understanding of the program can be assessed. An analysis of the results of the lenalidomide surveys from December 2005 to December 2006 showed that > 95% of FCBP and males on the drug demonstrated understanding of the teratogenic risks potentially associated with lenalidomide and the behaviors necessary to minimize the risk [8]. Where the survey results suggest poor understanding of the program goals, there is active follow-up with the patient and prescriber. Follow-up in most of these cases revealed an error in response rather than lack of understanding around the teratogenic risk of lenalidomide and measures necessary to mitigate that risk. Additional surveys to measure program effectiveness and compliance are ongoing in multiple countries.

FCBPs constitute about 3 - 5% of the population on thalidomide or lenalidomide. By April 2010, about 300,000 patients worldwide had been exposed to the Celgene thalidomide, with four confirmed fetal exposures in female patients. So far, there has not been a report of *in utero* exposure resulting in congenital malformation as a result of exposure to Celgene thalidomide. By June 2010, there were > 140,000 patients worldwide who had been exposed to lenalidomide. During this period, there were two confirmed fetal exposures to lenalidomide in pregnant female patients within the post-marketing setting. Similarly, there has not been a report of *in utero* exposure resulting in congenital malformation as a result of exposure to lenalidomide.

3. Operating the pregnancy prevention program: lessons learned

Celgene operates pregnancy prevention programs across multiple countries and regions with diverse regulatory environments, ranging from well-developed regulation or national guidelines (e.g., in North America and the EU [14,15]) to a complete absence of national pharmaceutical regulation on risk management programs that go beyond routine pharmacovigilance as a means of ensuring a product's benefits outweigh its risks. Celgene mandates all its territories to adopt a PPP for lenalidomide and thalidomide even if there is no local regulatory expectation, and as a matter of policy discusses the proposed PPP with national regulatory agencies. Currently, thalidomide and lenalidomide PPPs are under development or have been implemented in > 50 countries, and they take into account the established local medical practices and regulations and even cultural considerations.

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Source: Ex. 1072 at 5.