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. 6,045,501
GROUNDS FOR INSTITUTION OF IPR

Grounds for Institution of IPR

Institution Decision

Trials@uspto.gov
571.272.7822

Paper 20
Entered: October 27, 2015

UNITED STATES PATENT AND TRADE

BEFORE THE PATENT TRIAL AND AP

COALITION FOR AFFORDABLE DRU
Petitioner,

v.

CELGENE CORPORATION
Patent Owner.

Case IPR2015-01092
Patent 6,045,501

Before MICHAEL P. TIERNEY, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge*.

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

IV. ORDER

It is

ORDERED that an *inter partes* review is instituted on the following ground: Whether claims 1–10 of the '501 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over Powell, Mitchell, and Dishman.

Source: Paper No. 20, Institution Decision, at 16.

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)

’501 Patent – Independent Claim 1

’501 Patent — Claim 1

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

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

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

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

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

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

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

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

- prescriber registration
- pharmacist registration
- patient registration
- retrieving information on ability to become pregnant or impregnate
- counseling
- pregnancy determination
- authorizing filling Rx

Source: Ex. 1001 at claims.

’501 Patent — Dependent Claims

2. The method of claim **1** wherein said drug is thalidomide.

3. The method of claim **1** further comprising including in said registering information concerning male patients who are capable of impregnating females and including said males within said subpopulation.

4. The method of claim **1** wherein said determination comprises pregnancy testing.

5. The method of claim **1** wherein the issuance and fulfillment of said prescriptions are recorded in said computer readable storage medium.

6. The method of claim **1** wherein refilling of said prescriptions is authorizable only in response to information contained on said computer readable storage medium.

7. The method of claim **1** wherein said prescriptions are filled for no more than about 28 days.

8. The method of claim **1** wherein said prescriptions are filled together with distribution of literature warning of the effects of said drug upon foetuses.

9. The method of claim **1** further comprising providing said patients with contraception counseling.

10. The method of claim **1** further comprising:

h. providing to said patients who are capable of becoming pregnant a contraceptive device or formulation.

* * * * *

Patent Owner makes additional arguments for only claims 2, 5, 6, 7, and 10.

Source: Ex. 1001 at claims; Paper 40, Patent Owner Response, at 46.

PERSON OF ORDINARY SKILL IN THE ART

Petition: Dr. Fudin's Testimony

'501 Patent), would typically have either 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 in any one or more of the United States.

16. A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also work collaboratively with other team members that have their own unique specialized skillset, training, and knowledge base, in order to best solve given problems and care for varying patient populations.

V. The '501 Patent

A. The '501 Specification and Prosecution History

17. I have considered the disclosure and file history of the '501 patent from the perspective of a person of ordinary skill in the art as of August 28, 1998.

18. The '501 patent specification describes methods for delivering a drug—either teratogenic in nature or hazardous for another reason—to registered patients while preventing the exposure of a fetus or other contraindicated individuals to the drug. (Ex. 1001, Abstract, 3:21-23.)

19. A teratogenic drug is an agent that, upon administration to the mother or father, may disturb the normal growth and development of an embryo or fetus.

20. The background section of the '501 specification states that prior "methods for controlling the distribution of drugs have been developed in connection with" isotretinoin, including a "pregnancy prevention program." (Ex. 1001 at 1:48-

7

'501 Patent), would typically have either 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 in any one or more of the United States.

16. A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also work collaboratively with other team members that have their own unique specialized skillset, training, and knowledge base, in order to best solve given problems and care for varying patient populations.

POR: Dr. Frau's Proposed Definitions

PROTECTIVE ORDER MATERIAL

58. I understand that obviousness requires more than a mere showing that the prior art includes separate references covering each separate claim limitation. Rather, obviousness requires the additional showing that a POSA at the time of the invention would have selected and combined those prior-art elements in the normal course of research and development to yield the claimed invention. A party seeking to invalidate a patent based on obviousness must demonstrate by a preponderance of the evidence that a POSA would have been motivated to combine the teachings of the prior-art references to achieve the claimed invention and would have had a reasonable expectation of success in doing so.

VI. PERSON OF ORDINARY SKILL IN THE ART

59. I have been asked to opine on the qualifications of a POSA as August 1998. To help me ascertain the qualifications of a POSA, I reviewed the '501 patent and the pertinent patents and references cited in the '501 patent and file history.

60. It is my opinion that a POSA, as of August 1998, would be a person who held at least a bachelor's degree and at least 2 years of experience in risk management relating to pharmaceutical drug products, or a B.S. or M.S. in pharmaceutical drug product risk management or a related field. Alternatively, a POSA might have similar education, training, and industry experience that would confer an equivalent level of skill in the development and/or implementation of

- 24 -

60. It is my opinion that a POSA, as of August 1998, would be a person who held at least a bachelor's degree and at least 2 years of experience in risk management relating to pharmaceutical drug products, or a B.S. or M.S. in pharmaceutical drug product risk management or a related field. Alternatively, a POSA might have similar education, training, and industry experience that would confer an equivalent level of skill in the development and/or implementation of

Source: 37 C.F.R. § 42.100(b); Paper 49, Petitioner Reply, at 7.

POSA

Dr. Frau's Admissions

Q. Assuming that they performed some sort of work related to risk management in pharmaceutical drug products, would that person then be a POSA?

A. Could be.

Q. Could or would?

A. Yes.

Q. Yes, they would be? 04:54:18

A. Yes.

Q. Just so the record's clear.

And is it your testimony that such an individual would be able to design the claimed methods of the '501 patent? 04:54:27

A. No.

Source: Ex. 1067 at 165:18-166:7.

POSA

Dr. Frau's Admissions

5	Q. So according to this definition, a	04:57:39
6	person with a BS in pharmacoeconomics would be a	
7	POSA?	
8	A. Yes.	
9	Q. And would that person be able to design	
10	the claimed methods of the '501 patent?	04:58:08
11	A. No.	

Source: Ex. 1067 at 168:5-11.

Dr. DiPiro's Admissions

Q. Do you have two years of experience in any of these fields, at least two years?

MS. SHIH: Objection. Relevance.

A. In my experience, and another way of thinking about risk management, which may or may not be what they are thinking about, I or anyone who -- I mean, many pharmacists -- many types of pharmacists use risk management techniques in their practice on a day-to-day basis. It's common.

Source: Ex. 1066 at 95:17-96:1.

Dr. DiPiro's Admissions

Q. So just to make it clear, sitting here today, you are not offering an opinion on whether or not you meet Celgene's definition, correct?

A. I have not offered an opinion. I am not today offering an opinion related to Celgene's definition.

Q. So right now, though, because you haven't offered any opinion with respect to that, you can't say for sure whether your testimony would be relevant or wouldn't be relevant, correct?

A. Well, again, I disagree. My testimony is relevant and, clearly, under the definition that Dr. Fudin has posed. And I am rendering no opinion as to whether I would or would not be qualified as a POSA under some other definition, any other definition.

Source: Ex. 1066 at 96:13-19, 99:3-13.

Dr. DiPiro's Admissions

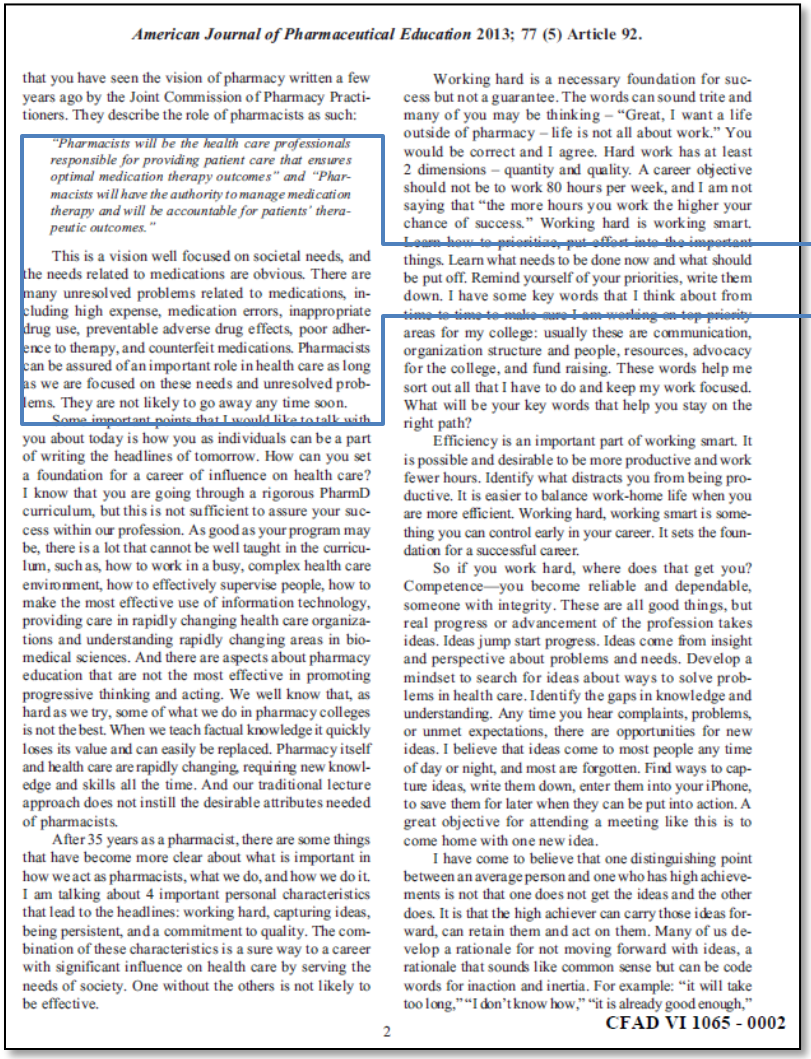
Q. In paragraph 17 you say that, "with Dr. Fudin's definition, a POSA cannot develop the claimed invention."

Is that a fair characterization of your testimony?

A. I would state specifically that they would certainly not have been able to design or implement such systems.

Source: Ex. 1066 at 104:23-105:5.

Dr. DiPiro's Publication



American Journal of Pharmaceutical Education 2013; 77 (5) Article 92.

that you have seen the vision of pharmacy written a few years ago by the Joint Commission of Pharmacy Practitioners. They describe the role of pharmacists as such:

> *"Pharmacists will be the health care professionals responsible for providing patient care that ensures optimal medication therapy outcomes" and "Pharmacists will have the authority to manage medication therapy and will be accountable for patients' therapeutic outcomes."*

This is a vision well focused on societal needs, and the needs related to medications are obvious. There are many unresolved problems related to medications, including high expense, medication errors, inappropriate drug use, preventable adverse drug effects, poor adherence to therapy, and counterfeit medications. Pharmacists can be assured of an important role in health care as long as we are focused on these needs and unresolved problems. They are not likely to go away any time soon.

Some important points that I would like to talk with you about today is how you as individuals can be a part of writing the headlines of tomorrow. How can you set a foundation for a career of influence on health care? I know that you are going through a rigorous PharmD curriculum, but this is not sufficient to assure your success within our profession. As good as your program may be, there is a lot that cannot be well taught in the curriculum, such as, how to work in a busy, complex health care environment, how to effectively supervise people, how to make the most effective use of information technology, providing care in rapidly changing health care organizations and understanding rapidly changing areas in biomedical sciences. And there are aspects about pharmacy education that are not the most effective in promoting progressive thinking and acting. We well know that, as hard as we try, some of what we do in pharmacy colleges is not the best. When we teach factual knowledge it quickly loses its value and can easily be replaced. Pharmacy itself and health care are rapidly changing, requiring new knowledge and skills all the time. And our traditional lecture approach does not instill the desirable attributes needed of pharmacists.

After 35 years as a pharmacist, there are some things that have become more clear about what is important in how we act as pharmacists, what we do, and how we do it. I am talking about 4 important personal characteristics that lead to the headlines: working hard, capturing ideas, being persistent, and a commitment to quality. The combination of these characteristics is a sure way to a career with significant influence on health care by serving the needs of society. One without the others is not likely to be effective.

Working hard is a necessary foundation for success but not a guarantee. The words can sound trite and many of you may be thinking – "Great, I want a life outside of pharmacy – life is not all about work." You would be correct and I agree. Hard work has at least 2 dimensions – quantity and quality. A career objective should not be to work 80 hours per week, and I am not saying that "the more hours you work the higher your chance of success." Working hard is working smart. Learn how to prioritize, put effort into the important things. Learn what needs to be done now and what should be put off. Remind yourself of your priorities, write them down. I have some key words that I think about from time to time to make sure I am working on top priority areas for my college: usually these are communication, organization structure and people, resources, advocacy for the college, and fund raising. These words help me sort out all that I have to do and keep my work focused. What will be your key words that help you stay on the right path?

Efficiency is an important part of working smart. It is possible and desirable to be more productive and work fewer hours. Identify what distracts you from being productive. It is easier to balance work-home life when you are more efficient. Working hard, working smart is something you can control early in your career. It sets the foundation for a successful career.

So if you work hard, where does that get you? Competence—you become reliable and dependable, someone with integrity. These are all good things, but real progress or advancement of the profession takes ideas. Ideas jump start progress. Ideas come from insight and perspective about problems and needs. Develop a mindset to search for ideas about ways to solve problems in health care. Identify the gaps in knowledge and understanding. Any time you hear complaints, problems, or unmet expectations, there are opportunities for new ideas. I believe that ideas come to most people any time of day or night, and most are forgotten. Find ways to capture ideas, write them down, enter them into your iPhone, to save them for later when they can be put into action. A great objective for attending a meeting like this is to come home with one new idea.

I have come to believe that one distinguishing point between an average person and one who has high achievements is not that one does not get the ideas and the other does. It is that the high achiever can carry those ideas forward, can retain them and act on them. Many of us develop a rationale for not moving forward with ideas, a rationale that sounds like common sense but can be code words for inaction and inertia. For example: "it will take too long," "I don't know how," "it is already good enough,"

"Pharmacists will be the health care professionals responsible for providing patient care that ensures optimal medication therapy outcomes" and "Pharmacists will have the authority to manage medication therapy and will be accountable for patients' therapeutic outcomes."

This is a vision well focused on societal needs, and the needs related to medications are obvious. There are many unresolved problems related to medications, including high expense, medication errors, inappropriate drug use, preventable adverse drug effects, poor adherence to therapy, and counterfeit medications. Pharmacists can be assured of an important role in health care as long as we are focused on these needs and unresolved problems. They are not likely to go away any time soon.

Source: Ex. 1065 at 2.

CLAIM CONSTRUCTION

CLAIM CONSTRUCTION

Standard:

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

Claim term in dispute:

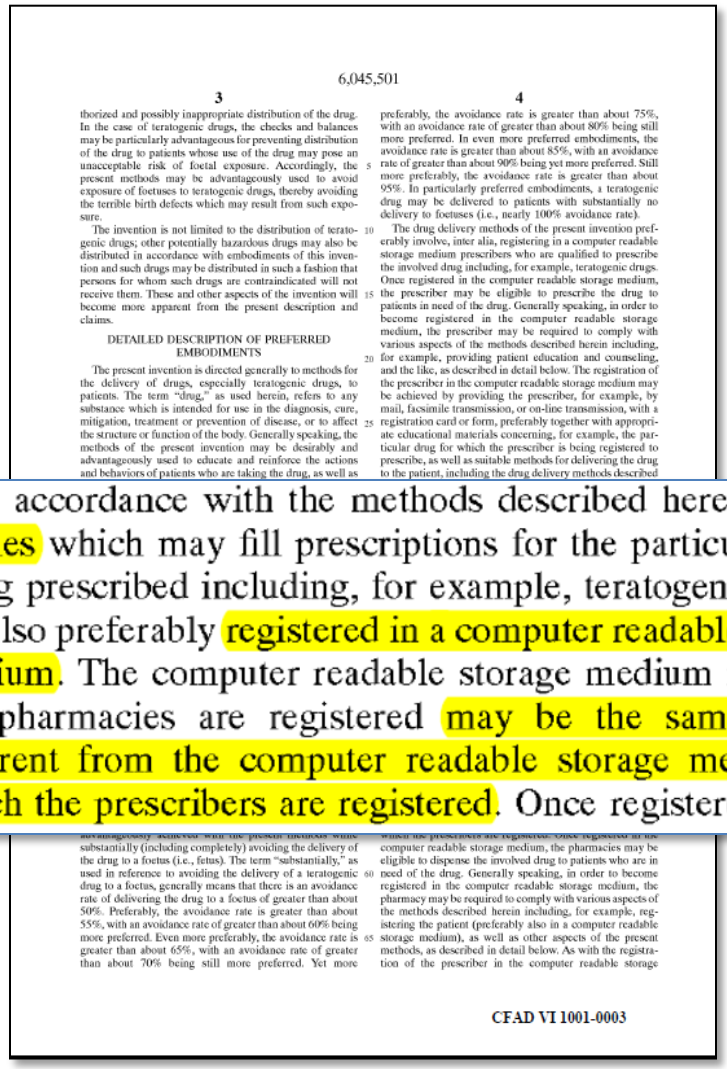
"computer readable storage medium"

Petitioner:	Patent Owner:
No construction necessary.	"centralized database that includes all registration information regarding the claimed prescribers, pharmacies, and patients"

Source: 37 C.F.R. § 42.100(b); Paper 49, Petitioner Reply, at 7.

CLAIM CONSTRUCTION

The '501 Patent Specification



6,045,501

3 4

thorized and possibly inappropriate distribution of the drug. In the case of teratogenic drugs, the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk of foetal exposure. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

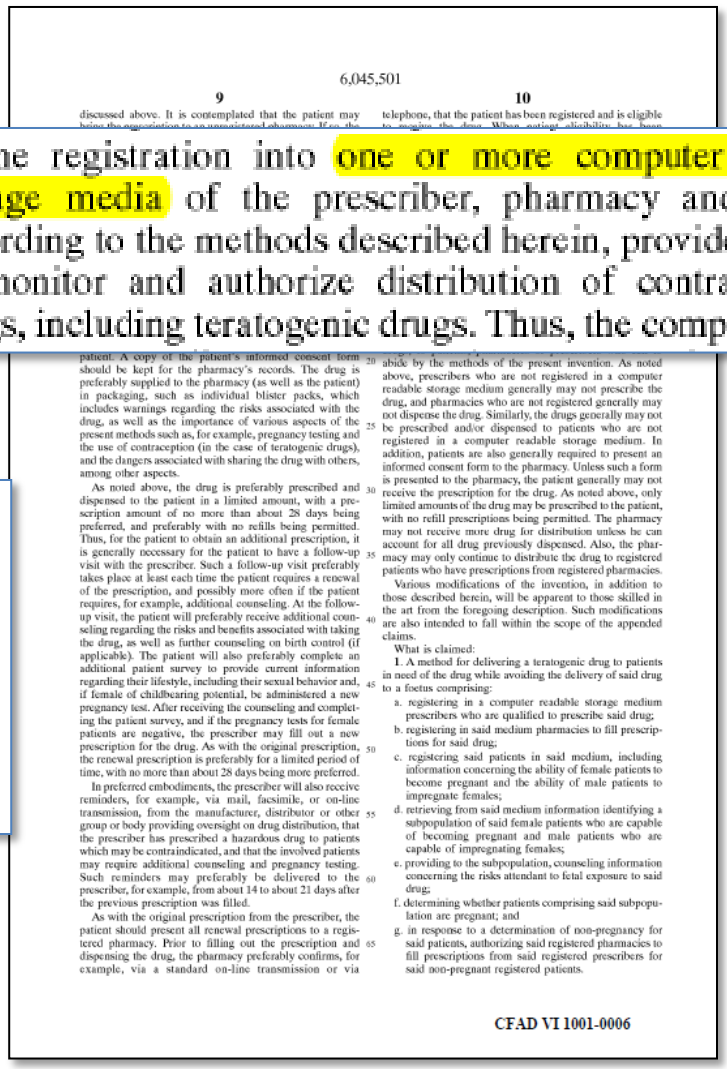
The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking the drug, as well as substantially (including completely) avoiding the delivery of the drug to a foetus (i.e., fetus). The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with substantially no delivery to foetuses (i.e., nearly 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described

CFAD VI 1001-0003



6,045,501

9 10

discussed above. It is contemplated that the patient may

telephone, that the patient has been registered and is eligible

patient. A copy of the patient's informed consent form should be kept for the pharmacy's records. The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In preferred embodiments, the prescriber will also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and pregnancy testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

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

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 pharmacies 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 are also generally required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, 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. The pharmacy may not receive more drug for distribution unless he can account for all drug previously dispensed. Also, the pharmacy may only continue to distribute the drug to registered patients who have prescriptions from registered pharmacies.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

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

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

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

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

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

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

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

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

CFAD VI 1001-0006

In accordance with the methods described herein, pharmacies which may fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the

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 read-

Source: Paper 49, Petitioner Reply, at 7-8; Ex. 1001 at 4:50–57, 10:12–13.

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: Paper 49, Petitioner Reply, at 8; Ex. 1067 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. 06:30:30

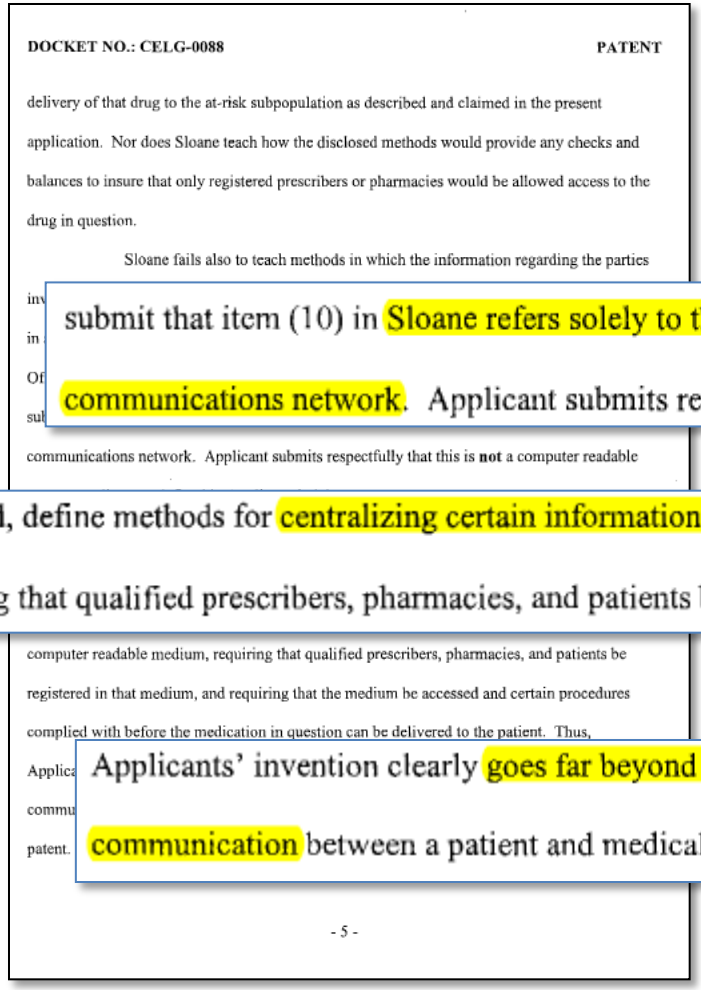
And so I'm viewing this paragraph, what you're saying -- the paragraph that you mentioned as a discussion point from which the final outcome of the discussion are the claims mentioned subsequent to what is claimed. 06:30:42

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

Source: Paper 49, Petitioner Reply, at 8; Ex. 1067 at 203:21-204:10.

CLAIM CONSTRUCTION

The Prosecution History



DOCKET NO.: CELG-0088 PATENT

delivery of that drug to the at-risk subpopulation as described and claimed in the present application. Nor does Sloane teach how the disclosed methods would provide any checks and balances to insure that only registered prescribers or pharmacies would be allowed access to the drug in question.

Sloane fails also to teach methods in which the information regarding the parties

submit that item (10) in Sloane refers solely to the internet (*see* column 2, line 65), *i.e.*, a communications network. Applicant submits respectfully that this is **not** a computer readable

Applicants' claims, on the other hand, define methods for centralizing certain information in a computer readable medium, requiring that qualified prescribers, pharmacies, and patients be

computer readable medium, requiring that qualified prescribers, pharmacies, and patients be registered in that medium, and requiring that the medium be accessed and certain procedures complied with before the medication in question can be delivered to the patient. Thus,

Applicants' invention clearly goes far beyond merely using computers to facilitate communication between a patient and medical service providers as described in the Sloane patent.

- 5 -

Source: Paper 49, Petitioner Reply, at 9; Ex. 1004 at 78.

PRIOR ART

PRIOR ART

Mitchell

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

SPECIAL ARTICLE

A PREGNANCY-PREVENTION PROGRAM IN WOMEN OF CHILDBEARING AGE RECEIVING ISOTRETINOIN

ALLEN A. MITCHELL, M.D., CARLA M. VAN BENNEKOM, M.P.H., AND CAROL LOUIK, SC.D.

Abstract *Background.* Isotretinoin is effective in treating severe acne, but it is also teratogenic. To minimize pregnancies among exposed women, the manufacturer, together with the U.S. Food and Drug Administration, implemented a multicomponent Pregnancy Prevention Program in 1988. We report the results of an ongoing survey designed to assess compliance with this program.

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.

Conclusions. The pregnancy rate among women receiving isotretinoin therapy was substantially lower than that in the general population and was compatible with the characteristics and behavior of the enrolled women. (N Engl J Med 1995;333:101-6.)

IN 1982, the vitamin A analogue isotretinoin (Accutane) was introduced in the United States for the treatment of severe recalcitrant cystic acne. Because studies in animals had suggested that isotretinoin might be teratogenic in humans, the drug was contraindicated in women who were or might become pregnant during therapy or in the following month. The concern about human teratogenicity proved well founded, because it was soon demonstrated that approximately 25 to 30 percent of exposed fetuses had birth defects — the so-called Accutane embryopathy, consisting of craniofacial, heart, and central nervous system defects.[1] Despite prominent warnings to physicians in direct mailings, advertisements, and the package insert, reports of pregnancies in exposed women continued to accumulate, and by 1989 approximately 78 malformed infants had been reported.[2]

In the spring of 1988, this issue was reviewed by an advisory committee to the U.S. Food and Drug Administration. There was little debate about the teratogenicity of isotretinoin, but dermatologists and others asserted that its unique efficacy in the treatment of severe acne, together with its relatively short treatment course (15 to 20 weeks), warranted its continued availability.[3,4] As an alternative to removing the drug from the market or formally restricting its use, the manufacturer proposed an aggressive program designed to reduce the risk of pregnancy among women taking the drug. The committee recommended that the major components of this program be implemented, and the manufacturer's Pregnancy Prevention Program commenced in the fall of 1988.

The program was targeted at both prescribers and patients. In late 1988, materials were distributed to every dermatologist and to all nondermatologists identified as prescribers of isotretinoin in the United States. The materials included guidelines for physicians (instructing them, for example, to warn patients of risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next normal menstrual period). They also included a patient-qualification checklist, an information brochure for patients, contraceptive information, information about and the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling), and a consent form. In addition, in mid-1989 the manufacturer replaced traditional medication bottles with a 10-capsule blister pack that contained information directed specifically at women: the package included warnings about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon behind each capsule, and line drawings of malformations associated with isotretinoin. The program was reinforced by periodic communications directed at prescribers and pharmacists.

We designed and conducted a survey to assess the compliance of physicians and patients with the program and to identify the rate of pregnancy during

From the Slone Epidemiology Unit, School of Public Health, Boston University School of Medicine, Boston. Address reprint requests to Dr. Mitchell at the Slone Epidemiology Unit, 1371 Beacon St., Brookline, MA 02146.

Presented in part at meetings of the International Conference on Pharmacoepidemiology, Minneapolis, September 5–8, 1989; the Teratology Society, Victoria, B.C., Canada, June 8–12, 1990; the American Epidemiological Society, Pittsburgh, March 25–26, 1993; and the American Osteopathic College of Dermatology, Boston, October 10–14, 1993.

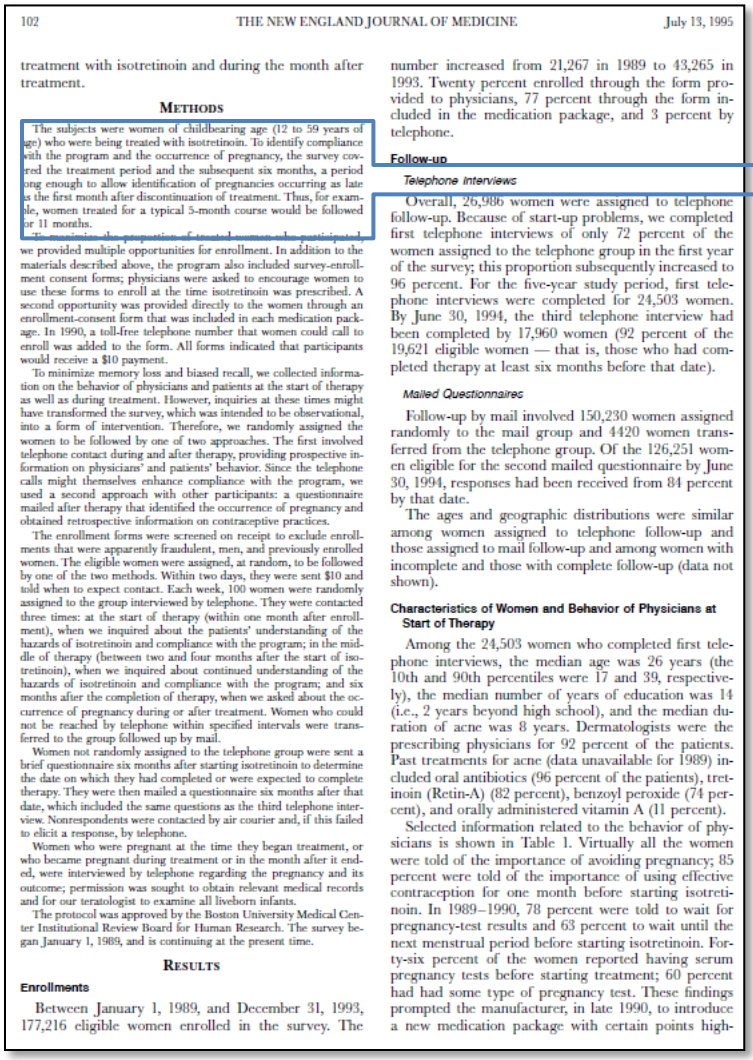
Supported by Hoffmann–La Roche.

The program was targeted at both prescribers and patients. In late 1988, materials were distributed to every dermatologist and to all nondermatologists identified as prescribers of isotretinoin in the United States. The materials included guidelines for physicians (instructing them, for example, to warn patients of risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next normal menstrual period). They also included a patient-qualification checklist, an information brochure for patients, contraceptive information, information about and the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling), and a consent form. In addition, in mid-1989 the manufacturer replaced traditional medication bottles with a 10-capsule blister pack that contained information directed specifically at women: the package included warnings about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon behind each capsule, and line drawings of malformations associated with isotretinoin. The program was reinforced by periodic communications directed at prescribers and pharmacists.

Source: Paper 1, Petition, at 25, 40-41, 44; Ex. 1006 at 101.

PRIOR ART

Mitchell



102 THE NEW ENGLAND JOURNAL OF MEDICINE July 13, 1995

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.

[illegible] 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.

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 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-

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.

Source: Paper 1, Petition, at 40; Ex. 1006 at 102.

PRIOR ART

Mitchell

Vol. 333 No. 2 PREVENTION OF PREGNANCY IN WOMEN RECEIVING ISOTRETINOIN 105

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.[8] 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 117,652 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., R. 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. Trussell, 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.

References

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

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.

Dr. Fudin's Testimony

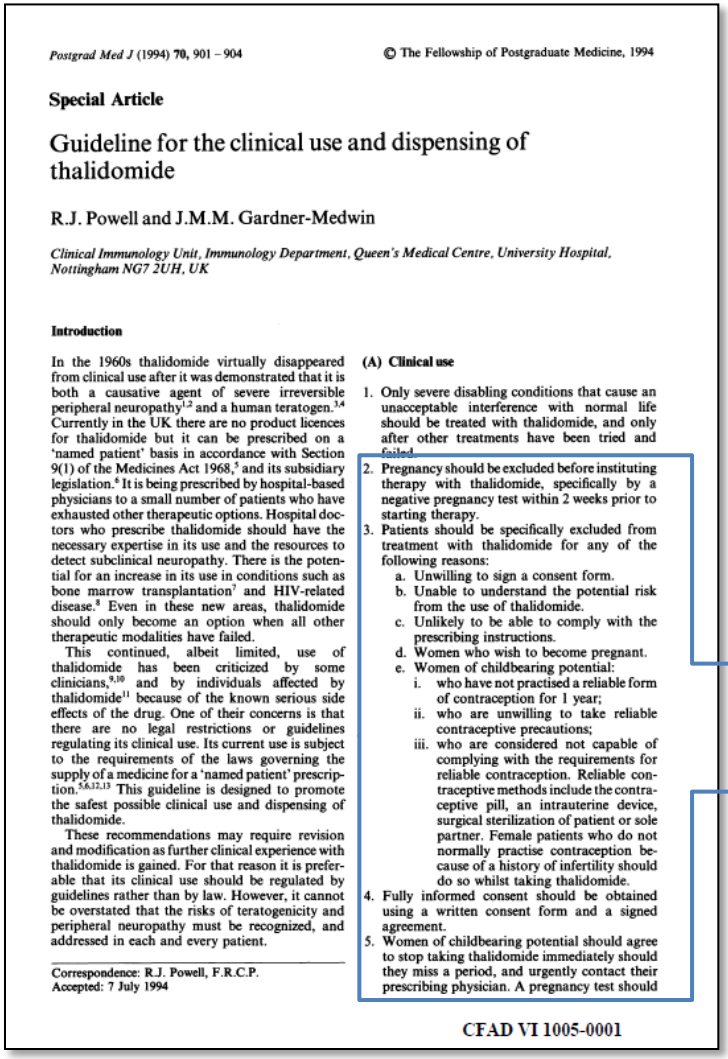
168. The *Mitchell* reference also discloses providing contraception with the drug. In the program described in *Mitchell*, patients are provided with "the necessary forms for a contraception referral program (in which the manufacturer would reimburse patients for a visit to another physician for contraceptive counseling)." (Ex. 1006 at 101.)

169. A person of ordinary skill in the art would have understood from this disclosure that the other physician would, after ensuring that it is medically appropriate, provide contraception—either in device or drug form.

Source: Ex. 1002 ¶¶ 168–169.

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

R.J. Powell and J.M.M. Gardner-Medwin

Clinical Immunology Unit, Immunology Department, Queen's Medical Centre, University Hospital, Nottingham NG7 2UH, UK

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

CFAD VI 1005-0001

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

PRIOR ART

Powell

be provided and, if positive, appropriate counselling should be given.
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.

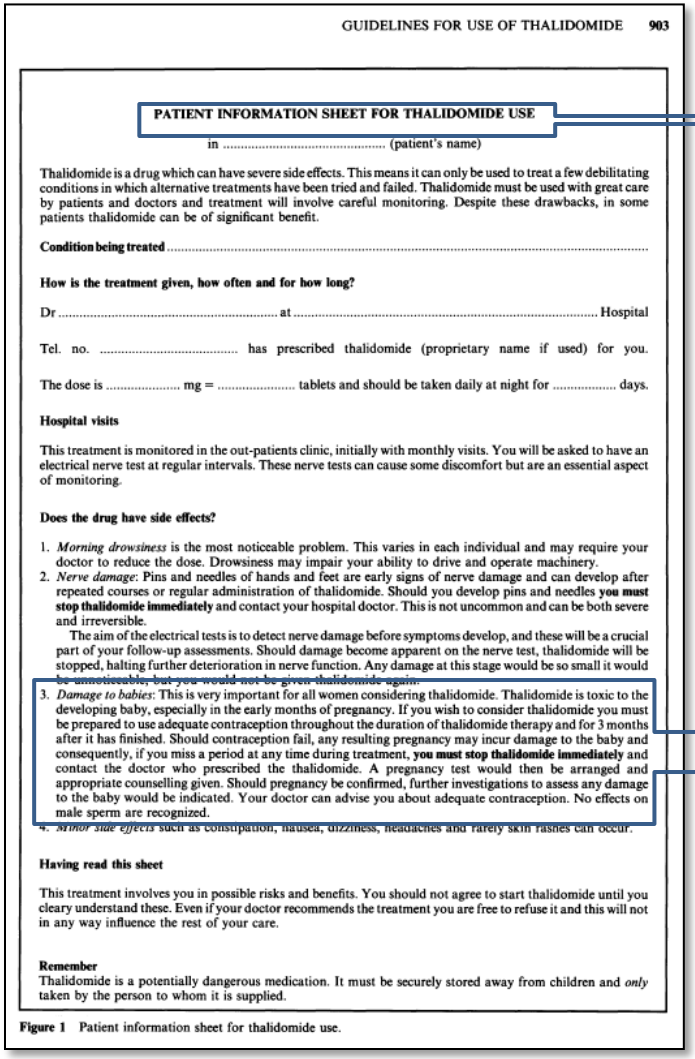
(D) Patient information

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.

Source: Paper 1, Petition, at 14, 24, 35, 40, 43-44; Ex. 1005 at 902.

PRIOR ART

Powell



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 cleary 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.

PATIENT INFORMATION SHEET FOR THALIDOMIDE USE

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.

PRIOR ART

Powell

be provided and, if positive, appropriate counselling should be given.
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

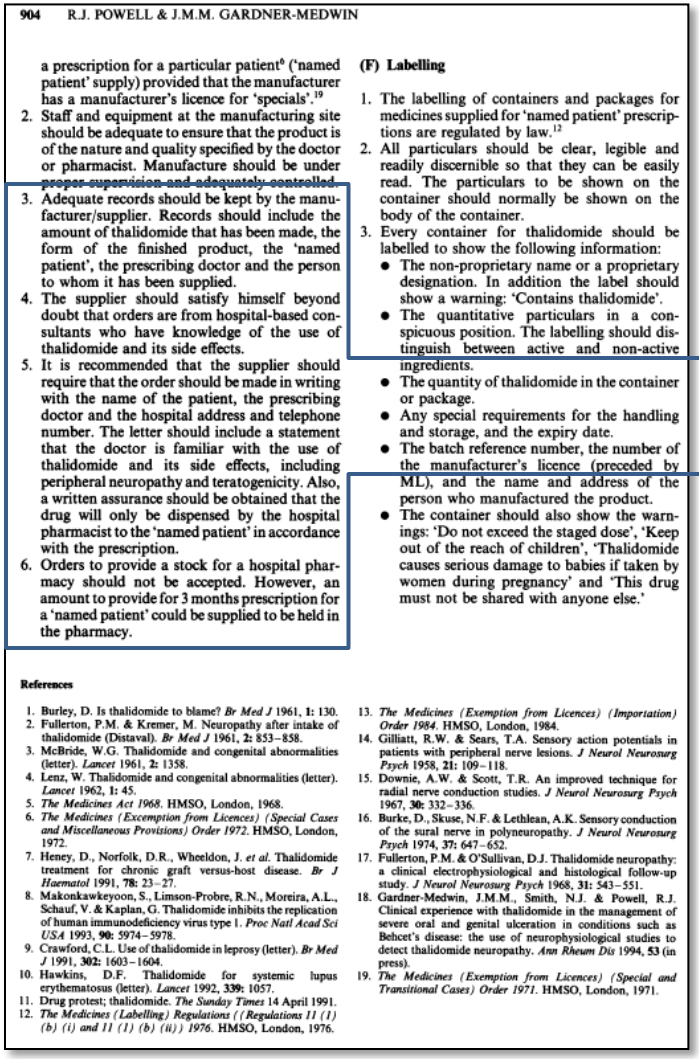
1. Thalidomide does not have a product licence in the UK. Nevertheless, a manufacturer or supplier may supply it to a medical practitioner for

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

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.

PRIOR ART

Powell



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.'

References

1. Burley, D. Is thalidomide to blame? *Br Med J* 1961, **1:** 130.
2. Fullerton, P.M. & Kremer, M. Neuropathy after intake of thalidomide (Distaval). *Br Med J* 1961, **2:** 853–858.
3. McBride, W.G. Thalidomide and congenital abnormalities (letter). *Lancet* 1961, **2:** 1358.
4. Lenz, W. Thalidomide and congenital abnormalities (letter). *Lancet* 1962, **1:** 45.
5. *The Medicines Act 1968*. HMSO, London, 1968.
6. *The Medicines (Exemption from Licences) (Special Cases and Miscellaneous Provisions) Order 1972*. HMSO, London, 1972.
7. Heney, D., Norfolk, D.R., Wheeldon, J. *et al.* Thalidomide treatment for chronic graft versus-host disease. *Br J Haematol* 1991, **78:** 23–27.
8. Makonkawkeyoon, S., Limson-Probre, R.N., Moreira, A.L., Schauf, V. & Kaplan, G. Thalidomide inhibits the replication of human immunodeficiency virus type 1. *Proc Natl Acad Sci USA* 1993, **90:** 5974–5978.
9. Crawford, C.L. Use of thalidomide in leprosy (letter). *Br Med J* 1991, **302:** 1603–1604.
10. Hawkins, D.F. Thalidomide for systemic lupus erythematosus (letter). *Lancet* 1992, **339:** 1057.
11. Drug protest; thalidomide. *The Sunday Times* 14 April 1991.
12. *The Medicines (Labelling) Regulations ((Regulations 11 (1) (b) (i) and 11 (1) (b) (ii)) 1976*. HMSO, London, 1976.
13. *The Medicines (Exemption from Licences) (Importation) Order 1984*. HMSO, London, 1984.
14. Gilliatt, R.W. & Sears, T.A. Sensory action potentials in patients with peripheral nerve lesions. *J Neurol Neurosurg Psych* 1958, **21:** 109–118.
15. Downie, A.W. & Scott, T.R. An improved technique for radial nerve conduction studies. *J Neurol Neurosurg Psych* 1967, **30:** 332–336.
16. Burke, D., Skuse, N.F. & Lethlean, A.K. Sensory conduction of the sural nerve in polyneuropathy. *J Neurol Neurosurg Psych* 1974, **37:** 647–652.
17. Fullerton, P.M. & O'Sullivan, D.J. Thalidomide neuropathy: a clinical electrophysiological and histological follow-up study. *J Neurol Neurosurg Psych* 1968, **31:** 543–551.
18. Gardner-Medwin, J.M.M., Smith, N.J. & Powell, R.J. Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behcet's disease: the use of neurophysiological studies to detect thalidomide neuropathy. *Ann Rheum Dis* 1994, **53** (in press).
19. *The Medicines (Exemption from Licences) (Special and Transitional Cases) Order 1971*. HMSO, London, 1971.

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.

Source: Paper 1, Petition, at 26, 33, 36-37, 39, 43; Ex. 1005 at 904.

Powell – The Institution Decision

IPR2015-01092
Patent 6,045,501

Patent Owner raises one argument specific to claim 7, which adds a limitation that "said prescriptions are filled for no more than about 28 days." Ex. 1001, claim 7. In Patent Owner's view, Petitioner fails to explain adequately how the applied art would have led one of ordinary skill in the art "to modify Powell's teaching to use a 3-month supply [of thalidomide] to arrive at the claimed 28-day limitation." Prelim. Resp. 35; *see* Ex. 1005, 904 (Powell's disclosure that "an amount to provide for 3 months prescription for a 'named patient' could be supplied to be held in the pharmacy").

Patent Owner's argument is not persuasive based on the record developed at this stage. In that regard, Petitioner directs us to Powell's disclosure "that, initially, 'follow-up visits' with prescribing physicians 'should be at monthly intervals or less.'" Pet. 33 (quoting Ex. 1005, 902). Petitioner also advances evidence that one of ordinary skill in the art "would understand that the follow up visits would be required before additional drug was dispensed." *Id.* (quoting Ex. 1002 ¶ 150). And Petitioner comes forward with information that a skilled artisan would have arrived at a 28-day restriction based on the "general knowledge in the field" that the "average woman's menstrual cycle is approximately 28 days." *Id.*; Ex. 1002 ¶ 152). Where "avoidance of pregnancy is of paramount importance," and "oral contraceptives are prescribed" in 28-day cycles, Petitioner shows sufficiently that "the claimed time period aligns with other prescribing habits of physicians." *Id.* at 34 (quoting Ex. 1002 ¶¶ 153–154).

On this record, there is a reasonable likelihood that Petitioner would prevail in showing that the subject matter of claims 2–10 would have been obvious over Powell, Mitchell, and Dishman.

15

Patent Owner's argument is not persuasive based on the record developed at this stage. In that regard, Petitioner directs us to Powell's disclosure "that, initially, 'follow-up visits' with prescribing physicians 'should be at monthly intervals or less.'" Pet. 33 (quoting Ex. 1005, 902). Petitioner also advances evidence that one of ordinary skill in the art "would understand that the follow up visits would be required before additional drug was dispensed." *Id.* (quoting Ex. 1002 ¶ 150). And Petitioner comes forward with information that a skilled artisan would have arrived at a 28-day restriction based on the "general knowledge in the field" that the "average woman's menstrual cycle is approximately 28 days." *Id.*; Ex. 1002 ¶ 152). Where "avoidance of pregnancy is of paramount importance," and "oral contraceptives are prescribed" in 28-day cycles, Petitioner shows sufficiently that "the claimed time period aligns with other prescribing habits of physicians." *Id.* at 34 (quoting Ex. 1002 ¶¶ 153–154).

Source: Paper 20, Institution Decision, at 15; Ex. 1005 at 904.

PRIOR ART

Mann

D. Rates of Drug Passage into Semen and the Semen/Blood-Plasma Concentration Ratio

The rates at which drugs pass into human semen have been investigated in respect to several antibiotics including ampicillin, erythromycin, and cephalexin.[50,51] In some of these studies, semen analyses were run concurrently with blood analyses. It was found that 2 hr after oral administration of 160 mg of trimethoprim and 800 mg of sulphamethoxazole, the concentration of trimethoprim was equal to or higher in semen than in blood plasma, while the values for sulphamethoxazole were 20 to 74 μg/mℓ in the seminal plasma and 58 to 76 in blood plasma.[52]

Methadone, phenytoin, valproic acid, tranexamic acid, and selenite are all capable of passing into semen. Methadone, the potent analgesic pharmacologically resembling morphine, is excreted in rabbit and human semen; the semen/blood concentration ratio of methadone was given as 1.8 in man,[53] and 6 to 10 in the rabbit.[54] Special significance attaches to the observation that when methadone is given to male rats before mating, the offspring of females mated to these males is adversely affected; namely, neonatal mortality is increased and the young show a distinctly reduced weight at the time of birth and weaning.[55,56] Phenytoin (diphenylhydantoin) injected to a male rabbit as a single dose of 4.64 mg, passes quickly into the blood and semen; the semen/blood plasma concentration ratio in such a rabbit is about 0.2 and persists at this level over a period of at least 8 hr.[57] The same anticonvulsant drug, when orally administered to epileptic patients, is established in blood plasma at a concentration of 13.8 μg/mℓ, but in the semen at 2.31 μg/mℓ; this corresponds to a semen/blood plasma concentration ratio of 0.17, i.e., close to the value of 0.2 which was found in rabbits.[57] A similar study was carried out with valproic acid (dipropylacetic acid).[54] In rabbits infused with valproic acid, the concentration of this drug was persistently lower in the semen (collected with artificial vagina) than in the blood, but the concentration-time curve in the semen was parallel (approximately) to that in blood plasma, indicating that the drug levels in semen are directly proportional to those in blood plasma. In the two human subjects used for this study who were given 500 mg valproic acid orally, the concentrations of the drug also remained at a lower level in semen than in the blood; in these two men the semen/blood plasma concentration ratio ranged from 0.052 to 0.091 (mean = 0.072).

The detection and determination of chemicals in semen gradually is becoming more reliable and simple, thanks to new sensitive analytical methods, so that compounds that may have escaped detection previously, even by gas chromatography-mass spectrometry, now can be screened routinely in human and animal semen. One such method is the application of negative-chemical-ionization mass spectral screening for detection of tris(dichloropropyl)phosphate (the flame retardant with mutagenic and antifertility properties). This screening technique also has been applied successfully to detect the presence of other chemicals such as hexachlorobenzene, DDT metabolites, and polychloronaphtalenes.[5,58]

E. Adsorption of Excreted Thalidomide and Tetracycline on Spermatozoa

The potential risk to the function of the spermatozoa in ejaculated semen, and ultimately to male fertility, need not be a serious one merely on the grounds that a given foreign chemical managed to pass into the seminal plasma. To ascertain the existence of such a risk, supplementary evidence would be required to show that this substance is in fact capable of interacting with spermatozoa. Such evidence has been provided for several chemicals. Thalidomide and tetracycline are drugs known to be strongly adsorbed by spermatozoa. Experiments indicating that thalidomide administered to male rabbits adversely affects the pregnancy of females mated to these males, for the first time drew attention to the until then unrecognized eventuality of drug-induced pregnancy-wastage occurring by the paternal route.[59,60] Subsequently, it was shown that

E. Adsorption of Excreted Thalidomide and Tetracycline on Spermatozoa

The potential risk to the function of the spermatozoa in ejaculated semen, and ultimately to male fertility, need not be a serious one merely on the grounds that a given foreign chemical managed to pass into the seminal plasma. To ascertain the existence of such a risk, supplementary evidence would be required to show that this substance is in fact capable of interacting with spermatozoa. Such evidence has been provided for several chemicals. Thalidomide and tetracycline are drugs known to be strongly adsorbed by spermatozoa. Experiments indicating that thalidomide administered to male rabbits adversely affects the pregnancy of females mated to these males, for the first time drew attention to the until then unrecognized eventuality of drug-induced pregnancy-wastage occurring by the paternal route.[59,60] Subsequently, it was shown that

Mann – The Institution Decision

281, 294 (Fed. Cir. 1985) (lack of objective support for expert opinion "may render the testimony of little probative value in a validity determination").

Mann reveals the state of the art at the time of the invention, and supports Dr. Fudin's testimony that a skilled artisan would have understood the necessity of counseling males, capable of impregnating females, about the risks that attend fetal exposure to a teratogenic drug. Pet. 23 (quoting Ex. 1002 ¶¶ 95–98 (citing Ex. 1018, 7–8) (Mann, suggesting that thalidomide was known to become "strongly adsorbed by spermatozoa" and adversely affect the pregnancy in female rabbits mated to males that were administered thalidomide prior to conception)). On this record, Dr. Fudin's opinion—that it would have been "apparent that the sperm of male patients could be damaged by teratogenic drugs and consequently result in birth defects, if the male was to impregnate a female"—is supported by objective factual evidence, namely, Mann. Pet. 23 (quoting Ex. 1002 ¶ 96).

We recognize that Powell's Patient Information Sheet, under a heading relating to "side effects," contains this statement: "No effects on male sperm are recognized." Ex. 1005, 903; *see* Prelim. Resp. 34 (arguing that this statement in "Powell teaches away from" including "males in any 'subpopulation'"). That isolated statement in Powell, standing alone, does not defeat the sufficiency of Petitioner's information that the sperm of male patients, treated with teratogenic drugs, could result in birth defects. Pet. 23 (quoting Ex. 1002 ¶ 96) (citing Mann (Ex. 1018, 7–8)). Significantly, the statement in Powell is preceded by a discussion of the necessity of using "adequate contraception throughout the duration of thalidomide therapy." Ex. 1005, 903. When read in the context of the surrounding disclosure, therefore, Powell suggests that no *contraceptive* "effects on male sperm are recognized" as a side effect of thalidomide therapy. *Id.*

Mann reveals the state of the art at the time of the invention, and supports Dr. Fudin's testimony that a skilled artisan would have understood the necessity of counseling males, capable of impregnating females, about the risks that attend fetal exposure to a teratogenic drug. Pet. 23 (quoting Ex. 1002 ¶¶ 95–98 (citing Ex. 1018, 7–8) (Mann, suggesting that thalidomide was known to become "strongly adsorbed by spermatozoa" and adversely affect the pregnancy in female rabbits mated to males that were administered thalidomide prior to conception)). On this record, Dr. Fudin's opinion—that it would have been "apparent that the sperm of male patients could be damaged by teratogenic drugs and consequently result in birth defects, if the male was to impregnate a female"—is supported by objective factual evidence, namely, Mann. Pet. 23 (quoting Ex. 1002 ¶ 96).

Source: Paper 20, Institution Decision, at 10.

Mann – The Institution Decision

IPR2015-01092
Patent 6,045,501

On this record, Petitioner shows sufficiently that a person of ordinary skill in the art would have recognized the desirability of identifying a subpopulation of male patients having "the ability . . . to impregnate females;" and further, the utility of providing that group with "counseling information concerning the risks attendant to fetal exposure to" a teratogenic drug, as specified in claim 1. Ex. 1001, claim 1 (steps (c) and (e)).

We next turn to whether the applied art would have suggested the steps of registering prescribers, pharmacies, and patients in a computer readable storage medium as specified in claim 1. Ex. 1001, claim 1 (steps (a)–(c)). The over-arching purpose of Powell and Mitchell is to prevent birth defects by limiting prescriptions for teratogenic drugs to only non-pregnant women. *See, e.g.*, Ex. 1005, 901 (Powell, explaining "[p]regnancy should be excluded before instituting therapy with thalidomide"); *see also* Ex. 1006, 101 (Mitchell, disclosing "an aggressive program designed to reduce the risk of pregnancy among women taking" Accutane®). Petitioner shows sufficiently that Dishman would have led a skilled artisan to advance that purpose through an obvious modification; that is, by storing patient, prescriber, and pharmacy records in a computer readable storage medium. *See* Pet. 37–39, 41 (claim chart, steps (a)–(c), (g)).

Dishman describes a nation-wide registry for patients requiring clozapine, a potent anti-psychotic drug with potential for serious side effects. Pet. 27 (quoting Ex. 1002 ¶¶ 116–117). Although Dishman does not expressly relate to side effects that include birth defects, Petitioner shows sufficiently that "a person of ordinary skill in the art would have been motivated to look to the system disclosed in Dishman to further implement a computerized registry for avoiding birth defects from a teratogenic drug." Pet. 26–27 (citing Ex. 1002 ¶ 115). We agree, on this record, that one would

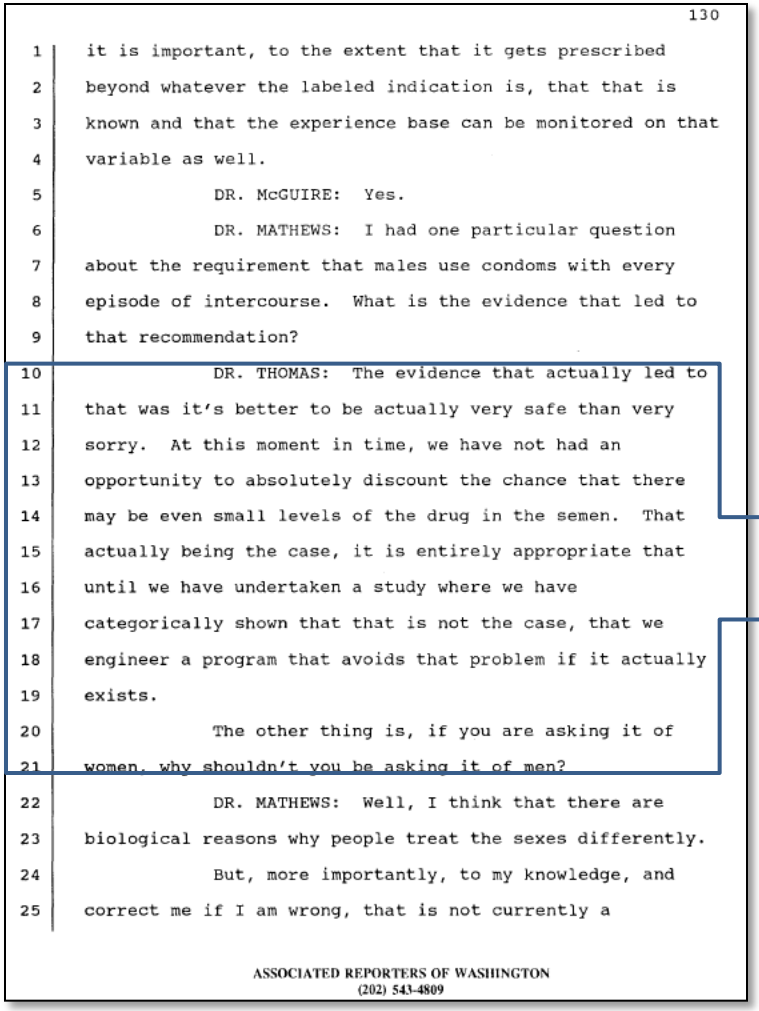
11

On this record, Petitioner shows sufficiently that a person of ordinary skill in the art would have recognized the desirability of identifying a subpopulation of male patients having "the ability . . . to impregnate females;" and further, the utility of providing that group with "counseling information concerning the risks attendant to fetal exposure to" a teratogenic drug, as specified in claim 1. Ex. 1001, claim 1 (steps (c) and (e)).

Source: Paper 20, Institution Decision, at 11.

PRIOR ART

FDA Meeting



130

it is important, to the extent that it gets prescribed beyond whatever the labeled indication is, that that is known and that the experience base can be monitored on that variable as well.

DR. McGUIRE: Yes.

DR. MATHEWS: I had one particular question about the requirement that males use condoms with every episode of intercourse. What is the evidence that led to that recommendation?

DR. THOMAS: The evidence that actually led to that was it's better to be actually very safe than very sorry. At this moment in time, we have not had an opportunity to absolutely discount the chance that there may be even small levels of the drug in the semen. That actually being the case, it is entirely appropriate that until we have undertaken a study where we have categorically shown that that is not the case, that we engineer a program that avoids that problem if it actually exists.

The other thing is, if you are asking it of women, why shouldn't you be asking it of men?

DR. MATHEWS: Well, I think that there are biological reasons why people treat the sexes differently.

But, more importantly, to my knowledge, and correct me if I am wrong, that is not currently a

ASSOCIATED REPORTERS OF WASHINGTON
(202) 543-4809

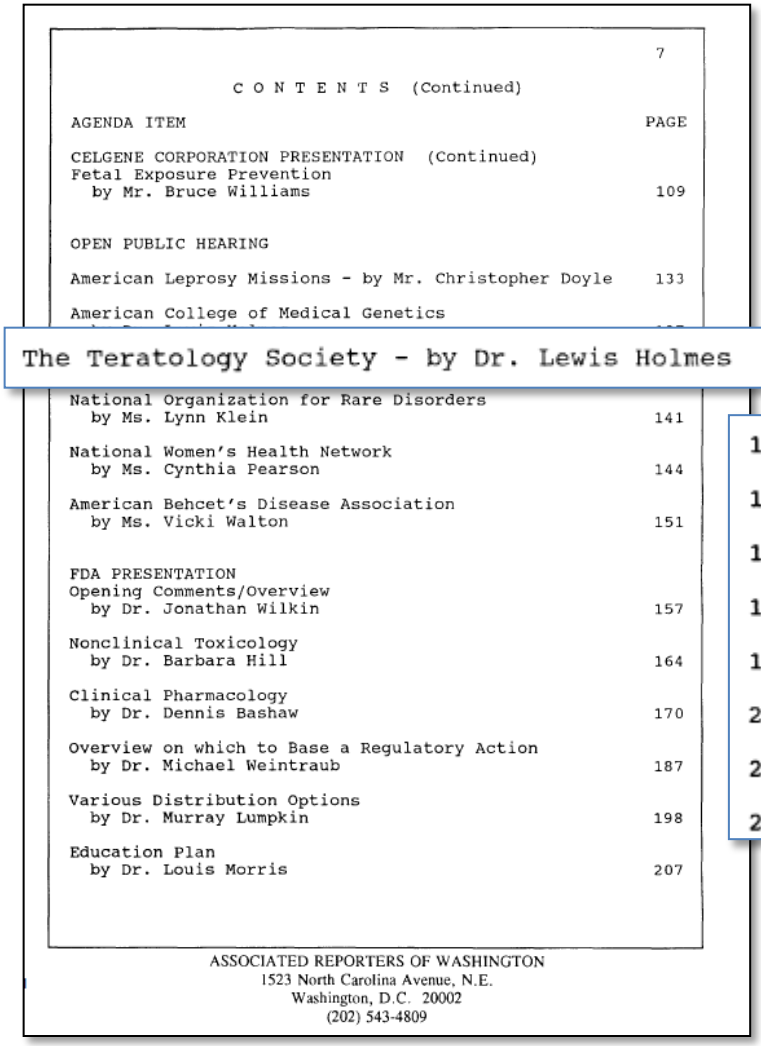
DR. THOMAS: The evidence that actually led to that was it's better to be actually very safe than very sorry. At this moment in time, we have not had an opportunity to absolutely discount the chance that there may be even small levels of the drug in the semen. That actually being the case, it is entirely appropriate that until we have undertaken a study where we have categorically shown that that is not the case, that we engineer a program that avoids that problem if it actually exists.

The other thing is, if you are asking it of women, why shouldn't you be asking it of men?

Source: Ex. 2094 at 130:10-21.

PRIOR ART

FDA Meeting

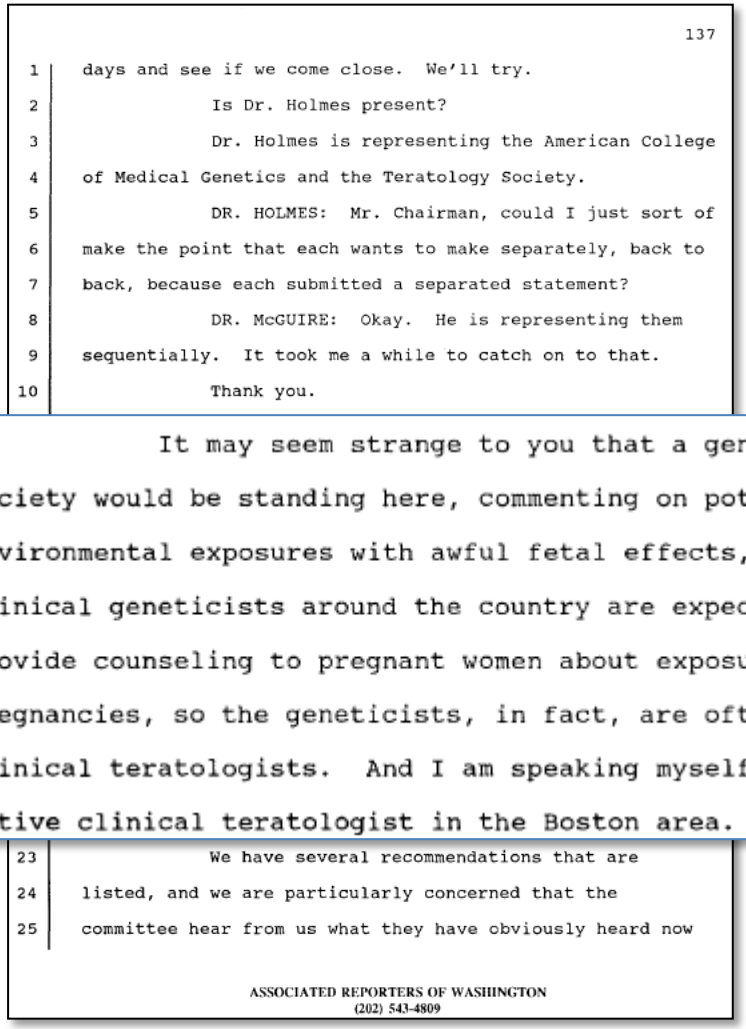


7

C O N T E N T S (Continued)

AGENDA ITEM	PAGE
CELGENE CORPORATION PRESENTATION (Continued)	
Fetal Exposure Prevention	
by Mr. Bruce Williams	109
OPEN PUBLIC HEARING	
American Leprosy Missions - by Mr. Christopher Doyle	133
American College of Medical Genetics	
The Teratology Society - by Dr. Lewis Holmes	
National Organization for Rare Disorders	
by Ms. Lynn Klein	141
National Women's Health Network	
by Ms. Cynthia Pearson	144
American Behcet's Disease Association	
by Ms. Vicki Walton	151
FDA PRESENTATION	
Opening Comments/Overview	
by Dr. Jonathan Wilkin	157
Nonclinical Toxicology	
by Dr. Barbara Hill	164
Clinical Pharmacology	
by Dr. Dennis Bashaw	170
Overview on which to Base a Regulatory Action	
by Dr. Michael Weintraub	187
Various Distribution Options	
by Dr. Murray Lumpkin	198
Education Plan	
by Dr. Louis Morris	207

ASSOCIATED REPORTERS OF WASHINGTON
1523 North Carolina Avenue, N.E.
Washington, D.C. 20002
(202) 543-4809



137

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.

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

ASSOCIATED REPORTERS OF WASHINGTON
(202) 543-4809

Source: Ex. 2094 at 7, 137:15-22.

PRIOR ART

Vanchieri

Annals of Internal Medicine

CURRENTS

...News for internists

Preparing for Thalidomide's Comeback

Thalidomide is on the verge of being introduced—with great care—into the U.S. marketplace. The news provokes polarized reactions: disbelief that such a potent teratogen could be made available after the lessons of almost 40 years ago, and impatience for a drug that can lead to exceptional improvements in some rare debilitating immune diseases.

In early September, an advisory committee to the U.S. Food and Drug Administration (FDA) recommended that the FDA approve marketing of thalidomide for erythema nodosum leprosum, an inflammatory manifestation of leprosy that results in painful cutaneous lesions on the arms, legs, and face. The committee also strongly recommended limiting distribution of thalidomide, with stringent safety measures put in place to avoid birth defects and other side effects.

The renewed interest in thalidomide comes from studies showing a complete response in 90% of patients with erythema nodosum leprosum who used thalidomide, according to Janet Woodcock, MD, chief of the FDA's Center for Drug Evaluation and Research. The drug is also under investigation to determine its effectiveness against graft-versus-host disease, the AIDS wasting syndrome, some solid tumors, certain serious primary dermatologic conditions, tuberculosis, aphthous ulcers, and macular degeneration. Woodcock said that evidence is most compelling for the drug's effect on aphthous ulcers in patients with HIV infection (N Engl J Med. 1997;335: 1487-93) and with Behçet disease. She considers the data on the AIDS wasting syndrome "promising" but preliminary.

The committee's recommendation was preceded by a year of intensive debate and planning because of the drug's potentially severe side effects. Even one dose of thalidomide, when taken during the early stages of pregnancy, can cause fetal deformities. The drug can also cause peripheral neuropathy, sometimes resulting in permanent nerve damage.

A Brief History

Thalidomide was originally marketed as a sedative and was often used for morning sickness outside of the United States in the 1950s and early 1960s. Although thalidomide was the third largest-selling drug in Europe—considered so safe it was sold over-the-counter in many places—it never passed FDA scrutiny. At least 8000 of the babies born to women who took the drug during pregnancy had phocomelia, which is characterized by missing digits, arms and legs, and internal organ deformities. In the United States, 17 babies were born with the rare birth defect; their mothers had received the drug from overseas sources or received premarketing samples distributed by drug company representatives. The thalidomide episode resulted in stricter review requirements for drug approval by the FDA, including proof of safety and efficacy plus informed consent by all participants in clinical trials.

Today, the FDA has in hand new data that indicate thalidomide's promise in fighting several serious diseases for which no effective alternate therapy exists, but the risks, of course, remain. Because many of the diseases in which thalidomide is potentially beneficial afflict young women (Behçet disease, the Sjögren syndrome, Crohn disease, and rheumatoid arthritis), issues of teratogenicity are critical. Because of a recent study showing thalidomide in rabbit semen and uncertainty about its presence in human semen, both women and men receiving the drug will be required to use contraception.

Concerns about birth defects have been so great that investigational use of thalidomide for erythema nodosum leprosum has been limited to men and postmenopausal or surgically sterilized women. The FDA is unlikely to limit general use of the drug to that extent, but if it is approved as proposed, thalidomide will be the most restricted drug in the United States, Woodcock confirmed. Every physician, pharmacist, and patient involved with thalidomide will be required to adhere to a tightly controlled protocol, according to Bruce J. Williams, from Celgene Corporation of Warren, New Jersey, the drug's marketer.

To gain access to the drug, patients will be required to receive risk–benefit counseling, sign an informed-consent agreement, use two forms of birth control, and participate in frequent surveys; monthly prescriptions will only be filled after pregnancy testing. Compliance and fetal exposures will be tracked. Only pharmacists registered to participate will be permitted to dispense the drug. By registering, they commit to dispense thalidomide in 28-day supplies in original packaging (special blister-packs with pregnancy warnings encasing each pill) only after seeing the signed informed-consent document. The drug cannot be dispensed as a simple refill, and patients will be advised to return unused doses.

When asked whether a patient using thalidomide can decline the use of birth control for religious or other reasons, Williams responded: "Women can make informed choices about whether or not to take the drug. But if they are of childbearing age and want the drug, they must use contraception." Boston University researchers will maintain a thalidomide users registry modeled after the registry that tracks use and pregnancy outcomes for users of isotretinoin, which is marketed by Hoffman-La Roche in Nutley, New Jersey, under the trade name Accutane (Box).

Zero Risk Impossible

Even with these unprecedented safety measures, experts admit that zero risk is an impossible goal. Babies will be born with birth defects if thalidomide is made available. But based on the isotretinoin experience, 20 years of testing in erythema nodosum leprosum, and limited use of thalidomide by 72 women with the AIDS wasting syndrome or aphthous ulcers, the FDA is prepared to move ahead.

Implications of this regulatory action go beyond U.S. borders. It sends a message to other countries, said Colin Crawford, MB, ChB, DPH&H, from London's Imperial

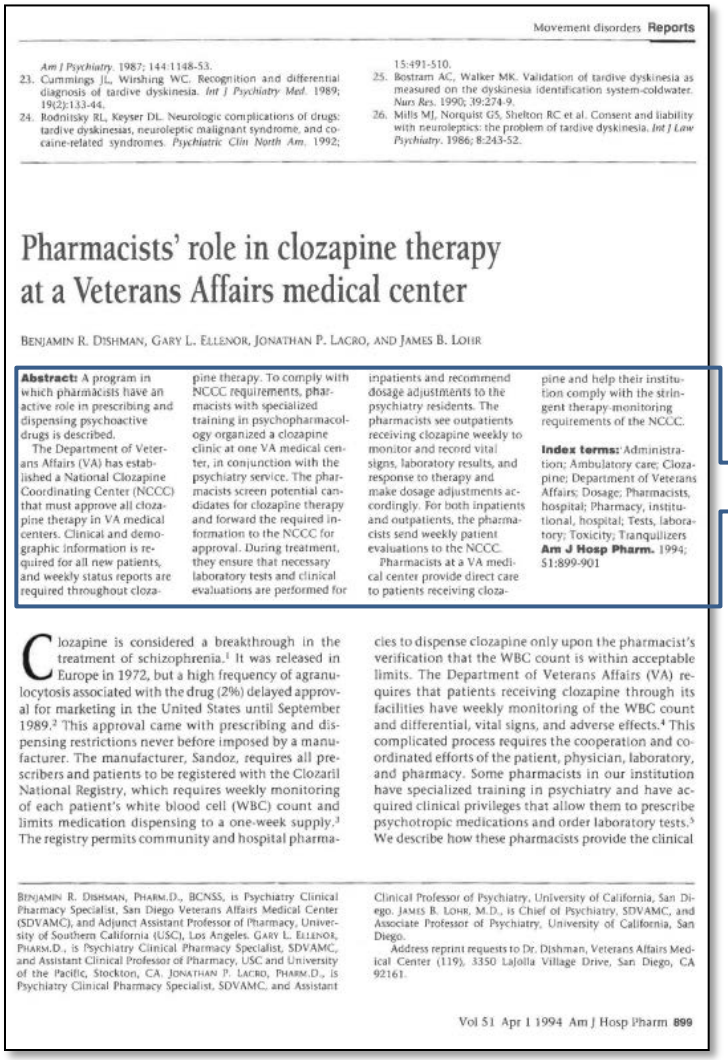
(Continued on next page)

Because of a recent study showing thalidomide in rabbit semen and uncertainty about its presence in human semen, both women and men receiving the drug will be required to use contraception.

Source: Ex. 2064 at 951.

PRIOR ART

Dishman



Am J Psychiatry. 1987; 144:1148-53.
23. Cummings JL, Wirshing WC. Recognition and differential diagnosis of tardive dyskinesia. *Int J Psychiatry Med*. 1989; 19(2):133-44.
24. Rodnitsky RL, Keyser DL. Neurologic complications of drugs: tardive dyskinesias, neuroleptic malignant syndrome, and cocaine-related syndromes. *Psychiatric Clin North Am*. 1992; 15:491-510.
25. Bostram AC, Walker MK. Validation of tardive dyskinesia as measured on the dyskinesia identification system-coldwater. *Nurs Res*. 1990; 39:274-9.
26. Mills MJ, Norquist GS, Shelton RC et al. Consent and liability with neuroleptics: the problem of tardive dyskinesia. *Int J Law Psychiatry*. 1986; 8:243-52.

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

BENJAMIN R. DISHMAN, PHARM.D., BCNSS, is Psychiatry Clinical Pharmacy Specialist, San Diego Veterans Affairs Medical Center (SDVAMC), and Adjunct Assistant Professor of Pharmacy, University of Southern California (USC), Los Angeles. GARY L. ELLENOR, PHARM.D., is Psychiatry Clinical Pharmacy Specialist, SDVAMC, and Assistant Clinical Professor of Pharmacy, USC and University of the Pacific, Stockton, CA. JONATHAN P. LACRO, PHARM.D., is Psychiatry Clinical Pharmacy Specialist, SDVAMC, and Assistant Clinical Professor of Psychiatry, University of California, San Diego. JAMES B. LOHR, M.D., is Chief of Psychiatry, SDVAMC, and Associate Professor of Psychiatry, University of California, San Diego.

Address reprint requests to Dr. Dishman, Veterans Affairs Medical Center (119), 3350 LaJolla Village Drive, San Diego, CA 92161.

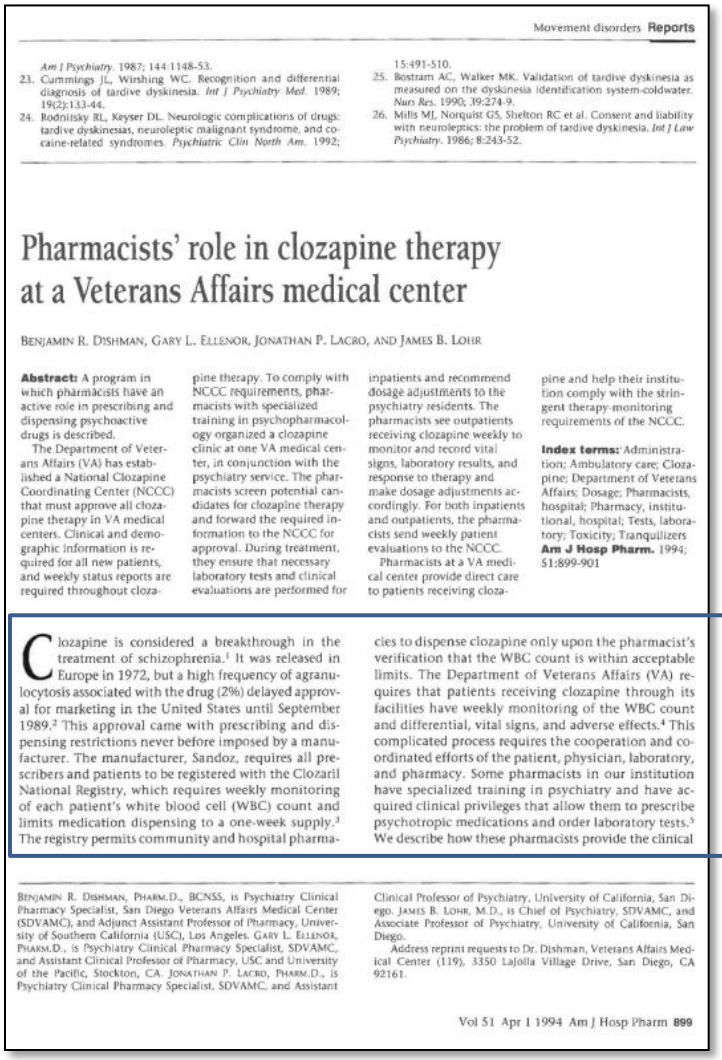
Abstract: A program in which pharmacists have an active role in prescribing and dispensing psychoactive drugs is described.

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 cloza-

PRIOR ART

Dishman



Am J Psychiatry. 1987; 144:1148-53.
23. Cummings JL, Wirshing WC. Recognition and differential diagnosis of tardive dyskinesia. *Int J Psychiatry Med*. 1989; 19(2):133-44.
24. Rodnitsky RL, Keyser DL. Neurologic complications of drugs: tardive dyskinesias, neuroleptic malignant syndrome, and cocaine-related syndromes. *Psychiatric Clin North Am*. 1992; 15:491-510.
25. Bostram AC, Walker MK. Validation of tardive dyskinesia as measured on the dyskinesia identification system-coldwater. *Nurs Res*. 1990; 39:274-9.
26. Mills MJ, Norquist GS, Shelton RC et al. Consent and liability with neuroleptics: the problem of tardive dyskinesia. *Int J Law Psychiatry*. 1986; 8:243-52.

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

BENJAMIN R. DISHMAN, PHARM.D., BCNSS, is Psychiatry Clinical Pharmacy Specialist, San Diego Veterans Affairs Medical Center (SDVAMC), and Adjunct Assistant Professor of Pharmacy, University of Southern California (USC), Los Angeles. GARY L. ELLENOR, PHARM.D., is Psychiatry Clinical Pharmacy Specialist, SDVAMC, and Assistant Clinical Professor of Pharmacy, USC and University of the Pacific, Stockton, CA. JONATHAN P. LACRO, PHARM.D., is Psychiatry Clinical Pharmacy Specialist, SDVAMC, and Assistant Clinical Professor of Psychiatry, University of California, San Diego. JAMES B. LOHR, M.D., is Chief of Psychiatry, SDVAMC, and Associate Professor of Psychiatry, University of California, San Diego.

Address reprint requests to Dr. Dishman, Veterans Affairs Medical Center (119), 3350 LaJolla Village Drive, San Diego, CA 92161.

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

PRIOR ART

Dishman

Reports Clozapine therapy

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.

The psychiatry service comprises 101 total beds: 15 intensive care, 44 acute care, 28 alcohol or drug treatment, and 14 research beds. The mental health ambulatory-care clinic handles approximately 35,000 visits per year. There are two full-time pharmacists and one half-time pharmacist designated as psychiatry clinical pharmacy specialists. The primary function of these specialists is to provide comprehensive care to the psychiatric inpatient and ambulatory-care areas. The specialists also help educate psychiatry residents; medical, pharmacy, and nursing students; and permanent members of the psychiatry staff. All three specialists have the doctor of pharmacy degree and have completed a one-year general hospital pharmacy residency program (two completed an ASHP-accredited program). Although none has completed a specialized psychiatry residency, all three pharmacists have clinical experience in psychiatry (2, 6, and 20 years).

VA program for clozapine monitoring

In 1991 the VA developed its own clozapine monitoring program and received approval from Sandoz to dispense clozapine. The VA Central Office established a National Clozapine Coordinating Center (NCCC). Physicians at the NCCC review each clozapine candidate's file before granting approval for use and review weekly tracking sheets that report patient status. Each VA medical center is required to establish a clozapine treatment team, headed by the chief of the psychiatry service and including representatives from the psychiatry, pharmacy, laboratory, medicine, and nursing services. The clozapine treatment team reviews new applications for clozapine use and provides clinical and demographic information for all new patients to the NCCC.

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.

Pharmacists' duties

Psychiatry residents at our facility rotate to other hospitals monthly; this creates concerns about continuity of patient care and follow-up. The psychiatry clinical pharmacy specialists coordinate the education of residents on the screening and physical-examination requirements 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.

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,

900 Am J Hosp Pharm Vol 51 Apr 15 1994

VA program for clozapine monitoring

In 1991 the VA developed its own clozapine monitoring program and received approval from Sandoz to dispense clozapine. The VA Central Office established a National Clozapine Coordinating Center (NCCC). Physicians at the NCCC review each clozapine candidate's file before granting approval for use and review weekly tracking sheets that report patient status. Each VA medical center is required to establish a clozapine treatment team, headed by the chief of the psychiatry service and including representatives from the psychiatry, pharmacy, laboratory, medicine, and nursing services. The clozapine treatment team reviews new applications for clozapine use and provides clinical and demographic information for all new patients to the NCCC.

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

Source: Paper 1, Petition, at 16-17, 28-29, 32, 37-38, 42-43; Ex. 1007 at 900.

Dishman – The Institution Decision

have turned to Dishman as a source of "ways to restrict access to drugs that could be potentially hazardous." *Id.* at 27 (quoting Ex. 1002 ¶¶ 116–117).

Dishman explains that "all prescribers and patients" of clozapine must "be registered with" the national registry, "which requires weekly monitoring of each patient's white blood cell (WBC) count" and also "limits medication dispensing to a one-week supply." Ex. 1007, 899. The national registry, moreover, is used to store a "pharmacist's verification" relating to the weekly WBC monitoring requirement. Pet. 28 (quoting Ex. 1007, 899); *see also* Ex. 1002 ¶ 122 (Dr. Fudin, testifying that Dishman discloses a need for cooperation between patients, physicians, laboratories, and pharmacies). In that context, Dishman refers to "a computerized clozapine prescription lockout system." Ex. 1007, 900; *see* Ex. 1002 ¶ 123 (Dr. Fudin, explaining "that each hospital [must] have a computerized clozapine prescription lockout system" that "ties the hospital's laboratory databases to the outpatient pharmacy dispensing software").

We are persuaded, on this record, that the combined disclosures of Powell, Mitchell, and Dishman would have prompted a skilled artisan to implement a pregnancy-prevention program for thalidomide patients that makes mandatory the use of a registry for patients, prescribers, and pharmacies; that limitation is suggested by Dishman's disclosure of registering a pharmacist's verification before any patient is authorized to receive a drug. Pet. 21–22 (citing Ex. 1002 ¶ 89). Based on the information presented, moreover, Petitioner shows sufficiently that Dishman would have led a skilled artisan, seeking to improve the methods of Powell and Mitchell, to maintain the mandatory registry of records in a computer readable storage medium for "ease in sharing and storing." Pet. 26 (quoting Ex. 1002 ¶ 114).

We are persuaded, on this record, that the combined disclosures of Powell, Mitchell, and Dishman would have prompted a skilled artisan to implement a pregnancy-prevention program for thalidomide patients that makes mandatory the use of a registry for patients, prescribers, and pharmacies; that limitation is suggested by Dishman's disclosure of registering a pharmacist's verification before any patient is authorized to receive a drug. Pet. 21–22 (citing Ex. 1002 ¶ 89). Based on the information presented, moreover, Petitioner shows sufficiently that Dishman would have led a skilled artisan, seeking to improve the methods of Powell and Mitchell, to maintain the mandatory registry of records in a computer readable storage medium for "ease in sharing and storing." Pet. 26 (quoting Ex. 1002 ¶ 114).

Source: Paper 20, Institution Decision, at 12.

Dishman – The Institution Decision

The only practical reason for storing information in a computer readable medium is to permit later retrieval of that information. *Cf.* Prelim. Resp. 32–33 (arguing that a failure to identify a prior art disclosure of a "retrieval" step dooms Petitioner's challenge); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (hypothetical person of ordinary skill in the art possesses ordinary creativity and is not an automaton). Furthermore, Dishman's disclosure of registering a pharmacist's verification, before any patient is authorized to receive a drug, implies a retrieval of such information. Pet. 21–22 (citing Ex. 1002 ¶ 89). On this record, the applied prior art suggests a method of registering prescriber, pharmacy, and patient information in "a computer readable storage medium," and retrieving information necessary to ensure that prescriptions for a teratogenic drug are authorized for only non-pregnant patients. Ex. 1001, claim 1 (steps (a)–(d)).

Petitioner shows sufficiently that the invention of claim 1 represents the "predictable use of prior art elements according to their established functions." *KSR Int'l*, 550 U.S. at 417. Based on the information presented, claim 1 is directed to a combination of known steps (registering patients, prescribers, and pharmacies in a computer readable medium; identifying and counseling a subpopulation of patients whose access to a teratogenic drug should be restricted; and authorizing drug therapy only for non-pregnant patients) to accomplish a known purpose (prescribing drug only to non-pregnant patients) and achieve a predictable result (preventing fetal exposure to the drug). Pet. 36–41 (claim chart).

The only practical reason for storing information in a computer readable medium is to permit later retrieval of that information. *Cf.* Prelim. Resp. 32–33 (arguing that a failure to identify a prior art disclosure of a "retrieval" step dooms Petitioner's challenge); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (hypothetical person of ordinary skill in the art possesses ordinary creativity and is not an automaton). Furthermore, Dishman's disclosure of registering a pharmacist's verification, before any patient is authorized to receive a drug, implies a retrieval of such information. Pet. 21–22 (citing Ex. 1002 ¶ 89). On this record, the applied prior art suggests a method of registering prescriber, pharmacy, and patient information in "a computer readable storage medium," and retrieving information necessary to ensure that prescriptions for a teratogenic drug are authorized for only non-pregnant patients. Ex. 1001, claim 1 (steps (a)–(d)).

Source: Paper 20, Institution Decision, at 13.

MOTIVATION TO COMBINE

MOTIVATION TO COMBINE

Petition

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

C. **Overview of the State of the Art and Summary of Prior Art Referen**

1. **State of the Relevant Art as of August 1998**

"By August of 1998, persons of ordinary skill in the art understood that teratogenic drugs may cause birth defects, and were aware that such drugs either already used, or needed, restrictive safeguards before prescription." (Ex. 1002 ¶ 33.)

"By August of 1998, persons of ordinary skill in the art understood that teratogenic drugs may cause birth defects, and were aware that such drugs either already used, or needed, restrictive safeguards before prescription." (Ex. 1002 ¶ 33.)

For example, one drug marketed using methods to prevent its use in pregnant patients was isotretinoin, marketed under the trade name Accutane®. (Ex. 1006 at 101; Ex. 1002 ¶ 34.) "This drug, suspected to be a potent teratogen based on animal testing, became part of a manufacturer-sponsored Pregnancy Prevention Program ("PPP"). (Ex. 1002 ¶ 34 (citing Ex. 1006 at 101).) The PPP had multiple components, including

Patent No. 6,045,501

"In addition to the Accutane PPP, another well-known restricted drug distribution program in existence prior to 1998 regulated clozapine (trade name Clozaril®). In early 1997, medical professionals made the observation that the methods used to control prescriptions for clozapine, an anti-psychotic with potential adverse effects indicated by white blood cell counts ("WBCs"), could be copied for thalidomide." (Ex. 1002 ¶ 36.) In particular, such methods included "comprehensive

only have a prescription for clozapine filled if the test results were within a certain range." (Ex. 1002 ¶ 36 (citing Ex. 1010 at 122).)

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

Source: Paper 1, Petition, at 9 - 10.

MOTIVATION TO COMBINE

Petition

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

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

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

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

Source: Paper 1, Petition, at 12.

MOTIVATION TO COMBINE

Petition

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

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

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

and in the announcement, the organizers specified that the purpose was to "enable

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

clozapine restricted distribution program." (Ex. 1002 ¶ 47.)

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

Source: Paper 1, Petition, at 11 - 12.

MOTIVATION TO COMBINE

Petition

Patent No. 6,045,501

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

One of ordinary skill in the art prior to August 28, 1998, when seeking to treat patients with thalidomide, would first look to *Powell* for guidance on "the clinical use and dispensing" of thalidomide, (Ex. 1005 at 901) and would garner from it recommendations for "delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus," as described in the preamble of Claim 1. *Powell* is a printed publication in a medical journal on the precise topic of preventing pregnancy in connection with the use of thalidomide, a known teratogenic, and therefore "would be a natural starting point for a pharmacist or medical professional." (Ex. 1002 ¶ 8791.) Although they appear in the form of

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

program that was well known in the art and disclosed in *Mitchell*—namely, that the use

21

Patent No. 6,045,501

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

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

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

22

Source: Paper 1, Petition, at 21 - 22.

MOTIVATION TO COMBINE

Petition

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

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

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

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

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

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

(Fed. Cir. 2011) ("[a] reference is reasonably pertinent if…it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem."); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 1740 (2007) ("patent's subject matter can be proved obvious . . . by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims").

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

Source: Paper 1, Petition, at 26 - 27.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

33. By August of 1998, persons of ordinary skill in the art understood that teratogenic drugs may cause birth defects, and were aware that such drugs either already used, or needed, restrictive safeguards before prescription.

34. One notable example of a drug marketed using methods to prevent its use in pregnant patients is isotretinoin, marketed under the trade name Accutane®. (Ex. 1006 at 101.) This drug, suspected to be a potent teratogen based on animal testing, became part of a manufacturer-sponsored Pregnancy Prevention Program ("PPP"). (Ex. 1006 at 101.)

35. The PPP program, which had multiple components, included the distribution to physicians of a kit that included informed consent documents and information for patient counseling. (Ex. 1006 at 101.) In particular, patients were warned against the teratogenic risk of Accutane® and the need to prevent pregnancy. Patients were also advised as to the proper methods of birth control available. (Ex. 1006 at 103.)

Source: Ex. 1002 ¶¶ 33 - 35.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

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

Source: Ex. 1002 ¶ 36.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

42. As a result, individuals of ordinary skill in the art recognized, well before 1997, that "[i]f thalidomide becomes widely available, stringent control measures must be taken to prevent the exposure of pregnant women, though the proportion of women at risk may be small" and that "[p]atient and physician educational campaigns and public awareness of the teratogenic effects of the thalidomide would no doubt play a crucial role in minimizing the teratogenic impact..." (Ex. 1011 at 252, 257.)

Source: Ex. 1002 ¶ 42.

MOTIVATION TO COMBINE

Bastani

Winberg, 1968; Källén et al., 1984a; Czeizel, 1973; Flynt and Hay, 1979a; Edmonds et al., 1981; Oakley, 1985; Holtzman and Khoury, 1986].

Although the birth defects surveillance systems in the world provide invaluable data for descriptive and analytical epidemiologic studies, their effectiveness in detecting subtle epidemics has been criticized [Chen, 1979, 1985; Klingberg et al., 1983; Källén et al., 1984a; Khoury and Holtzman, 1987]. The classification of malformations used in monitoring has been discussed [Bod and Czeizel, 1981; Källén et al., 1984b; Holtzman and Khoury, 1986]. Many recommendations have been made to improve the ability of birth defects monitoring to detect new teratogens [Källén et al., 1984a; Holtzman and Khoury, 1986; Khoury and Holtzman, 1987; Lynberg and Edmonds, 1992; Khoury and Edmonds, 1994].

Recent studies have shown that thalidomide may be beneficial for a range of conditions including cancer and AIDS [Burley, 1986; Maknokawkeyoon et al., 1993; D'Arcy and Griffin, 1994]. If thalidomide becomes widely available, stringent control measures must be taken to prevent the exposure of pregnant women, though the proportion of women at risk may be small [Jenkinson, 1993; Erickson, 1995; Castilla et al., 1997].

Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based surveillance system. The results of the study can also be used to evaluate the ability of birth defects monitoring to detect true subtle changes of birth defects under different circumstances of exposure frequency, teratogen potencies and etiologic heterogeneity of the outcome.

METHODS

The Metropolitan Atlanta Congenital Defects Program (MACDP) is a population-based birth defects surveillance system that has been in operation since 1967 [Edmonds et al., 1981; Lynberg and Edmonds, 1992; Khoury and Edmonds, 1994]. It monitors all births occurring in the five-county metropolitan Atlanta area. The number of births monitored has increased from about 25,000 per year in 1968 to about 40,000 per year in 1994. One main objective of MACDP is to monitor regularly and systematically the birth of malformed infants in order to detect changes in rates or unusual patterns suggesting environmental influences.

MACDP includes information on all live-born and stillborn infants, with at least one major birth defect with onset during the infants' first year of life. All diagnoses must be ascertained within their first 5 years of life [Lynberg and Edmonds, 1992]. Case ascertainment includes the review of maternal and infant medical records from multiple sources, including birth hospitals, pediatric referral hospitals, and cytogenetic laboratories, and the review of vital statistics from the Georgia Department of Human Resources.

MACDP case records include basic demographic information, the case diagnosis, birth related information, birth complications, prenatal data, pregnancy and family history, cytogenetic data, and information on other risk factors. Data on major birth defects are analyzed quarterly for changes in rates and any other unusual patterns. Until the early 1990s, the Poisson method was used to detect increases in birth defects rates [Khoury and Edmonds, 1994]. Since then, the cumulative sum (CUSUM) technique [Lucas, 1985] has been employed.

Limb deficiencies were defined according to the classification system of the International Clearinghouse for Birth Defects Monitoring Systems and EUROCAT [International Clearinghouse for Birth Defects Moni-

intercalary and preaxial limb deficiencies are subcategories of all limb deficiencies.

In the present study, we examined the ability of the program to detect a rate change of total limb deficiencies (TLD), bilateral nonsyndromic intercalary or preaxial deficiencies (BIPD), and intercalary limb deficiency (ILD). We excluded infants from the intercalary or preaxial categories when their limb deficiencies were not well described anatomically, or when the etiologies of their defects were clearly chromosomal or single gene mutations. We also excluded infants from the category of "bilateral" limb deficiencies if laterality was vague or unspecified.

Statistical Analysis

As shown by Khoury and Holtzman [1987], the increase of the prevalence of a birth defect is a function of the frequency of exposure to the teratogen, the strength of the teratogen, and the etiological heterogeneity of the outcome. The formula is given as follows:

$$P_u = p[1 + fh(R-1)], \quad (1)$$

where f is the frequency of exposure, h is the heterogeneity index, and R is the relative risk. If we define $\rho = p_{tr}/p = [1 + fh(R-1)]$, then ρ indicates relative changes

categories of thalidomide induced limb deficiency: ILD and BIPD. Our results suggested that by monitoring ILD, one would have more power to detect a change in rate of in utero exposure to thalidomide. For example, for exposure rate less than 1/1,000, we would need on average 50% less of births by monitoring ILD than by monitoring BIPD to detect a significant change in rate. Under the same circumstances for CUSUM, we would need about 35% less of ARL for monitoring ILD than for monitoring BIPD. The differences in timing of monitoring between ILD and BIPD reduces as the exposure rates increases. For example, for exposure rates between 1–3%, we would need 30% less births for moni-

Patient and physician educational campaigns and public awareness of the teratogenic effects of the thalidomide would no doubt play a crucial role in minimizing the teratogenic impact of thalidomide if it becomes widely available again. Under current regulations of testing drugs for reproductive adverse effects, a tragedy on the scale of thalidomide during the early 1960s seems unlikely. What seems more likely is the intro-

of better reporting), the incomplete or inaccurate reporting of defects; and delays in reporting defects, processing data, and conducting statistical analysis.

Our analysis emphasized the fact that the changes of birth prevalence of the specific birth defects are a function of the frequency of exposure to the teratogen (f), the relative risk associated with the exposure to the teratogen (R), and the etiologic heterogeneity of a measured defect (h) [Khoury and Holtzman, 1987]. As shown by Figures 1 and 2, as ρ approximates one, which could result from many combinations of f, h, and R, one loses power (or needs longer ARL for CUSUM) to detect significant changes for a given expected number of cases. Most birth defects surveillance systems monitor from 10,000 to 250,000 births annually [International Clearinghouse for Birth Defects Monitoring Systems, 1984; Holtzman and Khoury, 1986; Khoury and Holtzman, 1987]. For any rare birth defects, if the frequency of exposure is sufficiently low or the heterogeneity index is sufficient high, even for a potent teratogen like thalidomide ($R > 175$), the relative risk (ρ) could be close to one (Table I). If this occurs, either larger samples are needed or a longer period of time is needed for a given surveillance system to detect the true increase of birth prevalence rate of a birth defect.

Our methods may serve as a basic tool to evaluate the ability of birth defects monitoring to detect subtle increases in the birth prevalence of birth defects. Our results show that monitoring for BIPD or ILD could detect a resurgence of thalidomide in a surveillance system similar to MACDP only at levels of in utero exposure that would be unacceptably high. They also indicate that monitoring all limb deficiencies would be even more unacceptably inefficient in detecting a rate increase. These findings highlight the importance of a large monitored population, focused surveillance, and appropriate case classification. As suggested by Khoury and Holtzman [1987], the ability of birth defects monitoring to detect human teratogens can be improved by increasing the number of births monitored (for example, by pooling data from several programs as is routinely done by the International Clearinghouse

women). Either of these situations can result in true subtle changes in the birth prevalence of specific birth defects, changes that may go unnoticed by many birth defects surveillance systems. Therefore, it is important that birth defects surveillance systems focus on high-risk populations and classify birth defects as precisely as possible in order to detect possible subtle epidemics of birth defects.

ACKNOWLEDGMENTS

We are grateful to the Metropolitan Atlanta Congenital Defects Program (MACDP) abstractors, Charlie Mae Peters, Connie Thompson, Debbie Nurmi, Joan Garcia, Joann Donaldson, and Jo Anne Croghan, whose constant data collection efforts provide the foundation upon which MACDP research is built. We thank Dr. Cynthia Moore for her help in reviewing and clarifying the cases of limb deficiencies from MACDP. We thank Michael Atkinson and Yecal Liu for their technical assistance. We also thank two anonymous reviewers for their helpful suggestions.

REFERENCES

A EUROCAT Working Group (1993): EUROCAT Report 5. Surveillance of congenital anomalies, 1980–1990. Brussels: EUROCAT Central Registry, Institute of Hygiene and Epidemiology. Ministry of Public Health and Environment.

Bod M, Czeizel A (1981): Congenital malformation surveillance. Teratology 24:277–283.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

44. In March of 1997, the Centers for Disease Control and Prevention convened a meeting specifically to discuss an approach for the introduction of thalidomide to U.S. markets. This meeting was announced in the Federal Register, and in the announcement, the organizers specified that the purpose was to "enable academic and public health professionals to discuss strategies to prevent birth defects due to exposure to thalidomide and other human teratogens…to review existing strategies for limiting intrauterine exposure to human teratogens, and to discuss and provide individual input on new approaches for preventing birth defects due to future teratogens such as thalidomide." (Ex. 1013 (emphasis added).)

45. The announcement specifically outlined certain methods to be evaluated, such as the "(1)…Accutane® Pregnancy Prevention Program, (2) use and limitations of drug registries, (3) contraception efficacy, (4) ethical issues on teratogen exposure, and (5) measures to assure appropriate use of pharmaceuticals." (*Id.*)

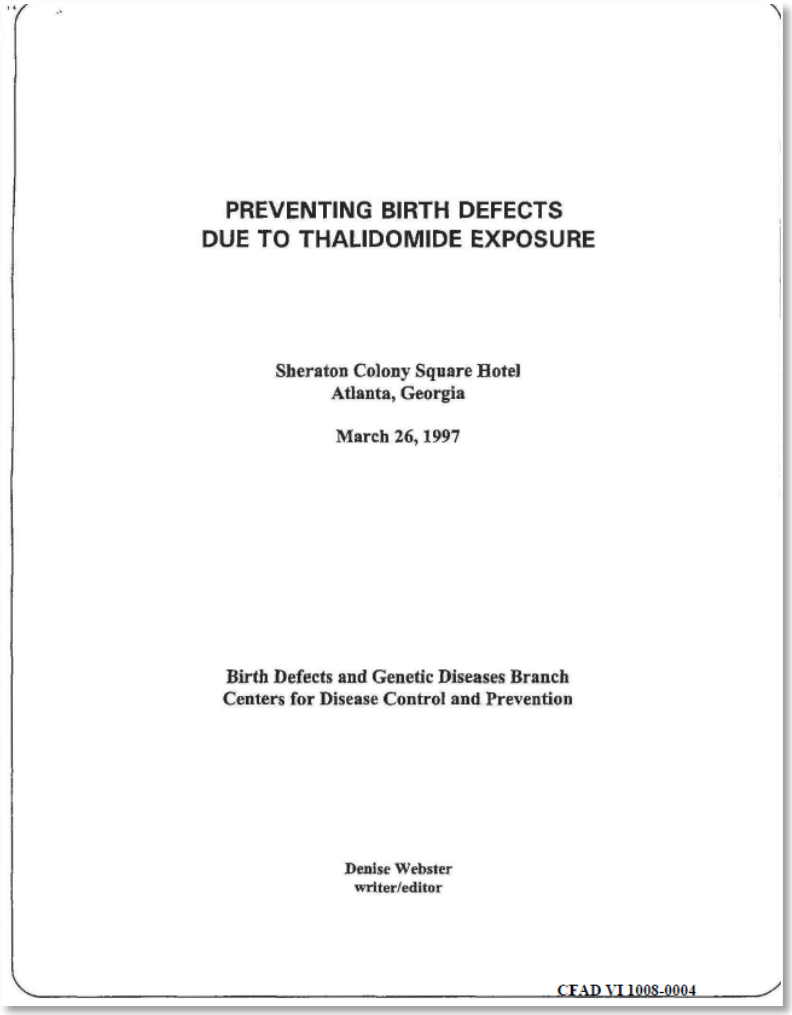
46. The agenda and minutes of this meeting were published. (Ex. 1008.)

47. 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.

Source: Ex. 1002 ¶¶ 44 - 47.

MOTIVATION TO COMBINE

CDC Meeting Materials



PREVENTING BIRTH DEFECTS
DUE TO THALIDOMIDE EXPOSURE

Sheraton Colony Square Hotel
Atlanta, Georgia

March 26, 1997

Birth Defects and Genetic Diseases Branch
Centers for Disease Control and Prevention

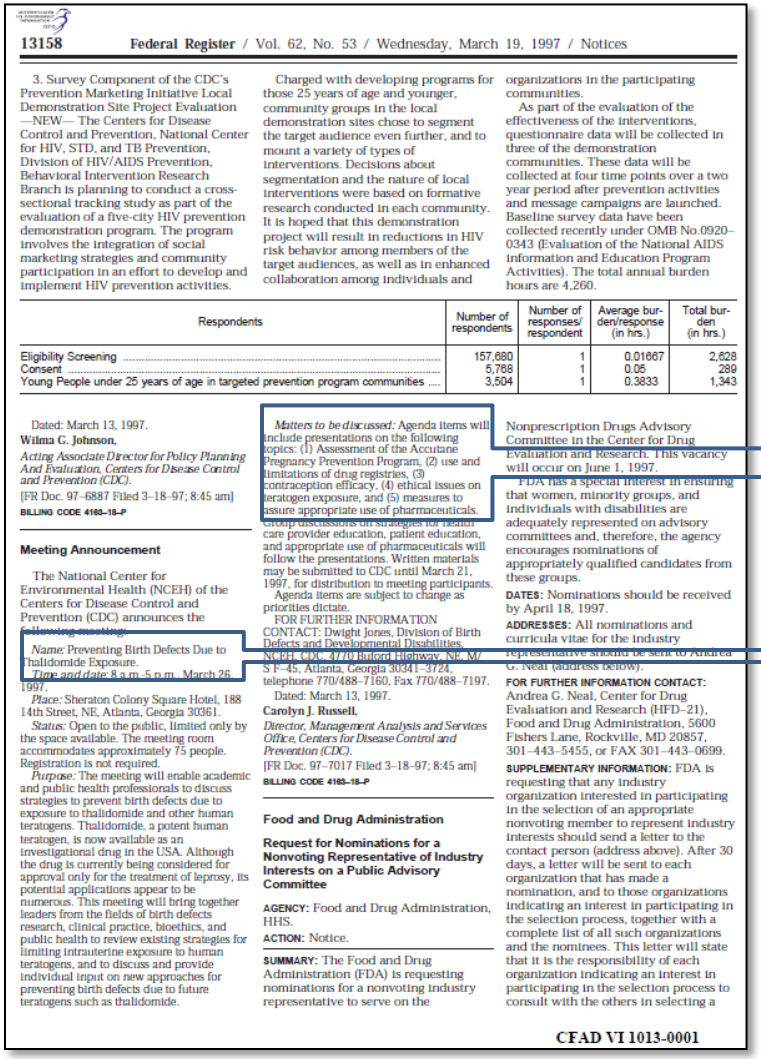
Denise Webster
writer/editor

CFAD VI 1008-0004

Source: Ex. 1008 at 4.

MOTIVATION TO COMBINE

CDC Meeting Materials



13158 **Federal Register** / Vol. 62, No. 53 / Wednesday, March 19, 1997 / Notices

3. Survey Component of the CDC's Prevention Marketing Initiative Local Demonstration Site Project Evaluation —NEW— The Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention, Division of HIV/AIDS Prevention, Behavioral Intervention Research Branch is planning to conduct a cross-sectional tracking study as part of the evaluation of a five-city HIV prevention demonstration program. The program involves the integration of social marketing strategies and community participation in an effort to develop and implement HIV prevention activities.

Charged with developing programs for those 25 years of age and younger, community groups in the local demonstration sites chose to segment the target audience even further, and to mount a variety of types of interventions. Decisions about segmentation and the nature of local interventions were based on formative research conducted in each community. It is hoped that this demonstration project will result in reductions in HIV risk behavior among members of the target audiences, as well as in enhanced collaboration among individuals and organizations in the participating communities.

As part of the evaluation of the effectiveness of the interventions, questionnaire data will be collected in three of the demonstration communities. These data will be collected at four time points over a two year period after prevention activities and message campaigns are launched. Baseline survey data have been collected recently under OMB No.0920–0343 (Evaluation of the National AIDS Information and Education Program Activities). The total annual burden hours are 4,260.

Respondents	Number of respondents	Number of responses/ respondent	Average burden/response (in hrs.)	Total burden (in hrs.)
Eligibility Screening	157,680	1	0.01667	2,628
Consent	5,768	1	0.05	289
Young People under 25 years of age in targeted prevention program communities	3,504	1	0.3833	1,343

Dated: March 13, 1997.
Wilma G. Johnson,
Acting Associate Director for Policy Planning And Evaluation, Centers for Disease Control and Prevention (CDC).
[FR Doc. 97–6887 Filed 3–18–97; 8:45 am]
BILLING CODE 4163–18–P

Meeting Announcement

The National Center for Environmental Health (NCEH) of the Centers for Disease Control and Prevention (CDC) announces the following meeting:

Name: Preventing Birth Defects Due to Thalidomide Exposure.

Time and date: 8 a.m.–5 p.m., March 26, 1997.

Place: Sheraton Colony Square Hotel, 188 14th Street, NE, Atlanta, Georgia 30361.

Status: Open to the public, limited only by the space available. The meeting room accommodates approximately 75 people. Registration is not required.

Purpose: The meeting will enable academic and public health professionals to discuss strategies to prevent birth defects due to exposure to thalidomide and other human teratogens. Thalidomide, a potent human teratogen, is now available as an investigational drug in the USA. Although the drug is currently being considered for approval only for the treatment of leprosy, its potential applications appear to be numerous. This meeting will bring together leaders from the fields of birth defects research, clinical practice, bioethics, and public health to review existing strategies for limiting intrauterine exposure to human teratogens, and to discuss and provide individual input on new approaches for preventing birth defects due to future teratogens such as thalidomide.

Matters to be discussed: Agenda items will include presentations on the following topics: (1) Assessment of the Accutane Pregnancy Prevention Program, (2) use and limitations of drug registries, (3) contraception efficacy, (4) ethical issues on teratogen exposure, and (5) measures to assure appropriate use of pharmaceuticals. Group discussions on strategies for health care provider education, patient education, and appropriate use of pharmaceuticals will follow the presentations. Written materials may be submitted to CDC until March 21, 1997, for distribution to meeting participants.

Agenda items are subject to change as priorities dictate.

FOR FURTHER INFORMATION CONTACT: Dwight Jones, Division of Birth Defects and Developmental Disabilities, NCEH, CDC, 4770 Buford Highway, NE, M/S F–45, Atlanta, Georgia 30341–3724, telephone 770/488–7160, Fax 770/488–7197.

Dated: March 13, 1997.
Carolyn J. Russell,
Director, Management Analysis and Services Office, Centers for Disease Control and Prevention (CDC).
[FR Doc. 97–7017 Filed 3–18–97; 8:45 am]
BILLING CODE 4163–18–P

Food and Drug Administration

Request for Nominations for a Nonvoting Representative of Industry Interests on a Public Advisory Committee

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting nominations for a nonvoting industry representative to serve on the Nonprescription Drugs Advisory Committee in the Center for Drug Evaluation and Research. This vacancy will occur on June 1, 1997.

FDA has a special interest in ensuring that women, minority groups, and individuals with disabilities are adequately represented on advisory committees and, therefore, the agency encourages nominations of appropriately qualified candidates from these groups.

DATES: Nominations should be received by April 18, 1997.

ADDRESSES: All nominations and curricula vitae for the industry representative should be sent to Andrea G. Neal (address below).

FOR FURTHER INFORMATION CONTACT: Andrea G. Neal, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–5455, or FAX 301–443–0699.

SUPPLEMENTARY INFORMATION: FDA is requesting that any industry organization interested in participating in the selection of an appropriate nonvoting member to represent industry interests should send a letter to the contact person (address above). After 30 days, a letter will be sent to each organization that has made a nomination, and to those organizations indicating an interest in participating in the selection process, together with a complete list of all such organizations and the nominees. This letter will state that it is the responsibility of each organization indicating an interest in participating in the selection process to consult with the others in selecting a

CFAD VI 1013-0001

Matters to be discussed: Agenda items will include presentations on the following topics: (1) Assessment of the Accutane Pregnancy Prevention Program, (2) use and limitations of drug registries, (3) contraception efficacy, (4) ethical issues on teratogen exposure, and (5) measures to assure appropriate use of pharmaceuticals.

Name: Preventing Birth Defects Due to Thalidomide Exposure.

Source: Ex. 1013 at 13158.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

88. *Powell* consists of guidelines. A person of ordinary skill in the art would understand how to practice these recommendations at the time of publication without undue experimentation. For example, counseling regarding adverse effects and pregnancy testing were routine parts of the work of an ordinary skill in the art prior to August of 1998. These recommendations were especially accessible in light of other prior art, such as the Accutane® and Clozaril® programs, as described below. Therefore, a person of ordinary skill in the art would have understood how to implement *Powell's* teachings in clinical and pharmacy settings.

89. A person of ordinary skill in the art would also recognize that *Powell* and *Dishman* would address the shortcomings of the Accutane program that was well known in the art and disclosed in *Mitchell*—namely, that the use of the registry was not mandatory for all patients, and that the system did not involve verification by pharmacists that a patient was authorized to receive the drug.

Source: Ex. 1002 ¶¶ 88 - 89.

MOTIVATION TO COMBINE

Dr. Fudin's Testimony

115. In light of the disclosures of *Powell* and *Mitchell*, a person of ordinary skill in the art would have been motivated to look to the system disclosed in *Dishman* to further implement a computerized registry for avoiding birth defects from a teratogenic drug.

116. *Dishman* describes such a registry in the context of clozapine. Clozapine is a potent anti-psychotic with the potential for serious side effects, and prior to 1998, it was well recognized that a successful system existed in the United States to maintain control over the dispensation of the drug.

117. A person of ordinary skill in the art would have sought resources, such as *Dishman*, that described ways to restrict access to drugs that could be potentially hazardous. The clozapine program constitutes one such method of controlled distribution and had proven to be successful prior to 1998.

118. It would have been obvious for a person of ordinary skill in the art to implement the methods used by the Clozaril® program for teratogenic drugs.

Source: Ex. 1002 ¶¶ 115 - 118.

MOTIVATION TO COMBINE

Patent Owner's Unsupported Arguments

> *Third*, CFAD has failed to prove that a POSA would have been motivated to combine the Ground 1 references. Indeed, CFAD's alleged motivations are

• • • • •

> CFAD relied on nothing but its expert's unsupported, conclusory opinions to support its alleged motivations. Pet. 21-22 (citing Ex. 1002 ¶ 89); Pet. 26-27 (citing Ex. 1002 ¶ 115). Dr. Fudin's opinions, however, are directly contradicted by the evidence of record, including Powell and Mitchell, both of which focus on teratogens, with Powell specifically focusing on thalidomide. *See generally* Ex.

Source: Paper 40, Patent Owner Response, at 2, 50.

MOTIVATION TO COMBINE

Patent Owner's Response

different products. Ex. 2061 at 96:21-97:8. CFAD has failed to provide any reason why a POSA that was developing a distribution system for a teratogenic drug to the general population would have been motivated to look to Dishman's disclosure regarding treating veterans with antipsychotics in an institutional setting. Celgene submits a POSA would not have done so.

Instead, a POSA would have understood that Dishman's discussion of treating VA patients with clozapine was irrelevant to the claimed inventions. Ex.

Source: Paper 40, Patent Owner Response, at 52.

MOTIVATION TO COMBINE

Petitioner's Reply

> Numerous documents—including one authored by two of the inventors and other Celgene employees—describing the development of the S.T.E.P.S. program show that these two programs were considered successful models. Moreover, as Celgene admits, *Powell* relates to guidelines for dispensing thalidomide and is undeniably relevant to a thalidomide distribution program. (*See* POR at 25.) Therefore, Celgene's argument that a POSA would not be motivated to combine these references must fail in light of the abundant evidence that a POSA *would* have considered these references relevant to designing methods for safely dispensing thalidomide (and the inventors in fact did).[4]

Source: Paper 49, Petitioner's Reply, at 10.

MOTIVATION TO COMBINE

Mitchell

Vol. 333 No. 2 PREVENTION OF PREGNANCY IN WOMEN RECEIVING ISOTRETINOIN 105

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 117,652 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., R. 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. Trussell, 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.

References

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

CFAD VI 1006-0005

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.

Source: Ex. 1006 at 105.

MOTIVATION TO COMBINE

Vanchieri

Annals of Internal Medicine

CURRENTS

...News for internists

Preparing for Thalidomide's Comeback

Thalidomide is on the verge of being introduced—with great care—into the U.S. marketplace. The news provokes polarized reactions: disbelief that such a potent teratogen could be made available after the lessons of almost 40 years ago, and impatience for a drug that can lead to exceptional improvements in some rare debilitating immune diseases.

In early September, an advisory committee to the U.S. Food and Drug Administration (FDA) recommended that the FDA approve marketing of thalidomide for erythema nodosum leprosum, an inflammatory manifestation of leprosy that results in painful cutaneous lesions on the arms, legs, and face. The committee also strongly recommended limiting distribution of thalidomide, with stringent safety measures put in place to avoid birth defects and other side effects.

The renewed interest in thalidomide comes from studies showing a complete response in 90% of patients with erythema nodosum leprosum who used thalidomide, according to Janet Woodcock, MD, chief of the FDA's Center for Drug Evaluation and Research. The drug is also under investigation to determine its effectiveness against graft-versus-host disease, the AIDS wasting syndrome, some solid tumors, certain serious primary dermatologic conditions, tuberculosis, aphthous ulcers, and macular degeneration. Woodcock said that evidence is most compelling for the drug's effect on aphthous ulcers in patients with HIV infection (N Engl J Med. 1997;335: 1487-93) and with Behçet disease. She considers the data on the AIDS wasting syndrome "promising" but preliminary.

The committee's recommendation was preceded by a year of intensive debate and planning because of the drug's potentially severe side effects. Even one dose of thalidomide, when taken during the early stages of pregnancy, can cause fetal deformities. The drug can also cause peripheral neuropathy, sometimes resulting in permanent nerve damage.

A Brief History

Thalidomide was originally marketed as a sedative and was often used for morning sickness outside of the United States in the 1950s and early 1960s. Although thalidomide was the third largest-selling drug in Europe—considered so safe it was sold over-the-counter in many places—it never passed FDA scrutiny. At least 8000 of the babies born to women who took the drug during pregnancy had phocomelia, which is characterized by missing digits, arms and legs, and internal organ deformities. In the United States, 17 babies were born with the rare birth defect; their mothers had received the drug from overseas sources or received premarketing samples distributed by drug company representatives. The thalidomide episode resulted in stricter review requirements for drug approval by the FDA, including proof of safety and efficacy plus informed consent by all participants in clinical trials.

Today, the FDA has in hand new data that indicate thalidomide's promise in fighting several serious diseases for which no effective alternate therapy exists, but the risks, of course, remain. Because many of the diseases in which thalidomide is potentially beneficial afflict young women (Behçet disease, the Sjögren syndrome, Crohn disease, and rheumatoid arthritis), issues of teratogenicity are critical. Because of a recent study showing thalidomide in rabbit semen and uncertainty about its presence in human semen, both women and men receiving the drug will be required to use contraception.

Concerns about birth defects have been so great that investigational use of thalidomide for erythema nodosum leprosum has been limited to men and postmenopausal or surgically sterilized women. The FDA is unlikely to limit general use of the drug to that extent, but if it is approved as proposed, thalidomide will be the most restricted drug in the United States, Woodcock confirmed. Every physician, pharmacist, and patient involved with thalidomide will be required to adhere to a tightly controlled protocol, according to Bruce J. Williams, from Celgene Corporation of Warren, New Jersey, the drug's marketer.

To gain access to the drug, patients will be required to receive risk–benefit counseling, sign an informed-consent agreement, use two forms of birth control, and participate in frequent surveys; monthly prescriptions will only be filled after pregnancy testing. Compliance and fetal exposures will be tracked. Only pharmacists registered to participate will be permitted to dispense the drug. By registering, they commit to dispense thalidomide in 28-day supplies in original packaging (special blister-packs with pregnancy warnings encasing each pill) only after seeing the signed informed-consent document. The drug cannot be dispensed as a simple refill, and patients will be advised to return unused doses.

When asked whether a patient using thalidomide can decline the use of birth control for religious or other reasons, Williams responded: "Women can make informed choices about whether or not to take the drug. But if they are of childbearing age and want the drug, they must use contraception." Boston University researchers will maintain a thalidomide users registry modeled after the registry that tracks use and pregnancy outcomes for users of isotretinoin, which is marketed by Hoffman-La Roche in Nutley, New Jersey, under the trade name Accutane (Box).

Zero Risk Impossible

Even with these unprecedented safety measures, experts admit that zero risk is an impossible goal. Babies will be born with birth defects if thalidomide is made available. But based on the isotretinoin experience, 20 years of testing in erythema nodosum leprosum, and limited use of thalidomide by 72 women with the AIDS wasting syndrome or aphthous ulcers, the FDA is prepared to move ahead.

implications of this regulatory action go beyond U.S. borders. It sends a message to other countries, said Colin Crawford, MB, ChB, DPH&H, from London's Imperial

(Continued on next page)

able. But based on the isotretinoin experience, 20 years of testing in erythema nodosum leprosum, and limited use of thalidomide by 72 women with the AIDS wasting syndrome or aphthous ulcers, the FDA is prepared to move ahead.

Source: Ex. 2064 at 951.

MOTIVATION TO COMBINE

Vanchieri

Annals of Internal Medicine

CURRENTS

...News for Internists

College of Science, Technology, and Medicine. If the U.S. government makes thalidomide available, developing countries may do the same, he predicted, most likely without the comprehensive safety and tracking program being planned for the United States.

Thalidomide is already available in 8 of 10 South American countries. Thirty-four cases of thalidomide embryopathy have been reported since 1965. Most have occurred in Brazil, where the prevalence of leprosy is high and where, until recently, thalidomide was available without a prescription.

In the United States, the communications challenges are twofold. A population of patients vividly remembers the first thalidomide tragedy. But an informal FDA poll found that most people under age 35 have never heard of thalidomide and are unaware of its potential harmful effects. "When communicating about risks of any disease to a patient, we have to be aware of the cohort experience that patient brings," said Gail J. Povar, MD, clinical professor of medicine and health care sciences at George Washington University School of Medicine in Washington, D.C. Recalling her own reaction to the thalidomide news in the 1960s, Povar stated that nothing could have convinced her to take the drug if she had any chance of becoming pregnant. But she predicts that 25-year-olds will be furious if their physicians refuse to prescribe it for them. She has seen this happen with isotretinoin. "Every week I have a teenager ask for Accutane inappropriately. We have to accept the fact that this will happen with thalidomide and be prepared."

Advocates for survivors of thalidomide defects are calling for efforts to develop analogues of thalidomide without the harmful side effects. But analogue development may take some time because researchers are not sure exactly how thalidomide works. Its immunomodulatory effects may occur through selective inhibition of tumor necrosis factor, the inflammatory cytokine involved in many diseases. It may also block angiogenesis, the most likely reason for its reported effectiveness against some solid tumors and perhaps the method by which it blocks fetal limb and organ development.

"Thalidomide will likely spark disagreements both within the medical community and between medicine and the public about what limits, if any, to impose on use in fertile women. In addition, because of its exciting potential in the amelioration of serious illnesses, thalidomide may tempt clinicians to go beyond well-documented indications to more experimental applications," said Povar. "Informed consent becomes much more important here. Our obligation goes way up. We need to be very clear that use is experimental.

"For the most part, thalidomide poses no more—and no less—a challenge to the practitioner than any other drug with substantial promise and potential toxic effects," she continued. "It would be unfortunate if thalidomide was considered too risky because of its past. Physicians just need to work closely with patients."

—Cori Vanchieri

Will Pregnancy Prevention Work?

A program to reduce pregnancies in women who use isotretinoin, a known teratogen, for severe, cystic acne is being considered as a model for thalidomide. In 1988, "an unprecedented and novel" pregnancy prevention program was developed for isotretinoin users, according to Allen A. Mitchell, MD, professor of epidemiology and pediatrics at the Boston University School of Public Health. Rates of oral contraceptive use and abstinence were higher in the isotretinoin users than in the general public. The pregnancy rate was 7% that of the U.S. population. Of the 210 009 women with complete follow-up, 623 became pregnant. Two thirds of the pregnancies resulted from contraceptive failure; 68% were electively aborted, 16% were spontaneously aborted, 3% were ectopic, and 11% resulted in live births. As expected, 25% to 30% of the babies had birth defects. Mitchell, who implemented the isotretinoin registry, has suggested that a more stringent program may be required for thalidomide users.

—Cori Vanchieri

Heart Disease: Women's Unique Risks Demand Attention

Responding to what it calls a "silent epidemic," the American Heart Association (AHA) has released new guidelines to help physicians prevent, diagnose, and treat heart disease in women (Circulation. 1997;96:2468-99). The AHA also unveiled a national survey of 1000 women ages 25 and older in which fewer than one third said they had discussed heart disease with a physician. Only 8% considered heart disease their biggest health threat. In reality, heart disease kills half a million women each year—more than all types of cancer combined (Box).

"Much of heart disease [in women] gets missed or misdiagnosed," said Martha Hill, RN, PhD, president of the Dallas-based AHA. "Now, we're learning a lot about the prevalence of heart disease and the benefits of treatment. This statement shares what we've learned."

Age and Coexisting Conditions

Differences in coronary heart disease (CHD) between men and women contribute to a disparity in the mortality rate. Women tend to develop CHD 7 to 10 years later than men—after menopause, when the cardiovascular benefit of estrogen is apparently lost. Because they present with heart disease at later ages, women are also more likely to have coexisting conditions that can reduce survival.

Women often present cardiac symptoms late, when the disease has progressed. And although women frequently experience the same kind of chest pain as men during a myocardial infarction (MI), they are also more likely to have confusing symptoms of upper abdominal pain, nausea, or fatigue. Finally, basic physiologic differences, such as smaller body size—hence smaller coronary arteries—make bypass surgery more difficult and lead to a higher operative mortality rate.

"All this means that physicians need to recognize that there are unique aspects of heart disease in women," said Lori Mosca, MD, PhD, a preventive cardiologist at the University of Michigan in Ann Arbor and lead author of the AHA statement. "You need to screen for the disease and then

(Continued on next page)

Will Pregnancy Prevention Work?

A program to reduce pregnancies in women who use isotretinoin, a known teratogen, for severe, cystic acne is being considered as a model for thalidomide. In 1988, "an unprecedented and novel" pregnancy prevention program was developed for isotretinoin users, according to Allen A. Mitchell, MD, professor of epidemiology and pediatrics at the Boston University School of Public Health. Rates of oral contraceptive use and abstinence were higher in the isotretinoin users than in the general public. The pregnancy rate was 7% that of the U.S. population. Of the 210 009 women with complete follow-up, 623 became pregnant. Two thirds of the pregnancies resulted from contraceptive failure; 68% were electively aborted, 16% were spontaneously aborted, 3% were ectopic, and 11% resulted in live births. As expected, 25% to 30% of the babies had birth defects. Mitchell, who implemented the isotretinoin registry, has suggested that a more stringent program may be required for thalidomide users.

—Cori Vanchieri

Source: Ex. 2064 at 952.

MOTIVATION TO COMBINE

Marwick

The Drug That Changed US Pharmaceutical History

The NIH workshop opened with a review of the history of thalidomide by Frances O. Kelsey, MD, currently deputy for scientific and medical affairs in the FDA's Office of Compliance. Kelsey was an FDA medical officer reviewing thalidomide when the manufacturer, William S. Merrell Company, a division of Richardson Merrell Inc, Cincinnati, Ohio, filed an application to market the drug as a sedative in September 1960. Kelsey recently related the circumstances under which drugs were reviewed at that time and summarized the accumulation of the evidence that finally resulted in the withdrawal of the new drug application for thalidomide.

Initially there were a number of technical concerns, she said; then there were the reports of peripheral neuritis; and, finally, in the fall of 1961, came the association of the drug with cases of fetal amelia and phocomelia in Germany, where the drug was available. The new drug application was withdrawn in March 1962, and Kelsey has long been hailed for the role she played.

Thalidomide was never approved for use in the United States, but few pharmaceutical agents have had a greater impact on drug development. The passage in 1962 of the Kefauver-Harris Act, which required that drugs be shown to be not only safe but effective (the Food, Drug, and Cosmetic Act of 1938 having required only safety), was a direct result of the experience with thalidomide, as Kelsey pointed out.

In a recent interview, she said it was not uncommon at the time for a pharmaceutical firm to send samples of a new drug to 1000 or so physicians before it received FDA marketing approval, explaining its use and saying it would soon be available—as was in fact the case with thalidomide. Ironically, it was a drug that, although effective for some indications, proved unsafe for so many that brought about a change in the accepted procedure.

"The thalidomide tragedy showed up big loopholes in the testing of drugs," Kelsey said. "Some of us knew what was going on, but we never had the backing to change it before. Sooner or later there would have been another tragedy, but it just happened that it was thalidomide that got the [Kefauver-Harris] bill through at lightning speed, and that was very satisfactory to us."

"There has never been a drug that has so profoundly affected drug development around the world as has thalidomide," said Sol Barer, the chief executive officer of thalidomide manufacturer Celgene Corporation. "It altered attitudes about drug regulation, it significantly broadened FDA authority, it affected all drug development. It changed history."—C. M.

ances the interests of future children and getting reasonable access to the drug."

Ethics Over Exclusion

Noting that thalidomide has the potential to be an effective agent for a number of conditions, Gail J. Povar, MD, clinical professor of medicine and health care science at George Washington University School of Medicine, Washington, DC, addressed the problem of off-label use—an issue that cropped up repeatedly during the workshop discussions. The data presented at the meeting provide a strong incentive to approve and promote the use of the drug, Povar noted, adding, "What worries me is that there may be desperate patients who will try to go beyond the well-documented indications to more experimental applications. When you do so, the ethical requirements go up. They extend beyond the informed consent and risk-benefit assessments of standard medical practice to those of clinical research."

Few drugs carry the pharmacologic political and emotional baggage that is attached to thalidomide, Povar said. Therefore, some maintain that the drug should be excluded from use by fertile women, that its teratogenic effects pose an ethical issue that makes it different from other drugs. This attitude, she said, is a mistake. "Thalidomide poses no more and no less of a challenge than any drug with substantial promise and toxicity. We are simply dealing with an agent that, like any pharmacologic agent, purchases its effects at a price. There are benefits, but there are also risks, and physicians must weigh them carefully."

In the expectation of marketing thalidomide, Celgene has drafted a plan that it hopes will prevent fetal exposure to the drug. "The goal is zero defects," said Bruce A. Williams, the firm's vice president for sales and marketing. The plan is built on experience with restrictions on such other drugs with severe adverse effects as Accutane (Hoffmann-La Roche, Nutley, NJ), used to treat severe acne, and Clozaril (Novartis Pharmaceuticals Corporation, East Hanover, NJ), used to treat schizophrenia. However, the plan has some unique elements, Williams said. The manufacturer will exert "a high degree of control" over distribution of the drug and, unlike the system used by Hoffmann-LaRoche to control the use of Accutane, a tracking system would be in place to ensure compliance.

The plan has yet to be finalized, but Williams said he believes it goes a long way toward solving the problem. "It's a model for the distribution of drugs that have great benefit yet significant risk. It is a response to both the need to prevent a new thalidomide tragedy and the humane need to ensure that those who need this therapy can have appropriate access to it," he said.

Essentials of the Plan

The goal is to limit risk by supporting appropriate use for serious, debilitating, life-threatening conditions for which current therapy is inadequate or unavailable. Williams described a scenario in which a patient, considering the use of thalidomide and in consultation with a physician, would agree to counseling regarding the relative risks and benefits to ensure that the risks, including the need to avoid fetal exposure, were understood. The patient would sign an informed consent document that acknowledged his or her understanding and would agree to participate in a confidential survey at the start, during, and on the completion of therapy. Patients would be warned against letting the drug be used by anyone for whom it had not been not prescribed.

Women would be counseled about contraception; the results of a pregnancy test would have to be in hand before therapy was started; and pregnancy tests would continue during the course of therapy. "This is not a contraceptive program, it's a fetal risk-exposure prevention program," Williams emphasized. A prescription would be written for only 4 weeks of therapy, and no automatic refills would be allowed.

Male patients who are prescribed the drug would be advised to use condoms if they are sexually active. "The authorities we've talked to strongly urge us to recommend the use of condoms, in part because it's good policy from the public health perspective and in part because we can't categorically rule out the risk of the drug being transmitted in the ejaculate, although when it's been looked for it has not been found," said Celgene's Barer.

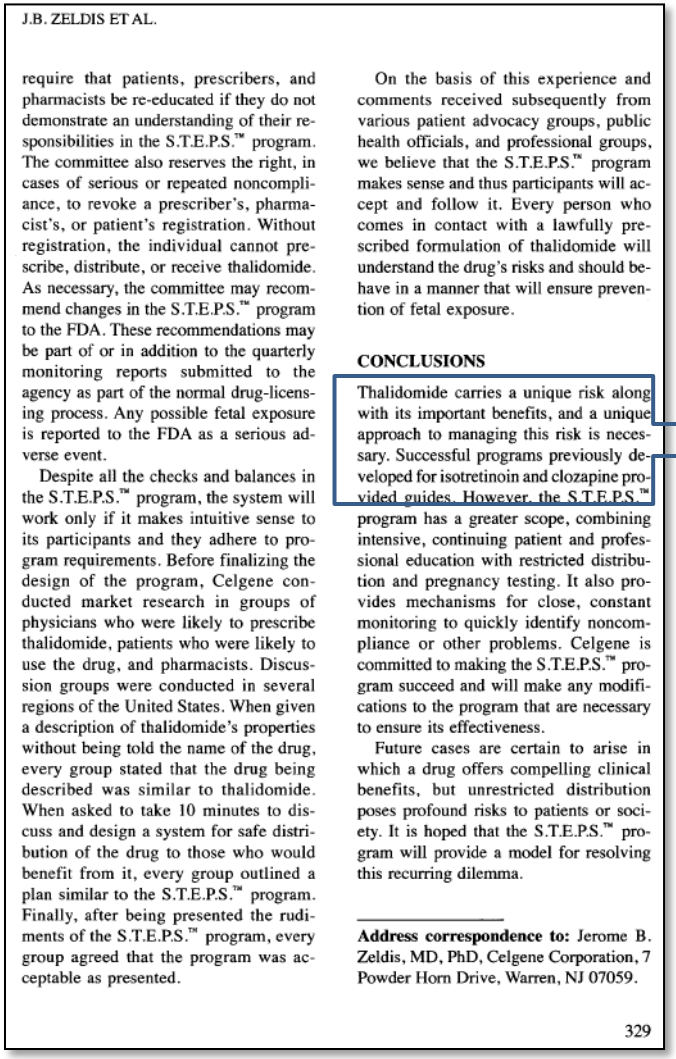
One unusual recommendation the advisory committee made was that warnings on the package include a photograph of a limb-deficient infant as a

dent for sales and marketing. The plan is built on experience with restrictions on such other drugs with severe adverse effects as Accutane (Hoffmann-La Roche, Nutley, NJ), used to treat severe acne, and Clozaril (Novartis Pharmaceuticals Corporation, East Hanover, NJ), used to treat schizophrenia. However, the plan

Source: Ex. 2063 at 1136.

MOTIVATION TO COMBINE

Zeldis



J.B. ZELDIS ET AL.

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.

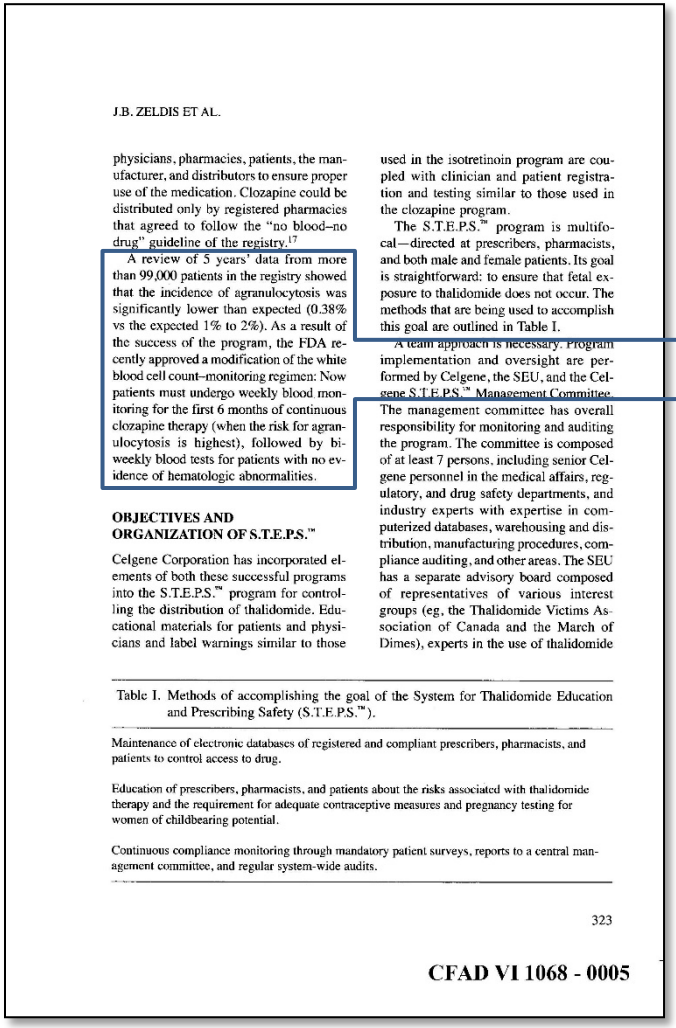
329

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.™

Source: Ex. 1068 at 329.

MOTIVATION TO COMBINE

Zeldis



J.B. ZELDIS ET AL.

physicians, pharmacies, patients, the manufacturer, and distributors to ensure proper use of the medication. Clozapine could be distributed only by registered pharmacies that agreed to follow the "no blood–no drug" guideline of the registry.[17]

A review of 5 years' data from more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected (0.38% vs the expected 1% to 2%). As a result of the success of the program, the FDA recently approved a modification of the white blood cell count–monitoring regimen: Now patients must undergo weekly blood monitoring for the first 6 months of continuous clozapine therapy (when the risk for agranulocytosis is highest), followed by biweekly blood tests for patients with no evidence of hematologic abnormalities.

OBJECTIVES AND ORGANIZATION OF S.T.E.P.S.™

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.™ program for controlling the distribution of thalidomide. Educational materials for patients and physicians and label warnings similar to those used in the isotretinoin program are coupled with clinician and patient registration and testing similar to those used in the clozapine program.

The S.T.E.P.S.™ program is multifocal—directed at prescribers, pharmacists, and both male and female patients. Its goal is straightforward: to ensure that fetal exposure to thalidomide does not occur. The methods that are being used to accomplish this goal are outlined in Table I.

A team approach is necessary. Program implementation and oversight are performed by Celgene, the SEU, and the Celgene S.T.E.P.S.™ Management Committee. The management committee has overall responsibility for monitoring and auditing the program. The committee is composed of at least 7 persons, including senior Celgene personnel in the medical affairs, regulatory, and drug safety departments, and industry experts with expertise in computerized databases, warehousing and distribution, manufacturing procedures, compliance auditing, and other areas. The SEU has a separate advisory board composed of representatives of various interest groups (eg, the Thalidomide Victims Association of Canada and the March of Dimes), experts in the use of thalidomide

Table I. Methods of accomplishing the goal of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™).

Maintenance of electronic databases of registered and compliant prescribers, pharmacists, and patients to control access to drug.
Education of prescribers, pharmacists, and patients about the risks associated with thalidomide therapy and the requirement for adequate contraceptive measures and pregnancy testing for women of childbearing potential.
Continuous compliance monitoring through mandatory patient surveys, reports to a central management committee, and regular system-wide audits.

323

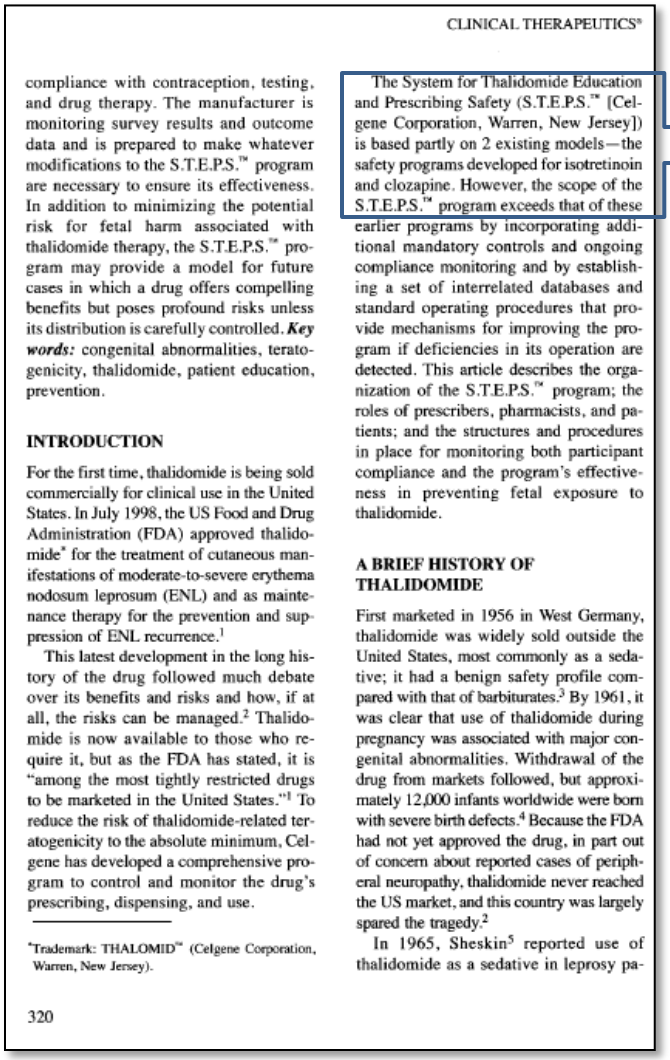
CFAD VI 1068 - 0005

A review of 5 years' data from more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected (0.38% vs the expected 1% to 2%). As a result of the success of the program, the FDA recently approved a modification of the white blood cell count–monitoring regimen: Now patients must undergo weekly blood monitoring for the first 6 months of continuous clozapine therapy (when the risk for agranulocytosis is highest), followed by biweekly blood tests for patients with no evidence of hematologic abnormalities.

Source: Ex. 1068 at 323.

MOTIVATION TO COMBINE

Zeldis



CLINICAL THERAPEUTICS®

compliance with contraception, testing, and drug therapy. The manufacturer is monitoring survey results and outcome data and is prepared to make whatever modifications to the S.T.E.P.S.™ program are necessary to ensure its effectiveness. In addition to minimizing the potential risk for fetal harm associated with thalidomide therapy, the S.T.E.P.S.™ program may provide a model for future cases in which a drug offers compelling benefits but poses profound risks unless its distribution is carefully controlled. ***Key words:*** congenital abnormalities, teratogenicity, thalidomide, patient education, prevention.

INTRODUCTION

For the first time, thalidomide is being sold commercially for clinical use in the United States. In July 1998, the US Food and Drug Administration (FDA) approved thalidomide* for the treatment of cutaneous manifestations of moderate-to-severe erythema nodosum leprosum (ENL) and as maintenance therapy for the prevention and suppression of ENL recurrence.[1]

This latest development in the long history of the drug followed much debate over its benefits and risks and how, if at all, the risks can be managed.[2] Thalidomide is now available to those who require it, but as the FDA has stated, it is "among the most tightly restricted drugs to be marketed in the United States."[1] To reduce the risk of thalidomide-related teratogenicity to the absolute minimum, Celgene has developed a comprehensive program to control and monitor the drug's prescribing, dispensing, and use.

*Trademark: THALOMID™ (Celgene Corporation, Warren, New Jersey).

The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™ [Celgene Corporation, Warren, New Jersey]) is based partly on 2 existing models—the safety programs developed for isotretinoin and clozapine. However, the scope of the S.T.E.P.S.™ program exceeds that of these earlier programs by incorporating additional mandatory controls and ongoing compliance monitoring and by establishing a set of interrelated databases and standard operating procedures that provide mechanisms for improving the program if deficiencies in its operation are detected. This article describes the organization of the S.T.E.P.S.™ program; the roles of prescribers, pharmacists, and patients; and the structures and procedures in place for monitoring both participant compliance and the program's effectiveness in preventing fetal exposure to thalidomide.

A BRIEF HISTORY OF THALIDOMIDE

First marketed in 1956 in West Germany, thalidomide was widely sold outside the United States, most commonly as a sedative; it had a benign safety profile compared with that of barbiturates.[3] By 1961, it was clear that use of thalidomide during pregnancy was associated with major congenital abnormalities. Withdrawal of the drug from markets followed, but approximately 12,000 infants worldwide were born with severe birth defects.[4] Because the FDA had not yet approved the drug, in part out of concern about reported cases of peripheral neuropathy, thalidomide never reached the US market, and this country was largely spared the tragedy.[2]

In 1965, Sheskin[5] reported use of thalidomide as a sedative in leprosy pa-

320

The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™ [Celgene Corporation, Warren, New Jersey]) is based partly on 2 existing models—the safety programs developed for isotretinoin and clozapine. However, the scope of the S.T.E.P.S.™ program exceeds that of these

Source: Ex. 1068 at 320.

MOTIVATION TO COMBINE

Zeldis

tients with ENL and indicated that the drug caused rapid and dramatic improvement in type II lepra reactions. Subsequent controlled studies confirmed the efficacy of the drug in the treatment of ENL.[6,7] In addition to being used widely in the treatment of ENL, thalidomide has been and continues to be investigated for the treatment of various other conditions.[8]

THALIDOMIDE-ASSOCIATED TERATOGENICITY

Fetal abnormalities related to thalidomide therapy include amelia (congenital absence of limbs), phocomelia (shortened limbs), hypoplasticity of the bones, absence of bones, external ear and eye abnormalities, facial palsy, and congenital heart defects.[9] A German retrospective study suggested that the greatest risk of teratogenicity occurs when thalidomide is ingested during the 34th to 50th day of pregnancy.[10] However, it cannot be inferred from the historical data that there is any period of pregnancy during which thalidomide administration is safe, nor is there any level of exposure during pregnancy at which the drug is known to be safe. For example, a single exposure to a

EXPERIENCE IN MANAGING SPECIAL DRUG-ASSOCIATED RISKS

Isotretinoin

perience in the use of drugs that offer important clinical benefits but carry potentially serious risks. Teratogenicity has been addressed in the case of isotretinoin,* an oral drug capable of producing prolonged remissions in patients with severe, recalcitrant cystic acne.[12] In 1988, after receiving reports of retinoic acid–induced embryopathy, the manufacturer of isotretinoin implemented a program designed to allow female patients access to the drug while minimizing the teratogenic hazard.[13]

In contrast to the case of thalidomide, retinoic acid's teratogenic effect was known before marketing; the initial labeling of isotretinoin included a warning against use during pregnancy. Nonetheless, reports of birth defects and spontaneous abortions appeared in women exposed to isotretinoin during the first trimester of pregnancy.[12] The reports mounted despite warnings to physicians through direct mailings, advertisements, and the package insert; by 1989, 78 malformed infants had been born to women taking isotretinoin.[11]

The FDA and the manufacturer of isotretinoin redoubled their efforts to alert physicians and patients to the teratogenic effects of the drug. In addition, the manufacturer implemented a variety of educational programs and made changes in la- ackaging.[12] In 1988 the revised to state that iso- apy is contraindicated in le of becoming pregnant, ption of those with severe, dular acne that is unrespon- rd therapies. In addition, e candidates for isotretinoin be judged capable of com- erapy and taking contracep-

*Trademark: Accutane® (Roche Pharmaceuticals, Nutley, New Jersey).

tive measures, must be given verbal and written warnings of the teratogenic hazard, and must have a negative result on a serum or urine pregnancy test within 14 days of starting therapy.

The manufacturer also instituted the Pregnancy Prevention Program to encourage attention to the above requirements.[13] This program comprises a kit containing educational material for patients, a standard patient consent form, and checklists for both the patient and physician to verify that the patient meets the criteria for therapy with isotretinoin. Awareness of the program has been reinforced by periodic communications to prescribers and pharmacists. The elements of the program that depart from usual medical practice include: (1) a formalized process for ensuring informed patient consent, (2) a provision by the manufacturer to reimburse patients for the cost of contraceptive counseling, and (3) the requirement that women use the drug solely for its labeled indication. Later the manufacturer repackaged isotretinoin in a 10-capsule blister pack containing information directed specifically at women: a warning about the risks of becoming pregnant while taking isotretinoin or during the month after treatment, an "avoid pregnancy" icon on each capsule, and line drawings of malformations associated with the drug.

In 1995, Mitchell and coworkers,[13] from the Slone Epidemiologic Unit (SEU) at the Boston University School of Medicine School of Public Health, reported that women receiving isotretinoin under the Pregnancy Prevention Program had a substantially lower pregnancy rate than the general population: 8.8 versus 109 per 1000 person-years. In addition, 24,258 (99%) of 24,503 women interviewed within 1 month of enrollment in the program said that they had been told to avoid pregnancy. Further, posttherapy tracking showed that pregnancy rates increased in the 4 months after cessation of isotretinoin therapy, which is consistent with avoidance of pregnancy during the period of

Cloz

Clozapine

A antipsychotic agent clozapine.* The drug benefited patients with schizophrenia who did not respond to other medications by improving negative as well as positive symptoms of the disease.[14,15] Unfortunately, clinical research findings and foreign postmarketing experience indicated that 1% to 2% of patients developed agranulocytosis, which is potentially fatal.[16] At the same time, however, the data showed that none of the patients whose agranulocytosis was detected through laboratory tests died before they developed infections. This suggested that patient surveillance could help prevent agranulocytosis.[16]

The FDA's approval of the drug in 1989 was contingent on such surveillance, and the manufacturer created the Clozaril National Registry, a program designed to register treating physicians and patients, ensure patient monitoring (regular blood testing), and limit distribution of the drug to compliant individuals. All patients who received clozapine were required to have a white blood cell count at baseline and weekly thereafter until 4 weeks after the end of treatment. Patients could receive medication only when data on their white blood cell count were current. The registry system also provided guidelines for

*Trademark: Clozaril™ (Sandoz Pharmaceuticals, Hanover, New Jersey).

Source: Ex. 1068 at 321 - 322.

MOTIVATION TO COMBINE

Zeldis

physicians, pharmacies, patients, the manufacturer, and distributors to ensure proper use of the medication. Clozapine could be distributed only by registered pharmacies that agreed to follow the "no blood–no drug" guideline of the registry.[17]

A review of 5 years' data from more than 99,000 patients in the registry showed that the incidence of agranulocytosis was significantly lower than expected (0.38% vs the expected 1% to 2%). As a result of the success of the program, the FDA recently approved a modification of the white blood cell count–monitoring regimen: Now patients must undergo weekly blood monitoring for the first 6 months of continuous clozapine therapy (when the risk for agranulocytosis is highest), followed by biweekly blood tests for patients with no evidence of hematologic abnormalities.

OBJECTIVES AND ORGANIZATION OF S.T.E.P.S.™

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.™ program for controlling the distribution of thalidomide. Educational materials for patients and physicians and label warnings similar to those used in the isotretinoin program are coupled with clinician and patient registration and testing similar to those used in the clozapine program.

The S.T.E.P.S.™ program is multifocal—directed at prescribers, pharmacists, and both male and female patients. Its goal is straightforward: to ensure that fetal exposure to thalidomide does not occur. The methods that are being used to accomplish this goal are outlined in Table I.

A team approach is necessary. Program implementation and oversight are performed by Celgene, the SEU, and the Celgene S.T.E.P.S.™ Management Committee. The management committee has overall responsibility for monitoring and auditing the program. The committee is composed of at least 7 persons, including senior Celgene personnel in the medical affairs, regulatory, and drug safety departments, and industry experts with expertise in computerized databases, warehousing and distribution, manufacturing procedures, compliance auditing, and other areas. The SEU has a separate advisory board composed of representatives of various interest groups (eg, the Thalidomide Victims Association of Canada and the March of Dimes), experts in the use of thalidomide

Table I. Methods of accomplishing the goal of the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™).

Maintenance of electronic databases of registered and compliant prescribers, pharmacists, and patients to control access to drug.
Education of prescribers, pharmacists, and patients about the risks associated with thalidomide therapy and the requirement for adequate contraceptive measures and pregnancy testing for women of childbearing potential.
Continuous compliance monitoring through mandatory patient surveys, reports to a central management committee, and regular system-wide audits.

Celgene Corporation has incorporated elements of both these successful programs into the S.T.E.P.S.™ program for controlling the distribution of thalidomide. Edu-

Source: Ex. 1068 at 323.

MOTIVATION TO COMBINE

Dr. DiPiro's Admissions

Q. Apart from that and those cites, you don't cite any other document to show a need prior to the Celgene product, correct?

A. Well, in addition, paragraph 107, I note that the literature clearly discloses that the problems associated with safe access to teratogenic drugs addressed by the claimed inventions were not solved by the PPP or Clozapine systems. Specifically, neither of these systems completely prevented the side effects that they were allegedly designed to avoid.

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. 1066 at 325:24-326:10, 326:20–327:5.

MOTIVATION TO COMBINE

Dr. Frau's Admissions

Under your definition of restricted distribution program, would you consider the Clozaril registry to be a restricted distribution program?

A. The clozapine program may have -- may have fitted the definition of a restriction distribution.

Q. Based on what you know about the program?

A. It could have met the definition, yes.

Q. Did it or did it not meet your definition?

A. Yes.

Source: Ex. 1067 at 112:7–15, 113:3–8.

MOTIVATION TO COMBINE

Dr. Frau's Admissions

Q. In order to identify a problem, does a POSA have to be able to cite to a particular reference?

MS. SHIH: Objection, form.

A. I would say it depends on the situation, it depends on the product, it depends on the situation -- it depends on the situation.

Q. In the situation that we are dealing with right now in your declaration.

MS. SHIH: Objection, form.

A. Yes.

Source: Ex. 1067 at 86:4–14.

MOTIVATION TO COMBINE

The Institution Decision

IPR2015-01092
Patent 6,045,501

1. Claim 1

The information presented shows sufficiently the following facts about the asserted prior art. Powell provides guidance regarding "the clinical use and dispensing" of thalidomide. Pet. 21 (quoting Ex. 1005, 901). Mitchell relates to an existing pregnancy-prevention program for women users of Accutane®, a Vitamin A analogue of isotretinoin and a known teratogenic drug. Pet. 15; Ex. 1006, 101–102. Dishman describes a registry for pharmacies, prescribers, and users of clozapine, a potent anti-psychotic drug with potential for serious side effects. Pet. 27–28 (quoting Ex. 1007, 899). Petitioner shows sufficiently that a person of ordinary skill in the art would have understood how to implement Powell's teachings "in clinical and pharmacy settings" in view "of the Accutane® Pregnancy Prevention Program described in Mitchell and the Clozaril® controlled distribution model outlined in Dishman." *Id.* at 21 (quoting Ex. 1002 ¶ 88).

Powell discloses that "women of childbearing potential" should not be treated with thalidomide if they "wish to become pregnant," "have not practiced a reliable form of contraception for 1 year," "are unwilling to take reliable contraceptive precautions," or "are considered not capable of complying with the requirements for reliable contraception." *Id.* at 22 (quoting Ex. 1005, 901). Similarly, Mitchell discloses a program of preventative measures, such as pregnancy-risk warnings on packaging, targeted "specifically at women." *Id.* (quoting Ex. 1006, 101). Mitchell also targets "women of childbearing age (12 to 59 years of age)" for the pregnancy-prevention program. *Id.* (quoting Ex. 1006, 102). On this record, Powell and Mitchell suggest identifying "a subpopulation" of female patients who are capable of becoming pregnant, from among a larger group of patients in need of a teratogenic drug. Ex. 1001, claim 1 (step (d)).

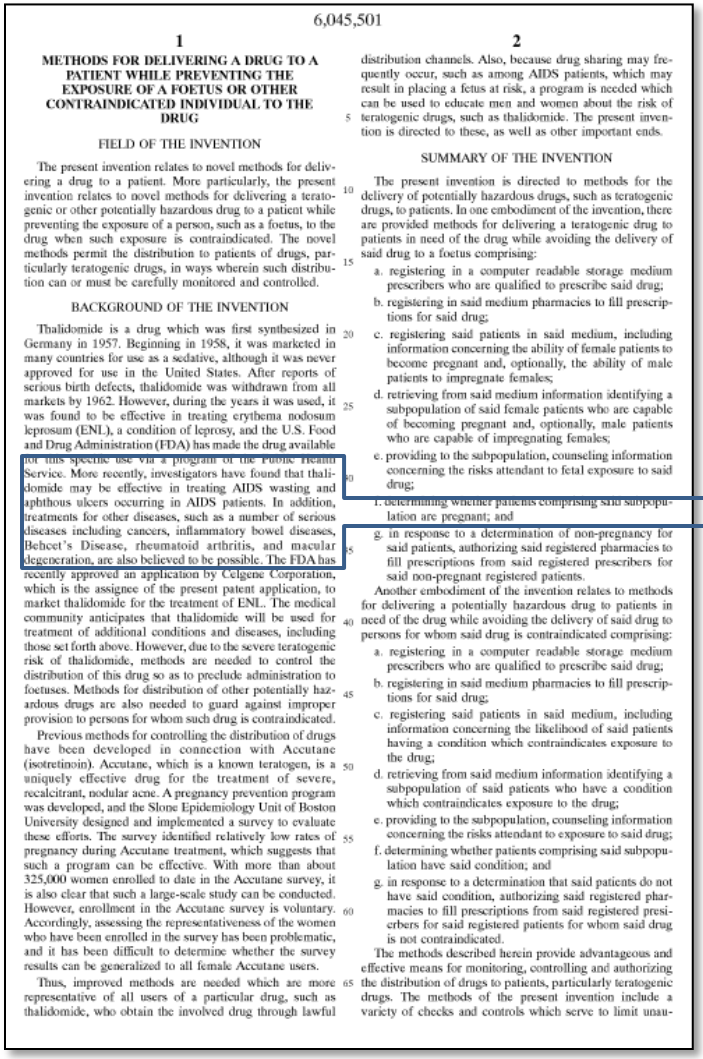
7

The information presented shows sufficiently the following facts about the asserted prior art. Powell provides guidance regarding "the clinical use and dispensing" of thalidomide. Pet. 21 (quoting Ex. 1005, 901). Mitchell relates to an existing pregnancy-prevention program for women users of Accutane®, a Vitamin A analogue of isotretinoin and a known teratogenic drug. Pet. 15; Ex. 1006, 101–102. Dishman describes a registry for pharmacies, prescribers, and users of clozapine, a potent anti-psychotic drug with potential for serious side effects. Pet. 27–28 (quoting Ex. 1007, 899). Petitioner shows sufficiently that a person of ordinary skill in the art would have understood how to implement Powell's teachings "in clinical and pharmacy settings" in view "of the Accutane® Pregnancy Prevention Program described in Mitchell and the Clozaril® controlled distribution model outlined in Dishman." *Id.* at 21 (quoting Ex. 1002 ¶ 88).

Source: Paper 20, Institution Decision, at 7.

Secondary Considerations of Non-Obviousness

No Nexus with the Claimed Methods



6,045,501

1

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

FIELD OF THE INVENTION

The present invention relates to novel methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient while preventing the exposure of a person, such as a foetus, to the drug when such exposure is contraindicated. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can or must be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of serious diseases including cancers, inflammatory bowel diseases, Behcet's Disease, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses. Methods for distribution of other potentially hazardous drugs are also needed to guard against improper provision to persons for whom such drug is contraindicated.

Previous methods for controlling the distribution of drugs have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. However, enrollment in the Accutane survey is voluntary. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users.

Thus, improved methods are needed which are more representative of all users of a particular drug, such as thalidomide, who obtain the involved drug through lawful

2

distribution channels. Also, because drug sharing may frequently occur, such as among AIDS patients, which may result in placing a fetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to methods for the delivery of potentially hazardous drugs, such as teratogenic drugs, to patients. In one embodiment of the invention, there are provided methods for delivering a teratogenic drug to patients in need of the drug while avoiding the delivery of said drug to a foetus comprising:

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

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

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

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

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

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

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

Another embodiment of the invention relates to methods for delivering a potentially hazardous drug to patients in need of the drug while avoiding the delivery of said drug to persons for whom said drug is contraindicated comprising:

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

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

c. registering said patients in said medium, including information concerning the likelihood of said patients having a condition which contraindicates exposure to the drug;

d. retrieving from said medium information identifying a subpopulation of said patients who have a condition which contraindicates exposure to the drug;

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

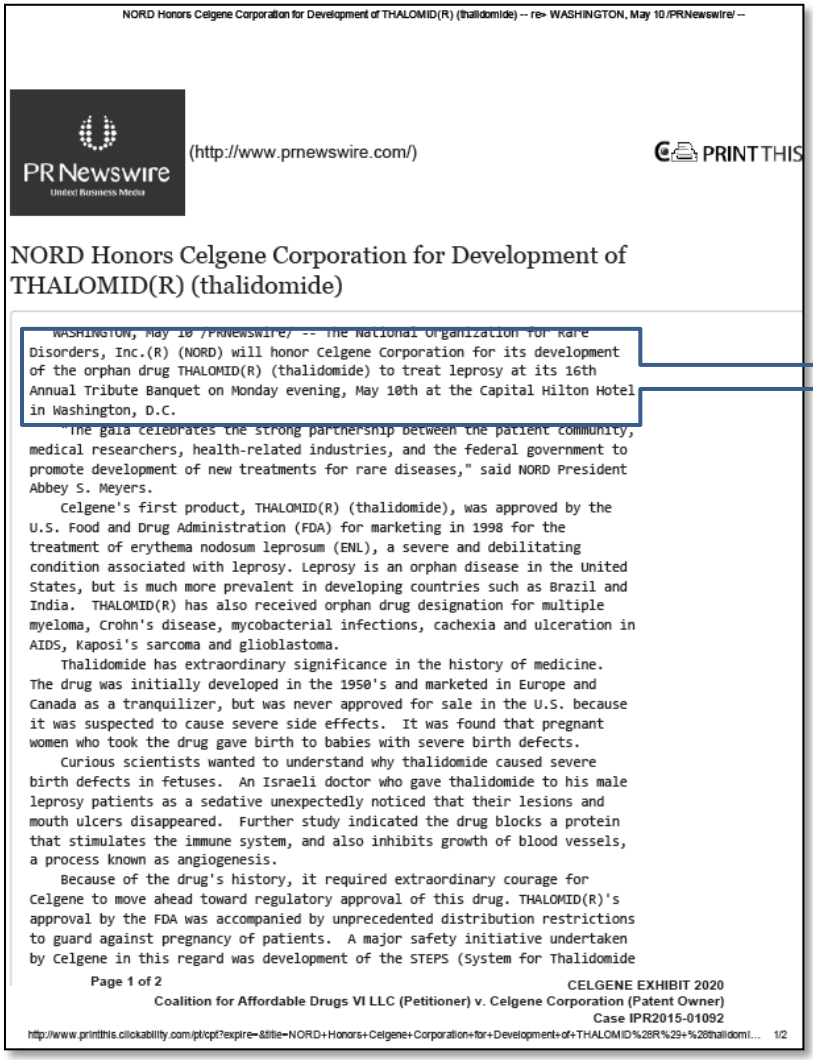
f. determining whether patients comprising said subpopulation have said condition; and

g. in response to a determination that said patients do not have said condition, authorizing said registered pharmacies to fill prescriptions from said registered prescribers for said registered patients for whom said drug is not contraindicated.

The methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution of drugs to patients, particularly teratogenic drugs. The methods of the present invention include a variety of checks and controls which serve to limit unau-

Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of serious diseases including cancers, inflammatory bowel diseases, Behcet's Disease, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has

No Nexus with the Claimed Methods



NORD Honors Celgene Corporation for Development of THALOMID(R) (thalidomide) -- re> WASHINGTON, May 10 /PRNewswire/ --

PR Newswire
United Business Media

(http://www.prnewswire.com/)

PRINT THIS

NORD Honors Celgene Corporation for Development of THALOMID(R) (thalidomide)

WASHINGTON, May 10 /PRNewswire/ -- The National Organization for Rare Disorders, Inc.(R) (NORD) will honor Celgene Corporation for its development of the orphan drug THALOMID(R) (thalidomide) to treat leprosy at its 16th Annual Tribute Banquet on Monday evening, May 10th at the Capital Hilton Hotel in Washington, D.C.

"The gala celebrates the strong partnership between the patient community, medical researchers, health-related industries, and the federal government to promote development of new treatments for rare diseases," said NORD President Abbey S. Meyers.

Celgene's first product, THALOMID(R) (thalidomide), was approved by the U.S. Food and Drug Administration (FDA) for marketing in 1998 for the treatment of erythema nodosum leprosum (ENL), a severe and debilitating condition associated with leprosy. Leprosy is an orphan disease in the United States, but is much more prevalent in developing countries such as Brazil and India. THALOMID(R) has also received orphan drug designation for multiple myeloma, Crohn's disease, mycobacterial infections, cachexia and ulceration in AIDS, Kaposi's sarcoma and glioblastoma.

Thalidomide has extraordinary significance in the history of medicine. The drug was initially developed in the 1950's and marketed in Europe and Canada as a tranquilizer, but was never approved for sale in the U.S. because it was suspected to cause severe side effects. It was found that pregnant women who took the drug gave birth to babies with severe birth defects.

Curious scientists wanted to understand why thalidomide caused severe birth defects in fetuses. An Israeli doctor who gave thalidomide to his male leprosy patients as a sedative unexpectedly noticed that their lesions and mouth ulcers disappeared. Further study indicated the drug blocks a protein that stimulates the immune system, and also inhibits growth of blood vessels, a process known as angiogenesis.

Because of the drug's history, it required extraordinary courage for Celgene to move ahead toward regulatory approval of this drug. THALOMID(R)'s approval by the FDA was accompanied by unprecedented distribution restrictions to guard against pregnancy of patients. A major safety initiative undertaken by Celgene in this regard was development of the STEPS (System for Thalidomide

Page 1 of 2

CELGENE EXHIBIT 2020
Coalition for Affordable Drugs VI LLC (Petitioner) v. Celgene Corporation (Patent Owner)
Case IPR2015-01092

http://www.printthis.clickability.com/pt/cpt?expire=&title=NORD+Honors+Celgene+Corporation+for+Development+of+THALOMID%28R%29+%28thalidomi... 1/2

WASHINGTON, May 10 /PRNewswire/ -- The National Organization for Rare Disorders, Inc.(R) (NORD) will honor Celgene Corporation for its development of the orphan drug THALOMID(R) (thalidomide) to treat leprosy at its 16th Annual Tribute Banquet on Monday evening, May 10th at the Capital Hilton Hotel in Washington, D.C.

Source: Ex. 2020 at 1.

SECONDARY CONSIDERATIONS

Alleged Skepticism - Marwick

Medical News & Perspectives

Thalidomide Back—Under Strict Control

THALIDOMIDE, the notoriously teratogenic agent of the 1960s, is about to become a prescribed drug. Just 17 days after an advisory committee of the Food and Drug Administration (FDA) recommended that the acting commissioner give marketing approval to thalidomide for treatment of erythema nodosum leprosum (ENL), a complication of lepromatous leprosy, FDA informed the maker that the drug would be approved.

This use has been studied since 1965. The condition is estimated to affect only a few thousand people in the United States, but when approval is granted, the door will be open for physicians to prescribe the drug as they wish. A number of uses of thalidomide are under active investigation and some have shown considerable promise. However, even apart from its teratogenic potential, the drug is not without such occasional serious adverse effects—especially with long-term use—as irreversible peripheral neuropathy.

Thalidomide is an inhibitor of the cytokine tumor necrosis factor α (TNF-α), a property that may make it useful in mediating such diseases characterized by an excess of TNF-α as human immunodeficiency virus (HIV) infection and tuberculosis. Other conditions in which thalidomide has been clinically studied include Behçet disease, lupus erythematosus, chronic graft-vs-host disease, gliomas, Sjögren syndrome, rheumatoid arthritis, and inflammatory bowel disease. The drug also seems to have antiangiogenic properties that have prompted interest in using it to treat some cancers and macular degeneration.

An investigator with Celgene Corporation, Warren, NJ, 1 of 4 US manufacturers of thalidomide, has said that he started to list the potential clinical uses and gave up when he got to 50. Overall, says the FDA, at least 1000 patients in this country are currently using thalidomide on a compassionate basis or in clinical trials. The agency has no figures but admits that there is probably also quite a bit of "under-the-counter" use.

In addition to its application for approval of thalidomide for treating ENL, Celgene is planning to apply also for marketing approval for the use of thalidomide to treat AIDS wasting syndrome, said Sol J. Barer, the company's president and chief executive officer. "We are also looking at its use in AIDS-associated chronic intractable diarrhea, graft-vs-host disease, and severe rheumatoid arthritis," said Barer in an interview, adding that the company has an ongoing program to develop and study the effectiveness of thalidomide analogs, compounds that retain its therapeutic benefits without the attendant toxic effects. In cell assay systems some of these compounds have shown potencies more than 10 000 times that of thalidomide, reported David Stirling, PhD, a research scientist at Celgene, at a recent meeting. He said he expected that some of these compounds would be ready to enter initial clinical trials later this year.

Federal Agency Workshop

Stirling spoke at a workship held last month at the National Institutes of Health (NIH) by that agency, the FDA, and the Centers for Disease Control and Prevention (CDC). The workshop was prompted by concern about burgeoning interest in the drug as a therapeutic agent and concomitant concern about thalidomide's teratogenic properties. At the meeting, federal officials, pharmaceutical firm representatives, physicians, and interested others—including persons with thalidomide-associated birth defects—reviewed and assessed the controversial drug. They discussed its clinical potential, risks to patients, ways to prevent birth defects associated with its use, and steps needed to monitor its safety and adverse effects. The meeting was held just days after the FDA advisory committee on dermatologic and ophthalmic drugs made its recommendation on the use of thalidomide to treat ENL.

The imminent availability of thalidomide and the increasing number of promising uses for it have raised concern that its inadvertent use by pregnant women could lead to a repetition of the situation in the 1960s when approximately 10 000 limb-reduction defects and other fetal abnormalities occurred worldwide (see sidebar). Despite the belief that there is considerable clandestine use of thalidomide, none of the fetal abnormalities associated with it have been reported recently, said Cynthia A. Moore, MD, acting deputy chief of the Birth Defects and Genetic Diseases Branch of the CDC.

No one at the workshop suggested banning the drug outright because of its teratogenic potential. Rather, the concern was that its use be adequately controlled and distribution carefully monitored, that some system of postmarketing surveillance be put in place, and that the medical profession and the public be adequately educated regarding the drug.

There is some evidence from a preliminary survey by the FDA on over-the-counter drug labels that those least aware of the teratogenic effects of thalidomide are those most at risk: persons under the age of 45 years. "We asked people to define a series of words just as if they had seen them in a dictionary, and one of them was *thalidomide*," said Louis A. Morris, PhD, chief of the FDA's Marketing Practices and Communications Branch. "We found that two thirds of those under 45 years didn't recognize the word, while those over 45 years of age at least recognized the word even if they didn't get all the details about thalidomide correct. Thalidomide rang a bell with them." Morris noted that the survey involved only 130 people, a very small sample, so, he said, "you don't want to make too much out of it. But the results are striking."

One way to prevent the occurrence of birth defects associated with thalidomide is to limit it strictly to proven uses and to patients who cannot become pregnant. This, however, would mean that much of the use of the drug would be in uncontrolled circumstances, said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

This point was picked up by Randolph Warren, chief executive officer of Thalidomide Victims Association of Canada, London, Ontario. A thalidomide victim himself, he expressed revulsion at the prospect of the drug's reappearance. "We will never accept a world with thalidomide in it," he said; "however, we are forced to adopt a position of preferring regulated thalidomide over unrestricted access." Warren also said he believes that when thalidomide is approved, some birth defects will inevitably follow.

He was not alone. Discussing ethical issues associated with the use of thalidomide by fertile women, Norman Fost, MD, director of the Program in Medical Ethics at University Hospital, Madison, Wis, warned, "There is no system that will prevent the single birth of a child with phocomelia. The problem is to find some middle ground that properly bal-

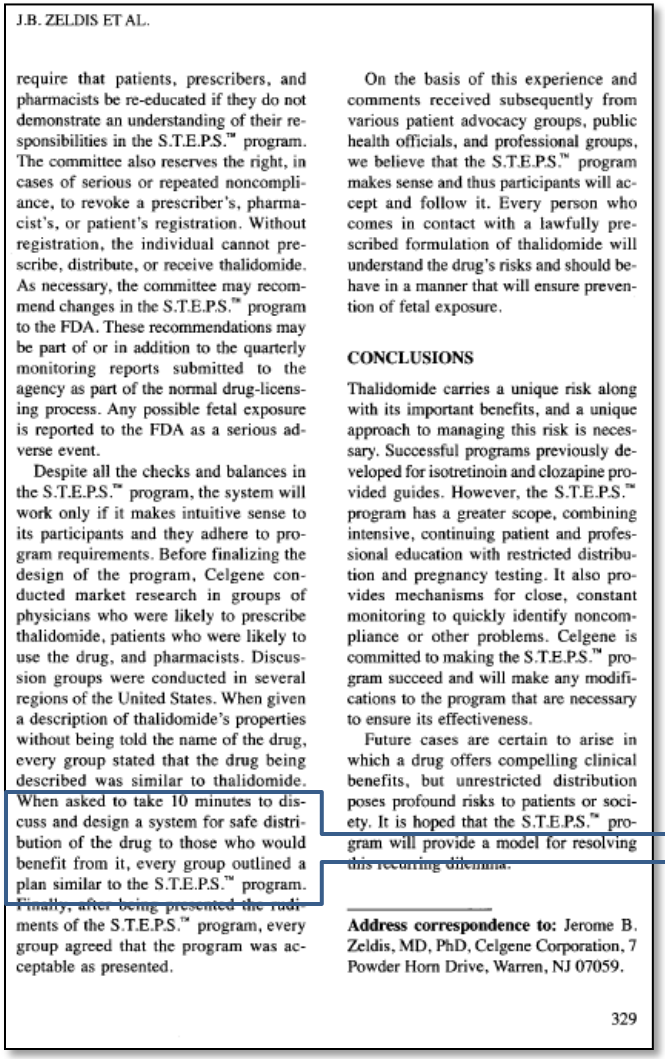
JAMA, October 8, 1997—Vol 278, No. 14

Medical News & Perspectives 1135

No one at the workshop suggested banning the drug outright because of its teratogenic potential. Rather, the concern

Source: Ex. 2063 at 1135.

Alleged Unexpected Results - Zeldis



J.B. ZELDIS ET AL.

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.

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.

Source: Ex. 1068 at 329.

SECONDARY CONSIDERATIONS

Alleged Unexpected Results

6,045,501

9

discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, the prescription may not be filled. In this case, the pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

Prior to filling out the prescription and dispensing the drug, the registered pharmacy preferably has a patient registration form filled out for the patient, and the patient is registered in an appropriate computer readable storage medium. The pharmacy may then dispense the drug to the patient. A copy of the patient's informed consent form should be kept for the pharmacy's records. The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In preferred embodiments, the prescriber will also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and pregnancy testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

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

10

telephone, 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 7 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, dispensation or prescriptions of 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 pharmacies 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 are also generally required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, 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. The pharmacy may not receive more drug for distribution unless he can account for all drug previously dispensed. Also, the pharmacy may only continue to distribute the drug to registered patients who have prescriptions from registered pharmacies.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

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

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

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

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

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

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

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

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

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

Source: Ex. 1001 at 10:43-45.

Alleged Unexpected Results - Bwire

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.

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.

Source: Ex. 1068 at 5.

SECONDARY CONSIDERATIONS

Alleged Unexpected Results – Dr. Frau

Q. Are you aware of any studies done to determine whether there were birth defects under S.T.E.P.S.?

A. It depends on what type of studies. I'm not aware of any clinical research studies. But I don't know.

Q. Are you personally aware of any studies, clinical research or otherwise?

A. Studies. No.

Q. So your claim that there was a hundred percent success rate is based entirely on Dr. Friedman's declaration?

(Pause.)

A. Yes.

Q. And Dr. Friedman is a Celgene employee; correct?

A. Yes.

Source: Ex. 1067 at 154:5–21.

SECONDARY CONSIDERATIONS

Alleged Unexpected Results – Dr. DiPiro

Q. Did you review any literature or studies that specifically examined whether there were birth defects resulting from thalidomide U.S. use -- thalidomide use in the U.S.?

A. I relied on the experience of Dr. Freeman in his testimony.

Q. Did you personally review any literature or studies that specifically examined that question?

A. I did not look for such studies.

Q. Are you aware of any such studies?

A. No.

Source: Ex. 1066 at 170:17–171:4.

The Board's Institution Decision

INSTITUTION DECISION

IPR2015-01092
Patent 6,045,501

The only practical reason for storing information in a computer readable medium is to permit later retrieval of that information. *Cf.* Prelim. Resp. 32–33 (arguing that a failure to identify a prior art disclosure of a "retrieval" step dooms Petitioner's challenge); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (hypothetical person of ordinary skill in the art possesses ordinary creativity and is not an automaton). Furthermore, Dishman's disclosure of registering a pharmacist's verification, before any patient is authorized to receive a drug, implies a retrieval of such information. Pet. 21–22 (citing Ex. 1002 ¶ 89). On this record, the applied prior art suggests a method of registering prescriber, pharmacy, and patient information in "a computer readable storage medium," and retrieving information necessary to ensure that prescriptions for a teratogenic drug are authorized for only non-pregnant patients. Ex. 1001, claim 1 (steps (a)–(d)).

Petitioner shows sufficiently that the invention of claim 1 represents the "predictable use of prior art elements according to their established functions." *KSR Int'l*, 550 U.S. at 417. Based on the information presented, claim 1 is directed to a combination of known steps (registering patients, prescribers, and pharmacies in a computer readable medium; identifying and counseling a subpopulation of patients whose access to a teratogenic drug should be restricted; and authorizing drug therapy only for non-pregnant patients) to accomplish a known purpose (prescribing drug only to non-pregnant patients) and achieve a predictable result (preventing fetal exposure to the drug). Pet. 36–41 (claim chart).

13

Petitioner shows sufficiently that the invention of claim 1 represents the "predictable use of prior art elements according to their established functions." *KSR Int'l*, 550 U.S. at 417. Based on the information presented, claim 1 is directed to a combination of known steps (registering patients, prescribers, and pharmacies in a computer readable medium; identifying and counseling a subpopulation of patients whose access to a teratogenic drug should be restricted; and authorizing drug therapy only for non-pregnant patients) to accomplish a known purpose (prescribing drug only to non-pregnant patients) and achieve a predictable result (preventing fetal exposure to the drug). Pet. 36–41 (claim chart).

Source: Paper 20, Institution Decision, at 13.