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March 25, 2002

VIA OVERNIGHT MAIL

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Dr.
Rockville MD 20857

To Whom It May Concern:

Please find enclosed four copies of a Petition for an Administrative Stay pursuant to 21 C.F.R. § 10.35 that we are filing on behalf of our client, Jerome Stevens Pharmaceuticals, Inc. Please be advised that the Petition cross-references documents that are confidential and trade secrets exempt from the Freedom of Information Act disclosure requirements pursuant to the Trade Secrets Act, 18 U.S.C.A. § 1905, the Food, Drug and Cosmetic, 21 U.S.C.A. § 331(j), FDA's regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4). The referenced exempt items are not included here to avoid unnecessary reduplication and risk of authorized disclosure.

Sincerely,


Jonathan W. Emord
Andrea G. Ferrenz

cc: Alex Azar, DHHS
Dan Troy, FDA

Enclosures

02P-0135

PSA1

**Before the
FOOD AND DRUG ADMINISTRATION
Washington, D.C.**

In Re: Jerome Stevens Pharmaceuticals, Inc.)
Petition for Stay) **Docket No.** _____

PETITION FOR A STAY OF ACTION

Jerome Stevens Pharmaceuticals Inc. (hereinafter "Jerome"), by counsel and pursuant to 21 C.F.R. § 10.35 (2001), hereby submits this petition requesting that the Commissioner of the Food and Drug Administration (FDA) immediately and indefinitely stay (1) all grants of drug pre-market authority that were based on New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) that used, relied on, or were based on Jerome's confidential and trade secret manufacturing information for orally-administered levothyroxine sodium (LS) and (2) all pending and prospective NDAs and ANDAs that use, rely on, or are based on Jerome's confidential and trade secret manufacturing information for orally-administered LS.¹

On August 22, 2000, the day after approving Jerome's NDA for Unithroid™ (an orally-administered LS drug), FDA published Jerome's confidential and trade secret manufacturing information on FDA's website without Jerome's approval and without notifying Jerome in advance. FDA's disclosure of Jerome's confidential and trade secret manufacturing information violated the FDCA, 21 U.S.C. § 331(j); FDA's regulations, 21 C.F.R. § 314.430, and the Federal Trade Secrets Act, 18 U.S.C. § 1905. Collectively, in the drug pre-market authorization context, those laws assure potential drug applicants that the trade secrets and confidences they are required to divulge to FDA will be held in strictest confidence. Having violated that law, FDA

¹ Jerome has simultaneously filed a Notice of Claims under the Federal Tort Claims Act with the Department of Health and Human Services for FDA's tortious misappropriation of Jerome's trade secrets and its breach of its confidential relationship with Jerome through unlawful publication of those secrets and confidences on the web at

must stem further erosion of the NDA and ANDA process by denying pre-market authorization to those who have, or may in future make, use of Jerome's secrets and confidences in their NDA and ANDA applications. The FDA's unlawful disclosure of Jerome's secrets and confidences has undermined the NDA process; public confidence in that process is unlikely to be restored unless it can be shown that FDA will act promptly and responsibly to mitigate damages to the party injured by FDA's malfeasance. Immediate grant of the requested stay is that act of mitigation.

A. DECISION INVOLVED

Jerome has manufactured orally-administered LS since 1990 (under the trade name Thyrox,TM from 1990 to 2000, and under the trade name Unithroid, since 2000).² In 1990, Jerome invented a secret formula for stabilizing orally-administered LS. Only Jerome President Jerome Steinlauf, Jerome Vice President Ronald Steinlauf, and Jerome's scientist William Cardone (who has operated under a confidentiality agreement) knew of the invention. Each held the invention in strictest confidence, closely guarding it, aware of its substantial economic value to Jerome.³

www.fda.gov. A copy of the Notice (with all exhibits except 1, 2, 6, 7, and 8) is attached to this Petition as Exhibit A and is incorporated by reference herein.

² LS is taken daily by users to control thyroid diseases, including hypothyroidism. The American Association of Clinical Endocrinologists estimates that 13 million Americans have been diagnosed with thyroid disease. Facts About Thyroid Disease, <http://www.aace.com/pub/tam2002/facts.php> (last visited 3/5/02). Exhibit G. One study on the prevalence of thyroid disease indicates there may be an additional 13 million Americans or more who are unaware that they have a thyroid condition. Canaris et al., "The Colorado Thyroid Disease Prevalence Study," Archives of Internal Medicine, 160:4 (Feb. 28, 2000) cited in New Study Shows Twice as Many Americans May Suffer from Undiagnosed Thyroid Disease, <http://www.riskworld.com/pressrel/2000/PR00a049.htm> (last visited 3/13/02) (attached as Exhibit H).

³ FDA defines a trade secret as any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. 21 C.F.R. § 20.61. To qualify as a trade secret, there must be a direct relationship between the trade secret and the productive process. 21 CFR § 20.61(a); see also Consumers Union v. Veterans Admin., 301 F. Supp. 796, 801 (S.D. N.Y. 1969) (distinguishing between data relating to processes and methods which relate to private innovation and are protected from disclosure, and safety and efficacy data which are in the public interest to disclose). Data and information submitted to FDA that meet the definition of a trade secret are not available for public disclosure. 21 CFR § 20.61(c); see also, Public Citizen Health Research Group v. FDA, 539 F. Supp. 1320, 1325 (D.D.C. 1982)(stating that once a document is determined to be a trade secret the document

On October 19, 1999, Jerome filed an NDA for Unithroid™. Jerome was the first LS manufacturer to submit an application for stabilized LS. Jerome filed its application, including its trade secrets for the manufacture of safe, stable and effective LS, confident in the knowledge that federal law required FDA to keep that information confidential and not divulge it to any member of the public or any Jerome competitor.

Prior to 1997 FDA did not require orally-administered LS drugs to have an NDA. Orally administered LS has been available since the 1950s. In response to a number of adverse events arising from manufacturers' problems with LS stability and potency, FDA issued a notice in 1997 stating that by August 14 2000⁴ all current manufacturers of LS had to have an approved NDA. 62 F.R. 43535 (1997). Thus, when Jerome discovered a method of manufacturing a safe, stable and potent version of LS and FDA issued its NDA requirement, Jerome could have become the only approved manufacturer of an LS drug. Indeed, on August 21, 2000, when FDA approved Jerome's Unithroid, that was the case. However, FDA unlawfully disclosed Jerome's confidential and trade secret manufacturing information the following day on the worldwide web at www.fda.gov, thereby eliminating that possibility.⁵

After FDA granted pre-market approval to Jerome, the company prepared feverishly to meet the need for stabilized and effective LS and to exploit its exclusive license to sell the only stable effective dose of the drug. In the Fall of 2000 Jerome hired approximately 22 people (more than doubling its staff); it also invested approximately 2 million dollars in a large

is exempt from disclosure). Jerome's confidential LS manufacturing process and formulation are trade secrets. Jerome's was the first formulation of a safe, stabilized, potent LS drug in a \$630 million/year market. Since the 1950s no other manufacturer has been able to manufacture a safe, stabilized, potent orally administered LS drug.
⁴ The August 14, 2000 approval deadline was later extended to a filing deadline of August 14, 2001. 65 F.R. 24488(2000)

⁵ Exhibit 6 to Exhibit A identifies Jerome's confidential and trade secret information that FDA disclosed on its website. That Exhibit is privileged and confidential and is labeled as such. Pursuant to the Trade Secrets Act, 18 U.S.C.A. § 1905, the FDCA 21 U.S.C. § 331(j), FDA's regulations, 21 C.F.R. § 314.430, and the Freedom of

expansion of its manufacturing facility and in the acquisition of new equipment specifically designed to manufacture Unithroid to satisfy an anticipated substantial increase in demand.

Approximately four months passed from Unithroid's approval before Jerome first discovered the trade secret disclosure on December 18, 2000. On that day, Jerome's counsel, Mark Scheineson, immediately notified Roy V. Castle, Jr. in FDA's Freedom of Information Office, Center for Drug Evaluation and Research (CDER), of the agency's unlawful disclosure in violation of 21 C.F.R. § 314.430 and demanded that FDA without delay remove the confidential and trade secret manufacturing information from FDA's website. Exhibit 7 to Exhibit A.⁶ The call was followed the next day by a confidential letter from Scheineson to the same FDA official, with copies to the Director of the Freedom of Information Office Betty B. Dorsey and the Director of the Office of New Drugs Dr. John K. Jenkins. The letter identified the specific confidential and trade secret information disclosed and demanded that the information be removed immediately from FDA's website. See id.

On or about January 3, 2001, approximately two weeks after Scheineson's December 19th letter, FDA still had not responded to Jerome's demands. Jerome's manufacturing information remained posted on the worldwide web at www.fda.gov despite Jerome's insistence that the secrets and confidences be removed. Jerome's counsel contacted Ms. Dorsey again by phone and demanded that the confidential and trade secret information be removed. On January 12, 2001, FDA then removed only some of the confidential and trade secret information from its site, inexplicably leaving other confidential and trade secret information on the web. Exhibit 8 to

Information Act (FOIA), 5 U.S.C.A. § 552(b)(4), that information cannot be publicly disclosed or otherwise distributed.

⁶ Exhibit 7 to Exhibit A contains Jerome's confidential and trade secret information and is exempt from disclosure. See footnote 5 supra.

Exhibit A.⁷ FDA removed the manufacturing method and description of the manufacturing steps but left secret composition data on the website.

On January 18, 2001, Jerome's Vice President Ronald Steinlauf called and spoke separately with Mr. Castle; Freedom of Information Officer Carol Assouad; FDA Deputy Director for Office Training and Communications and Temporary Acting Division Director for Freedom of Information John Friel; and Assistant General Counsel Seth Ray demanding that each immediately act to remove the confidential and trade secret information still posted on the agency's website. Incredibly, FDA still failed to remove the secrets from the web. On January 23, 2001, FDA finally removed the remainder of the information from www.fda.gov. Exhibit 9 to Exhibit A. FDA caused Jerome's confidential and trade secret manufacturing information to remain on the worldwide web on its web site for the extraordinary period of five months, from August 22, 2000 to January 23, 2001, enabling all interested in entering the LS market as well as Jerome's competitors to learn everything necessary to duplicate or closely mimic what was prior thereto a closely guarded Jerome secret, the only cost effective invention for ensuring a safe, stable, and effective LS dose.

Since Unithroid's approval, FDA has approved one other LS drug, LevoxyITM on May 25, 2001, manufactured by Jones Pharma. In addition, currently pending before the FDA is the NDA for Abbott Laboratories' LS product, Synthroid[®], the best-selling LS drug.⁸ Moreover, generic orally-administered LS drug manufacturers may seek ANDA approval under 21 U.S.C. § 355(j) because Unithroid did not receive "new product exclusivity" which would have blocked generics from entering the market for a certain time period. See Guidance for Industry,

⁷ Exhibit 8 to Exhibit A contains Jerome's confidential and trade secret information and is exempt from disclosure. See footnote 5, supra.

⁸ In July 2001 FDA issued a Guidance for Industry that permits Synthroid to be distributed until 2003 while FDA is reviewing its NDA. 66 F.R. 36794.

Levothyroxine Sodium Questions and Answers, FDA, Center for Drug Evaluation and Research (CDER) (February 2001). Any granted NDA or ANDA to stabilize an LS drug could have used Jerome's confidential and trade secret manufacturing information to obtain FDA approval and then compete with Unithroid in the LS marketplace. Any pending or prospective application for a stabilized LS drug could make use of Jerome's trade secrets and confidential information. Immediate grant of an administrative stay is therefore necessary to minimize the injuries Jerome suffers from FDA's unlawful disclosure.

B. ACTION REQUESTED

Jerome requests that the FDA indefinitely stay its approval of all NDAs or ANDAs heretofore granted that used, relied on, or were based on Jerome's confidential and trade secret manufacturing information. Jerome further requests that FDA stay the grant of any pending or future NDA or ANDA for a LS drug that uses, relies on, or is based on Jerome's trade secrets.

B. STATEMENT OF GROUNDS

I. GRANT OF JEROME'S REQUEST FOR A STAY IS MANDATED BY LAW AND PUBLIC POLICY

"Neither the filing of a petition for a stay of action nor action taken by an interested person in accordance with any other administrative procedure in this part or in any other section of this chapter...will stay or otherwise delay any administrative action by the Commissioner, including enforcement action of any kind, unless one of the following applies: (1) the Commissioner determines that a stay or delay is in the public interest and stays the action; (2) a statute requires that the matter be stayed; (3) a court orders that the matter be stayed." 21 C.F.R. § 10.35(d). . An administrative stay is in the public interest to preserve the confidentiality protections of the NDA process in furtherance of federal law and to restore, as much as is now possible, the status quo ante before FDA unlawfully disclosed Jerome's secrets and confidences.

**1. A STAY IS NECESSARY TO MITIGATE JEROME'S INJURIES FROM
FDA'S UNLAWFUL ACTS**

The FDCA and the Federal Trade Secrets Act require that FDA keep confidential trade secrets that are submitted in an NDA. Failure of agency employees to do so is a criminal act. Criminal acts by agency employees are also violations of the Administrative Procedures Act (APA) as agency action not in accordance with the law. 5 U.S.C. § 706(2)(A). FDA disclosed Jerome's confidential and trade secret LS manufacturing information in violation of the FDCA, the Trade Secrets Act, and the APA. A stay is necessary to mitigate Jerome's injury from that unlawful disclosure.

a. The Federal Trade Secrets Act

The Trade Secrets Act prevents the government from disclosing confidential information received in an official capacity. 18 U.S.C. § 1905. The Act in pertinent part provides:

Whoever, being an officer or employee of the United States or of any department or agency thereof, ... publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; or permits any income return or copy thereof or any book containing any abstract or particulars thereof to be seen or examined by any person except as provided by law; shall be fined not more than \$ 1,000, or imprisoned not more than one year, or both; and shall be removed from office or employment.

18 U.S.C. § 1905. The Trade Secrets Act is a criminal statute, providing for sanctions against violators, but does not convey or imply a private right of action. Chrysler Corp. v. Brown, 441 U.S. 281, 317 (1979); MegaPulse v. Lewis, 672 F.2d 959, 966 (D.C. Cir. 1982). Nevertheless, Courts have held that "any disclosure that violates § 1905 of the Trade Secrets Act is 'not in

accordance with law” within the meaning of section 10(a) the Administrative Procedure Act. Id.
Thus, a violation of the Trade Secrets Act is reviewable as a violation of the APA. Id.

In applying § 1905 federal courts looks at factors such as whether the disclosure would significantly aid the agency in performing functions, whether the disclosure would harm producers and the public generally, and whether alternatives to full disclosure could serve the public interest. Doctors Hospital of Sarasota, Inc. v. Califano, 455 F. Supp. 476 (M. Fla. 1978). In this case not one of those factors weighs in FDA’s favor. The unauthorized disclosure of Jerome’s trade secrets does not aid FDA’s functioning; in fact, it harms FDA by calling into question the confidential relationship upon which it depends for full disclosure of manufacturing procedures, processes, and formulas in NDAs, disclosures that must be made to evaluate drug safety and efficacy. The disclosure has substantially and irreparably harmed Jerome and has called into question the integrity of FDA’s drug approval process. If left unmitigated, the wrong may produce a significant disincentive for companies to disclose trade secrets in future NDAs. Thus, FDA’s disclosure of Jerome’s confidential and trade secret information violates the Trade Secrets Act and the APA and grant of the requested stay will best serve the public interest.

b. The FDCA

FDA’s disclosure of Jerome’s trade secrets also violates the FDCA, 21 U.S.C. § 331(j), which states, in pertinent part, that:

The following acts are thereby prohibited... (j) The using by any person to his own advantage or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act [21 USCS §§ 301 et seq.], any information acquired under authority of section ... 505... [21 U.S.C.A. § ...355...], concerning any method or process which as a trade secret is entitled to protection...

Id. (2001). Section 505 is the new drug approval section of the FDCA. 21 U.S.C.A. § 355.

Thus trade secrets concerning methods or processes in a NDA are entitled to protection and

cannot be disclosed. 21 U.S.C. § 331(j). Violation of § 331 is a crime. 21 U.S.C.A. § 333 (a)(1) (“ Any person who violates a provision of section 301 [21 U.S.C. § 331] shall be imprisoned for not more than one year or fined not more than \$ 1,000, or both.”). Like the Trade Secrets Act, a private party cannot enforce the FDCA. Nevertheless, an agency’s violation of the FDCA is a violation of the APA as an act not in accordance with the law. 5 U.S.C.A. § 706(2)(A). Thus, FDA has violated federal law by revealing confidential and trade secret information it obtained in an NDA application.

2. A STAY FURTHERS THE PUBLIC INTEREST IN ASSURING THE INTEGRITY OF THE NDA PROCESS

The integrity of the NDA process is dependent upon FDA maintaining the confidentiality of confidences and trade secrets submitted in NDA’s by applicants. The NDA requirements place a heavy burden on drug manufacturers, requiring extensive development and scientific validation. 21 U.S.C. § 355. An applicant must reveal confidential information to the agency to obtain FDA pre-market drug approval. Webb, *supra*, at 102-103. As the courts have recognized,

If citizens fear uncontrolled disclosure of the trade secrets, tips, and other confidential data the government asks them to provide, they will be less willing to cooperate in the government’s efforts to collect the data ... The Supreme Court recently suggested that the government has particularly extensive power to control the disclosure of sensitive information within its custody, and that the government may sanction its employees where ‘the mishandling of sensitive information leads to its dissemination.’

U.S. v. Wallington, 889 F.2d 573 (5th Cir. 1989) citing The Florida Star v. B.J.F., 491 U.S. 524, 109 S.Ct. 2603, 2609, 105 L.Ed.2d 443 (1989) (citation omitted).

The Solicitor General of the United States recently estimated the total cost for NDA approval of a drug not closely similar to an approved one, to be on average in excess of \$200 million, citing V. Henry, Problems with Pharmaceutical Regulations in the United States, 14 J.Leg. Med. 617 (1993); J.A. Henderson, Jr. & A.D. Twerski, Drug Designs are Different, 111

Yale L.J. 151, 164-165 (2001). See Brief for Petitioners in Thompson v. Western States Medical Center, et al., Case No. 01-344 at 26 (December 13, 2001). The Solicitor General estimated the cost for NDA approval of a new drug that closely resembles an approved drug (like a generic drug approved under an ANDA) to range from \$300,000 to \$500,000, citing Balaji, K., Generics: the Opportunity Beckons (July 2001) <<http://www.inpharm.com/intelligence/frost010701.html>>. See Brief for Petitioners at 26-27. Thus, the expense of a NDA is considerable and revelation of trade secrets redounds to competitors benefits in this process by removing cost barriers to market entry that otherwise confront all prospective applicants.

The United States Court of Appeals for the D.C. Circuit has explained the grave economic dangers posed to drug manufacturers by unlawful disclosure of their drug trade secrets. Moreover, the integrity of the FDA's drug approval process is sorely rent every time an agency official breaches his or her legal duty and divulges trade secrets to the public. So grave are the consequences flowing from federal officer's unlawful disclosure of trade secrets that the law provides criminal sanctions for them when found guilty of the offense. Our Court of Appeals has explained:

Every manufacturer of a new drug must obtain a separately approved NDA. Thus, a drug manufacturer which has submitted an NDA has a competitive interest in seeing that the information contained in its NDA is not prematurely released to the public. If a manufacturer's competitor could obtain all the data in the manufacturer's NDA, it could utilize them in its own NDA without incurring the time, labor, risk, and expense involved in developing them independently. Premature disclosure of NDA data is further discouraged by the existence of criminal sanctions for FDA officials who release trade secrets without the submitter's consent. These sanctions are contained in both the Food, Drug, and Cosmetic Act⁹ and the Trade Secrets Act.¹⁰

⁹ "21 U.S.C. § 331(j) (Supp. IV. 1980) The cited section makes it a crime for 'any person to...reveal[]...any information acquired under authority of section...355[the new drug provision, 21 U.S.C. § 355] of this title concerning any method or process which as a trade secret is entitled to protection.'" Webb, supra, at 102-103; 21 U.S.C.A. § 331(j) (2001).

¹⁰ "18 U.S.C. § 1905 (Supp. IV 1980) The Trade Secrets Act covers all federal officers or employees and prohibits the disclosure of 'any information coming to him in the course of his employment...which information concerns or relates to the trade secrets... of any person...'" Webb, supra, at 102-103. "The Trade Secrets Act, 18 U.S.C. § 1905, is a general criminal statute that provides a penalty for any employee of the United States Government who

Webb v. DHHS, 696 F.2d 101, 102-103 (D.C.Cir. 1982).

Aware of the serious consequences that would flow from not punishing those who divulge trade secrets, this agency has never denied “that it has a statutory obligation to protect ... trade secrets.” Serono Labs. Inc. v. Shalala, 35 F.Supp.2d 1, 2 (D.D.C. 1999). The Serono Labs Court noted that

In a field as competitive and technical as the pharmaceutical industry, success or failure will turn in large measure on innovation and the members of the industry justifiably hoard their trade secrets as jealously as a miser hoards his gold. Before, however, that innovation yields a profit, a government agency has the responsibility to insure that the drug is safe... Thus, concerned companies may have to disgorge their trade secrets so that the agency can fulfill its responsibilities. They would resist doing so with all their power if doing so permitted their competitors instantaneous access to what they had so carefully guarded from them. The obvious public interest in inducing the drug companies’ utmost cooperation with the government’s investigation of the new drug would suffer. It is therefore understandable that Congress has required the FDA to guard the trade secrets to which it has been given access and to require it to return them to the company which generated them. 21 U.S.C. §331(j)(Supp. 1998); 5 U.S.C. §552(b)(4)(1996)(trade secrets exempt from Freedom of Information Act); 18 U.S.C. § 1905 (1984)(crime for federal employee to disclose trade secrets).

Id. at 2. Thus, the FDA’s protection of trade secrets submitted in a NDA is an essential duty fundamental to its ability to fulfill its overall statutory mission in the evaluation and pre-market approval of drugs. FDA has failed to fulfill its duty of confidentiality by disclosing Jerome’s trade secrets. A stay is necessary to protect the public interest in the integrity of the NDA approval process. The requested stay will assure the public and all prospective applicants that FDA will act promptly to mitigate harms to a party injured by its unlawful disclosure of trade secrets and confidences.

II. GRANT OF JEROME’S REQUEST FOR A STAY IS REQUIRED UNDER SECTION 10.35

discloses, in a manner not authorized by law, any trade-secret information that is revealed to him during the course of his official duties.” Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1008 (1984).

FDA's regulations state "the Commissioner shall grant a stay in any proceeding if all of the following apply: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting the stay; (4) the delay resulting from the stay is not outweighed by public health or other public interests." 21 C.F.R. § 10.35(e).

Jerome will suffer irreparable injury in the utter destruction of the value of its LS manufacturing process and formulation if its competitors are permitted to capitalize on FDA's unlawful disclosure by obtaining FDA approval of their NDAs or ANDAs for LS drugs that use, rely on or are based on Jerome's protected information. Jerome's petition is not frivolous. The LS drug market is one of the largest drug markets in the United States and Jerome's economist Dr. Paul Rubin has estimated Jerome's injury due to FDA's disclosure to be \$1,345,316,242. Jerome is requesting the stay in a good faith effort to minimize its injury due to FDA's disclosure. Finally, Jerome is fully prepared to meet the demand for orally-administered LS drugs and the stay will cause no delay or other risk to public health due to loss of market authority to those who have used (or seek to use) the trade secrets and confidences FDA unlawfully divulged

1. JEROME WILL SUFFER IRREPARABLE INJURY WITHOUT A STAY

FDA's disclosure of Jerome's confidential and trade secret manufacturing information caused Jerome irreparable harm. Courts have consistently held that the loss of a trade secret cannot be measured in money damages and constitutes irreparable harm. E.g. North Atlantic Instrubments, Inc., v. Haber, 188 F.3d 38, 49 (2d Cir. 1999) citing FMC Corp. v. Taiwan Tainan

Giant Indus. Co., 730 F.2d 61, 63 (2d Cir. 1984).¹¹ The nature of the United States pharmaceutical market, requiring FDA's pre-market approval of drugs, affords FDA an opportunity to mitigate its damages through grant of the requested stay.. Without that stay, Jerome will continue to suffer injuries flowing from FDA's disclosure into the indefinite future.

2. JEROME'S PETITION IS NOT FRIVOLOUS AND IS IN GOOD FAITH

FDA's actions have been unlawful, indeed criminal. An administrative stay is an opportunity for FDA to mitigate Jerome's damages. Jerome's request is not frivolous and is made in a good faith attempt to stem the flow of damages from FDA's unlawful disclosure. The orally-administered LS drug market is one of the largest drug markets in the United States with over \$ 630 million in sales per year. Exhibit 2 to Exhibit A.¹² In Jerome's Notice under the Federal Tort Claims Act, Jerome's economist Dr. Paul Rubin has estimated Jerome's injury due to FDA's disclosure to be \$1,345,316,242 over the next ten years. See Exhibit A at Exhibit 5. Jerome is requesting an administrative stay in a good faith effort to mitigate its damages.

3. PUBLIC POLICY DEMANDS A STAY AGAINST USERS OF JEROME'S MANUFACTURING INFORMATION

As discussed above, the federal courts have repeatedly recognized the substantial public interest in protecting the confidentiality of trade secrets and confidences in NDAs. The courts have recognized FDA's duty to keep that information confidential and the criminal sanctions that can be imposed on public officials who breach that duty. Grant of the requested administrative stay furthers those public interests.

4. THE STAY WILL NOT RESULT IN A DELAY OR OTHER RISK TO PUBLIC HEALTH

¹¹ That legal principle is equally applicable to information that is kept confidential, but does not rise to the level of a trade secret. Once confidential information is disclosed its value is effectively eliminated and monetary damages cannot not provide complete restitution for its disclosure.

¹² This Exhibit is privileged and confidential. It is exempt from FOIA disclosure. IMS Health's confidentiality policy is attached to the Exhibit along with a letter from IMS granting Jerome permission to use it in this case.

Finally, Jerome is fully prepared to meet the demand for orally-administered LS drugs and thus the requested stay will cause no delay in service to, or other risk to, public health. When its NDA was approved on August 21, 2000, Jerome quickly hired and trained 22 employees and spent approximately \$2 million in an extension of its manufacturing facilities and in the purchase of equipment for the manufacture of quantities of Unithroid that would meet anticipated demand. Jerome is thus ready, willing, and able to supply the entire United States LS market upon FDA's institution of the stay. Jerome already has the facilities and equipment necessary. Thus, there will be no delay or other risk to public health by instituting the requested stay.

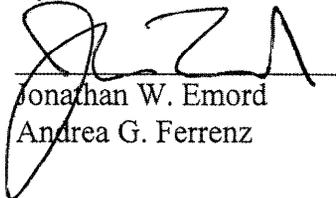
C. CONCLUSION

Jerome respectfully requests that the FDA Commissioner immediately and indefinitely stay (1) all grants of drug pre-market authority (for NDAs or ANDAs) that used, relied on, or were based on Jerome's confidential and trade secret manufacturing information for orally-administered LS and (2) all pending and prospective NDAs and ANDAs that use, rely on, or are based on Jerome's confidential and trade secret manufacturing information for orally-administered LS.

Sincerely,

JEROME STEVENS
PHARMACEUTICALS, INC.

By Counsel:


Jonathan W. Emord
Andrea G. Ferrenz

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Date Submitted: March 26, 2002

Before the
FOOD AND DRUG ADMINISTRATION
Washington, D.C.

In Re: Jerome Stevens Pharmaceuticals Inc.)
Petition for Stay) Docket No. _____

EXHIBIT LIST

Notice of Claims Pursuant to the Federal Tort Claims Act	Exhibit A
AACE, "Facts about Thyroid Disease"	Exhibit B
Riskworld, "New Study Shows Twice as Many Americans May Suffer from Undiagnosed Thyroid Disease"	Exhibit C

Exhibit A

Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Washington, D.C.

In Re: Claims for Jerome Stevens)
Pharmaceuticals, Inc. for financial redress) **Docket No.** _____
under the Federal Tort Claims Act,)
28 U.S.C. § 2671 et seq.)

NOTICE OF CLAIMS PURSUANT TO THE FEDERAL TORT CLAIMS ACT

Jerome Stevens Pharmaceuticals, Inc. (hereinafter "Jerome"), makers of the FDA-approved drug Unithroid™, by counsel and pursuant to 28 U.S.C. § 2671 et seq. and 45 C.F.R. § 35.1 et seq., hereby notifies the Claims Officer of the Department of Health and Human Services (DHHS) of tortious and unlawful actions by the Food and Drug Administration (FDA) for which Jerome seeks financial redress under the federal Tort Claims Act.¹ As explained below, FDA has misappropriated Jerome's confidential and trade secret manufacturing information and has unlawfully divulged that information to the public. In addition to torts and statutory violations arising from those acts, FDA has violated Jerome's Fifth Amendment due process rights.²

Established under the laws of New York in 1979 (as Jerome Stevens, Inc.), Jerome is family owned by the Steinlaufs. In 1990, Jerome invented a secret formula for stabilizing orally administered LS. Since 1990 Jerome has manufactured orally-administered levothyroxine sodium ("LS") (under the trade name Thyrox™ from 1990 to 2000 and under the trade name Unithroid since 2000).³ Only Jerome President Jerome Steinlauf, Jerome Vice President Ronald

¹ Jerome has simultaneously filed a Petition for a Stay of Action with the FDA Commissioner in which Jerome asks the agency to stay all current and prospective grants of new drug pre-market authorization for all companies that are now selling or seek authorization to sell orally administered levothyroxine sodium (hereinafter "LS") in reliance upon any of the concepts in the confidences and trade secrets of Jerome that FDA unlawfully divulged to the public. A copy of the Petition is attached to this notice as Exhibit 1 (without Exhibit A).

² Jerome's Fifth Amendment and APA claims are included in this notice to inform the United States of all claims against FDA consistent with 28 U.S.C.A. § 2675; see also, e.g., Franz v. United States, 414 F.Supp. 57 (Ariz. Dist. 1976).

³ Jerome's Unithroid is the oldest continually manufactured and longest used levothyroxine sodium product on the market.

Steinlauf, and Jerome's scientist William Cardone (who has operated under a confidentiality agreement) knew of the invention. Each held the invention in strictest confidence, closely guarding it, aware of its substantial economic value to Jerome.

In 1997, FDA ordered all companies then selling orally-administered LS to submit new drug applications for pre-market approval. FDA stated that if such applications were not granted by the agency on or before August 14, 2000, the companies involved that nevertheless continued to market LS would be subject to adverse regulatory action. The FDA explained that it acted based on concerns that LS products then on the market did not deliver a stable, effective dose and thus threatened the health of patients. On October 19, 1999 Jerome filed its application for pre-market approval confident in the knowledge that the Food Drug and Cosmetic Act, 21 U.S.C. § 331, FDA's regulations, 21 C.F.R. § 314.430, and the federal Trade Secrets Act, 18 U.S.C. § 1905, were among the federal laws that prohibited FDA from divulging its invention to the public. Jerome also understood that at the time of its filing no other company had developed a LS stabilization process or formula.

On August 21, 2000, Jerome was the first company to receive FDA pre-market authorization to market its stabilized form of LS, Jerome's Unithroid. On August 22, 2000, without notice to, and without the consent of, Jerome, the FDA publicly disclosed the confidential and trade secret manufacturing information in Jerome's new drug approval application. On that date FDA divulged the contents of Jerome's confidential and trade secret manufacturing information to the public by posting those secrets on the worldwide web at www.fda.gov. Jerome discovered FDA's action on December 18, 2001. On that day (and repeatedly thereafter), Jerome urgently demanded that FDA delete Jerome's confidential and trade secret information from the world wide web, but FDA did not do so until January 23, 2002,

fully five months after FDA first divulged the secrets on the web. The loss of its secrets has caused Jerome to lose the economic value of its invention, including sunk costs in capital improvements and equipment and reasonably anticipated substantial increases in revenue from a rapid roll-out of the then extant only stabilized version of LS. In addition, FDA's unlawful publication of Jerome's confidential and trade secret information (and its subsequent capricious regulatory actions explained in detail below) have given Jerome's competitors a permanent unfair advantage (the opportunity to exploit Jerome's invention to Jerome's economic disadvantage and to remain in the market with unstable LS for years after FDA's initial August 14, 2000 deadline for new drug application approval).

Jerome's manufacturing process is confidential information and a trade secret protected from disclosure by state and federal laws. The Supreme Court has long recognized the intrinsic value of a trade secret and the harm its holders experience when the secrets are wrongfully disclosed. See, e.g., Nollan v. California Coastal Commission, 483 U.S. 825 (1987); see also, Kaiser Aetna v. U.S., 444 U.S. 164 (1979). A trade secret is a property interest, including the right to exclude others and maintain the confidentiality of the secret, that government may not deprive constitutionally without the due process required by the Fifth Amendment. Moreover, the FDCA, FDA's regulations, the federal Trade Secret Act, and federal criminal law require FDA to keep trade secrets confidential, prohibiting FDA and its employees on threat of civil and criminal sanctions from divulging those secrets to the public. 21 U.S.C.A. § 331(j); 21 C.F.R. § 314.430(g)(2002); 5 U.S.C. § 552(b)(4); and 18 U.S.C.A. § 1905.

I. FEDERAL TORT CLAIMS ACT REQUIREMENTS

The federal government and private defendants are held to the same standard of tort liability, but the government is statutorily relieved of the duty to pay pre-judgment interest and

punitive damages.⁴ In the first instance, before it seeks judicial relief, a tort claimant must demand that the government provide the relief to which it is entitled due to the government's tortious activity. If the government fails to provide redress, the claimant may then proceed to court.⁵ To be timely, the action must be pled to the agency no later than two years after the tort on which it is based accrues.⁶ A FTCA claim accrues when the injured party knows both the existence and the cause of injury. Peterson v. U.S., 694 F.2d 943 (3rd Cir. 1982). The present claim arose on December 18, 2000 when Jerome discovered the government's publication of the secrets on the worldwide web at www.fda.gov. This notice is thus timely filed. If the government denies Jerome's claim, or six months pass from the date of Jerome's notice submission without the grant of the relief requested herein, Jerome shall file a complaint seeking redress in federal court. 28 U.S.C.A. § 2675.

II. SUMMARY OF THE FACTS

LS tablets have been prescribed by physicians since the 1950's for the treatment of thyroid diseases including hypothyroidism.^{7, 8} The American Association of Clinical Endocrinologists estimates that 13 million Americans have been diagnosed with thyroid disease.

⁴ "The United States shall be liable, respecting the provisions of this title relating to tort claims, in the same manner and to the same extent as a private individual under like circumstances, but shall not be liable for interest prior to judgment or for punitive damages." 28 U.S.C.A. § 2674 (2001).

⁵ "An action shall not be instituted upon a claim against the United States for money damages for injury or loss of property... caused by the negligent or wrongful act or omission of any employee of the Government while acting within the scope of his office or employment, unless the claimant shall have first presented the claim to the appropriate Federal agency and his claim shall have been finally denied by the agency in writing and sent by certified or registered mail." 21 U.S.C.A. § 2675(a) (2001).

⁶ "A tort claim against the United States shall be forever barred unless it is presented in writing to the appropriate Federal agency within two years after such claim accrues or unless action is begun within six months after the date of mailing, by certified or registered mail, of notice of final denial of the claim by the agency to which it was presented." 28 U.S.C.A. § 2401.

⁷ Hypothyroidism occurs when the thyroid gland fails to produce sufficient hormones. It may be caused by a birth defect or thyroiditis, goiter, or surgical removal of the thyroid gland. Symptoms include fatigue, extreme sensitivity to cold, dry skin, lethargy, and weight gain. See FDA Talk Paper, "FDA Approves First NDA for Levothyroxine Sodium," T00-36 (August 22, 2000); Exh. 4.

⁸ Levothyroxine is a synthetic derivative of thyroxine and has a "narrow therapeutic index," meaning a patient's dosage levels must be individually set through a process of trial and error. Overdosing or underdosing can cause

Facts About Thyroid Disease, <http://www.aace.com/pub/tam2002/facts.php> (last visited 3/5/02).

A study on the prevalence of thyroid disease indicates there may be an additional 13 million Americans or more who are unaware that they have a thyroid condition. Canaris et al., "The Colorado Thyroid Disease Prevalence Study," Archives of Internal Medicine, 160:4 (Feb. 28, 2000) cited in New Study Shows Twice as Many Americans May Suffer from Undiagnosed Thyroid Disease, <http://www.riskworld.com/pressrel/2000/PR00a049.htm> (last visited 3/13/02)

The market for LS is expected to grow 13% a year. Exhibit 5 at 1. LS is not patented and is available from many vendors, including Jerome. Synthroid[®] is the trade name of the first orally administered levothyroxine product. In re: Synthroid Marketing Litigation, 264 F.3d 712 (2001). Synthroid[®], previously owned by Knoll Laboratories but sold in 2001 to Abbott Laboratories, dominates the LS market, representing more than two-thirds of LS sales. See, id; IMS Health, Therapy Area Sales Report, Sales of Thyroid Preparations (H3A) – U.S.A. (2002) (Attached as Exhibit 2).⁹ For the calendar year 2000, Synthroid[®] was the third most frequently prescribed drug in the U.S. with more than 43 million prescriptions. IMS Health, US Top 10 Products Ranked on Total Dispensed Prescriptions, IMS HEALTH. (2002) (Attached as Exhibit 3).¹⁰

On August 14, 1997, FDA announced in the Federal Register that, despite a long history of use, LS drug products were "new drugs" and that manufacturers who wished to continue marketing them would have to submit NDAs for agency approval. 62 FR 43535 (hereinafter "1997 Notice"). The notice stated that "no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and, thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as

severe heart, brain, psychological and reproductive problems (hence, FDA's concern that LS ought to be removed from the market in each instance where a manufacturer could not achieve a stable, effective dose). Id. at 714.

⁹ This Exhibit is privileged and confidential. It is exempt from FOIA disclosure. IMS Health's confidentiality policy is attached to the Exhibit along with a letter from IMS granting Jerome permission to use it in this case.

safe and effective.” 62 F.R. 43535 at 43538. In the notice, FDA stated that after August 14, 2000 any orally administered drug product containing LS introduced or delivered for introduction into interstate commerce without an approved new drug application would be subject to adverse regulatory action. Id.¹¹

A. FACTS CONCERNING JEROME’S UNITHROID

On October 19, 1999, Jerome filed an NDA for Unithroid™. It was the first LS manufacturer to submit an application for stabilized LS. Jerome filed its application, including its trade secrets for the manufacture of safe, stable and effective LS, confident in the knowledge that federal law required FDA to keep that information confidential and not divulge it to any member of the public or any Jerome competitor.

On April 26, 2000, FDA did not alter its public health justification for immediate compliance with the NDA requirements but nevertheless changed its August 14, 2000 deadline. FDA had required approval of LS NDAs by August 14, 2000 but its April 26, 2000 order created a new August 14, 2001 deadline that required only the filing of an LS NDA by that date. 65 FR 24488 (emphasis added). FDA did not explain how the gross extension of time comported with its demand for prompt NDA filing and approval of stable LS drugs, said to be necessary to protect patients from the serious adverse effects that can flow from unstable LS dosing.

On August 21, 2000, FDA approved Jerome’s NDA for Unithroid™, the first LS drug approved by the FDA under the new requirements. Exhibit 4 at 1. The FDA announced: “With the approval of the NDA for Unithroid, patients and physicians now have available to them an oral levothyroxine sodium drug product that has been determined to be safe and effective by the

¹⁰ This document is publicly available on IMS Health’s website.

¹¹ The 1997 Notice stated that LS drugs may submit a Petition for GRAS/E status as an alternative to submitting a NDA. Id. A drug FDA finds to be “Generally Recognized as Safe and Effective” (GRAS/E) is exempt from NDA requirements. Id.

FDA and that also meets FDA standards for manufacturing processes, purity, potency and stability.” Id. As explained more fully in the attached affidavit of economist Paul Rubin, the market value of Jerome’s then exclusive pre-market authorization was substantial, equaling approximately \$630,000,000 in reasonable anticipated gross annual U.S. sales. See Exhibit 5 at 2.

On August 22, 2000, the day after the approval, FDA posted on the worldwide web (on its website [www.fda.gov]), unbeknownst to Jerome and without Jerome’s approval, Jerome’s confidential and trade secret manufacturing information for Unithroid.^{12,13} By divulging Jerome’s confidential and trade secret manufacturing information to the world on the agency’s web site, FDA enabled all readers familiar with pharmaceutical manufacturing (and, in particular, all of Jerome’s LS competitors¹⁴) to discern precisely how to create a safe, stable LS dose at low cost, an invention that no one in the industry had achieved despite over fifty years of effort.¹⁵

After FDA granted pre-market approval to Jerome, the company prepared feverishly to meet the need for stabilized and effective LS and to exploit its exclusive license to sell the only stable effective dose of the drug. In the Fall of 2000 Jerome hired approximately 22 people

¹² Exhibit 6 identifies Jerome’s trade secret information that FDA disclosed on its website. That Exhibit is privileged and confidential and is labeled as such. Pursuant to the Trade Secrets Act, 18 U.S.C.A. § 1905, the FDCA, 21 U.S.C.A. § 331(j), FDA’s regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4), that information must not be disclosed to any member of the public. Trade secrets are exempt from the FOIA; thus, Exhibit 6 is exempt from disclosure in response to a FOIA request. 5 U.S.C. § 552(b)(4).

¹³ FDA was aware that Jerome considered the inactive ingredients to be particularly important and trade secret. During its NDA’s review Jerome requested that FDA omit starch and acacia from the list of inactive ingredients on the package insert. Dr. Duu-Gong Wu, Ph.D. (chemistry team leader, Division of Metabolic and Endocrine Drug Products) agreed to the request. Later Dr. Jean Temeck, health and safety officer, informed Jerome that those inactives had to be listed due to potential allergic reactions to them. Jerome objected and consulted with medical experts who stated that there was not a shred of evidence that either starch or acacia caused allergies in the small amounts present in Unithroid. Over Jerome’s objections, FDA required those inactives to be listed on the package insert.

¹⁴ At the time of the disclosure, Jerome had 10 competitors: Abbott Pharmaceutical Product, Jones Pharmaceuticals, Forest Pharmaceuticals, Qualitest Products, United Research Laboratories, Vintage Pharmacies, Pecos Pharmacies, American Pharmaceutical Partners, Lederle SP, and Bedford Labs. Exh. 2.

(more than doubling its staff); it also invested approximately \$2 million in a large expansion of its manufacturing facility and in the acquisition of new equipment specifically designed to permit Unithroid to satisfy an anticipated substantial increase in demand.

On November 17, 2000, Jerome filed a Citizen's Petition with FDA requesting that FDA not extend the NDA filing deadline for manufacturers of orally administered LS drug products. Exhibit 11. In its Petition Jerome assured FDA that it was ready, willing, and able to satisfy market demand for stabilized LS. Id. at 1.

Approximately four months passed from Unithroid's approval before Jerome first discovered the FDA's disclosure of Jerome's confidences and trade secrets. On the day of discovery, December 18, 2000, Jerome's counsel, Mark Scheineson, immediately notified Roy V. Castle, Jr. in FDA's Freedom of Information Office, Center for Drug Evaluation and Research (CDER), of the agency's unlawful disclosure in violation of 21 C.F.R. § 314.430 and demanded that FDA immediately remove Jerome's confidential and trade secret manufacturing information from FDA's website. Exhibit 7.¹⁶ The call was followed the next day by a confidential letter from Scheineson to the same FDA official, with copies to the Director of the Freedom of Information Office Betty B. Dorsey and the Director of the Office of New Drugs Dr. John K. Jenkins. The letter identified the specific confidential and trade secret information disclosed and demanded that the information be removed immediately from FDA's website. See Exhibit 7.

On or about January 3, 2001, approximately two weeks after Scheineson's December 19th letter, FDA still had not responded to Jerome's demands. Jerome's confidences and trade secrets remained posted on the worldwide web at www.fda.gov despite Jerome's insistence that they be

¹⁵ See 62 F.R., supra, at 43538.

¹⁶ Exhibit 7 contains Jerome's confidential trade secrets and is exempt from disclosure. See footnote 9 supra. It is identified as containing confidential trade secrets.

removed without delay. Jerome's counsel contacted Ms. Dorsey again by phone and demanded that the confidences and trade secrets be removed. On January 12, 2001 FDA then removed only some of the trade secrets from its site, inexplicably leaving others. Exhibit 8. FDA removed the manufacturing method and description of the manufacturing steps but left secret composition data on the website.

On January 18, 2001, Jerome's Vice President Ronald Steinlauf called and spoke separately with Mr. Castle; Freedom of Information Officer Carol Assouad; FDA Deputy Director for Office Training and Communications and Temporary Acting Division Director for Freedom of Information John Friel; and Assistant General Counsel Seth Ray demanding that each immediately act to remove the confidential and trade secret manufacturing information still posted on the agency's website. Incredibly, FDA still failed to remove the secrets from the web. On January 23, 2001, FDA finally removed the remainder of the trade secrets from www.fda.gov. Exhibit 9.

FDA caused Jerome's confidential and trade secret manufacturing information to remain on the worldwide web for the extraordinary period of five months, from August 22, 2000 to January 23, 2001, enabling all interested in entering the LS market as well as Jerome's competitors to learn everything necessary to duplicate or closely mimic what was prior thereto the only cost effective invention for ensuring a safe, stable, and effective LS dose.

On January 19, 2001, Jerome sent Jane A. Axelrad, FDA Associate Director for Policy, Center for Drug Evaluation and Research, a letter requesting a meeting to address FDA's tentative decision to extend its August 14, 2001 filing deadline. Exhibit 12. Jerome wished to discuss the fact that it was then prepared to meet the entire U.S. population's demands for LS and that no extension was necessary. FDA would not meet with Jerome.

On March 8, 2001, FDA issued a “Guidance for Industry, Levothyroxine Sodium: Questions and Answers.” 66 F.R. 13935 (hereinafter “March Guidance”). The March Guidance states that Unithroid did not receive “New Product Exclusivity”¹⁷ because LS had been previously approved as an active ingredient in two NDAs¹⁸ and that no new clinical investigations were necessary for Unithroid’s approval. See March Guidance at 4

On July 13, 2001, FDA released its “Guidance for Industry: Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications” (hereinafter “July Guidance”). 66 F.R. 36794. In the July Guidance, FDA announced its decision “to continue to exercise its enforcement discretion by establishing a gradual phase-out of unapproved products.” Id. at 3. It outlined a proposed distribution phase down for those manufacturers that had an NDA pending at FDA on August 14, 2001. Id. The proposed phase down ends on August 14, 2003 when all distributors of oral LS with applications pending must cease all distribution. Id. at 4. Once again, despite granting an extraordinary three year delay beyond the original August 14, 2000 date (which was, after all, a deadline for achievement of grant of pre-market authorization not simply NDA filing), the FDA afforded no necessary or sufficient explanation of how the years of delay comported with the immediate public health need to ensure patients stable, safe, and effective LS.

On July 18, 2001, Jerome’s Vice-President Ron Steinlauf called Ms. Axelrad concerning the July 13 Guidance. Assistant General Counsel Chris Rogers was present in Ms. Axelrad’s office and participated in the call. During the call Mr. Steinlauf raised the subject of FDA’s

¹⁷ The FDCA gives “New Product Exclusivity” to NDA holders affording them limited protection from competition in the marketplace in recognition of the innovation represented by an approved NDA. “Frequently Asked Questions for New Drug Product Exclusivity” FDA, CDER www.fda.gov/cder/about/smallbiz/exclusivity.htm (last visited 2/21/02). See also 21 U.S.C. § 355(c)(3)(D) and (j)(5)(D). The protection precludes ANDA applications for generic drugs during the exclusivity period. ANDAs rely on an approved NDA, particularly for its safety and effectiveness data, to avoid unnecessary recurrence of expenses originally incurred by the NDA applicant. 21 U.S.C. § 355(j).

disclosure of Jerome's confidential and trade secret manufacturing information on FDA's website. Axelrad admitted that the disclosure "was a mistake."

Following the July 2001 Guidance, Abbott Laboratories, the manufacturer of Synthroid, seized the initiative and flooded the retail market with mass quantities of its then unstable LS product. Having lost de facto market exclusivity due to FDA's publication of its secrets and FDA's extension of compliance deadlines, Jerome laid off all 22 people that it had hired in anticipation of supplying most, if not all, of the demand for orally-administered stable LS. Over the next few months Jerome and its partner, Watson Laboratories, destroyed drums of Unithroid worth an estimated \$3 million due to lack of previously anticipated demand.

B. FACTS CONCERNING JEROME'S COMPETITORS

Synthroid

On December 15, 1997, Synthroid's manufacturer (then Knoll Laboratories) submitted a Petition for GRAS/E Status for Synthroid rather than a NDA. See Exh. 10. Knoll's Petition relied on Synthroid's history as the best-selling orally administered LS drug. Id.

On April 26, 2001, FDA rejected Knoll's Citizen's Petition stating that Synthroid's "history of potency failures ... indicates that Synthroid has not been reliably potent and stable." Exh. 10 at 7. Noting that Synthroid's formula "has been changed numerous times throughout its marketing history," FDA stated,

To be generally recognized as safe and effective, there must be some consistent drug product for experts to recognize. In the case of Synthroid, there is no such consistent product because the composition of Synthroid has been changed repeatedly.

Id. at 4. The agency also noted that Synthroid had violated current good manufacturing practices; consumers had reported numerous adverse reactions that FDA believed stemmed from

¹⁸ Both of which had been removed from the market because of the manufacturer's inability to produce a stable, potent drug containing LS.

Synthroid's instability; Synthroid lots had been recalled numerous times due to potency problems; and the manufacturer had failed to investigate properly or to "conduct adequate stability studies" for its formulation changes. Id. at 6.

Despite FDA's rejection of Synthroid's Petition for GRAS/E status and the agency's findings of significant safety and potency risks with the product, FDA issued its July 2001 Guidance, discussed above, to permit Synthroid to be sold across the United States over the following year in an unstable dose form, without an approved NDA. The agency gave no explanation for how the gratuitous year long extension served the agency's identified interest in ridding the market of harmful, unstable LS products.

On August 1, 2001, Abbott Laboratories submitted a NDA for Synthroid[®]. That application is pending as of the date of this Notice.

Levoxyl

On July 28, 2000, Jones Pharma submitted an NDA for Levoxyl[™], another orally administered LS product (ND 21-301). On May 25, 2001, Levoxyl's NDA was approved. On January 7, 2002, more than seven months after the drug's approval, Levoxyl's NDA review documents were posted on the FDA website. FDA redacted confidences and trade secrets from Levoxyl's NDA application and omitted Levoxyl's manufacturing processes. FDA did not disclose Jones Pharma's trade secrets.

III. FACTS AND LAW CONCERNING NDAs AND TRADE SECRETS

The NDA requirements place a heavy burden on drug manufacturers, requiring extensive development and scientific validation. 21 U.S.C. § 355. The Solicitor General of the United States recently estimated the total cost for NDA approval of a drug not closely similar to an approved one, to be on average in excess of \$200 million, citing V. Henry, Problems with

Pharmaceutical Regulations in the United States, 14 J.Leg. Med. 617 (1993); J.A. Henderson, Jr. & A.D. Twerski, Drug Designs are Different, 111 Yale L.J. 151, 164-165 (2001). See Brief for Petitioners in Thompson v. Western States Medical Center, et al., Case No. 01-344 at 26 (December 13, 2001). The Solicitor General estimated the cost for NDA approval of a new drug that closely resembles an approved drug (like a generic drug approved under an ANDA) to range from \$300,000 to \$500,000, citing Balaji, K., Generics: the Opportunity Beckons (July 2001) <<http://www.inpharm.com/intelligence/frost010701.html>>. See Brief for Petitioners at 26-27. Thus, the expense of a NDA is considerable and revelation of trade secrets redounds to a competitor's benefit in this process by removing cost barriers to market entry that otherwise confront all prospective applicants.

The United States Court of Appeals for the D.C. Circuit has explained the grave economic dangers posed to drug manufacturers by unlawful disclosure of their drug trade secrets. Moreover, the integrity of the FDA's drug approval process is sorely rent every time a FDA official breaches his or her legal duty and divulges trade secrets to the public. So grave are the consequences from a FDA officer's unlawful disclosure of trade secrets that the law provides criminal sanctions for each one found guilty of the offense. Our Court of Appeals has explained:

Every manufacturer of a new drug must obtain a separately approved NDA. Thus, a drug manufacturer which has submitted an NDA has a competitive interest in seeing that the information contained in its NDA is not prematurely released to the public. If a manufacturer's competitor could obtain all the data in the manufacturer's NDA, it could utilize them in its own NDA without incurring the time, labor, risk, and expense involved in developing them independently. Premature disclosure of NDA data is further discouraged by the existence of criminal sanctions for FDA officials who release trade secrets without the submitter's consent. These sanctions are contained in both the Food, Drug, and Cosmetic Act¹⁹ and the Trade Secrets Act.²⁰

¹⁹ 21 U.S.C. § 331(j) (Supp. IV, 1980) The cited section makes it a crime for "any person to...reveal[]...any information acquired under authority of section...355[the new drug provision, 21 U.S.C. § 355] of this title concerning any method or process which as a trade secret is entitled to protection." Webb, supra, at 102-103; 21 U.S.C.A. § 331(j) (2001).

²⁰ 18 U.S.C. § 1905 (Supp. IV 1980) The Trade Secrets Act covers all federal officers or employees and prohibits the disclosure of "any information coming to him in the course of his employment...which information concerns or

Webb v. DHHS, 696 F.2d 101, 102-103 (D.C.Cir. 1982).

Aware of the serious consequences that would occur if those who divulge trade secrets go unpunished, the FDA has never denied “that it has a statutory obligation to protect ... trade secrets.” Serono Labs. Inc. v. Shalala, 35 F.Supp.2d 1, 2 (D.D.C. 1999). The Serono Labs Court noted that

In a field as competitive and technical as the pharmaceutical industry, success or failure will turn in large measure on innovation and the members of the industry justifiably hoard their trade secrets as jealously as a miser hoards his gold. Before, however, that innovation yields a profit, a government agency has the responsibility to insure that the drug is safe... Thus, concerned companies may have to disgorge their trade secrets so that the agency can fulfill its responsibilities. They would resist doing so with all their power if doing so permitted their competitors instantaneous access to what they had so carefully guarded from them. The obvious public interest in inducing the drug companies' utmost cooperation with the government's investigation of the new drug would suffer. It is therefore understandable that Congress has required the FDA to guard the trade secrets to which it has been given access and to require it to return them to the company which generated them. 21 U.S.C. §331(j)(Supp. 1998); 5 U.S.C. §552(b)(4)(1996)(trade secrets exempt from Freedom of Information Act; 18 U.S.C. § 1905 (1984)(crime for federal employee to disclose trade secrets).

Id. at 2. Thus, the FDA's protection of trade secrets submitted in a NDA is an essential duty fundamental to its ability to fulfill its drug evaluation and pre-market approval mission.

IV. FDA'S DISCLOSURE OF JEROME'S TRADE SECRETS VIOLATES THE FEDERAL TORT CLAIMS ACT

Through carelessness, recklessness, or deliberate wrongful misconduct, FDA has succeeded in divulging Jerome's trade secrets to the world (thereby permitting Jerome's competitors to develop competitive strategies to counteract the secrets economic value). An economic assessment by economist Dr. Paul Rubin places the market value lost at

relates to the trade secrets... of any person...” Webb, supra, at 102-103. “The Trade Secrets Act, 18 U.S.C. § 1905, is a general criminal statute that provides a penalty for any employee of the United States Government who discloses, in a manner not authorized by law, any trade-secret information that is revealed to him during the course of his official duties.” Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1008 (1984).

\$1,345,316,242.60. Exhibit 5. It is quite possible that Jerome will lose its current 1.2% LS market share as other competitors reposition themselves to negate the market advantages of Jerome's trade secrets. The trade secrets FDA divulged and FDA's subsequent repeat extensions of time for the submission of grantable LS NDAs have enabled Jerome's competitors to deprive Jerome of the opportunity to capitalize rapidly on its invention which, before FDA's publication, made Jerome the only company in the field that had satisfied the new federal standard in the 1997 Notice.

A. FDA MISAPPROPRIATED JEROME'S TRADE SECRETS

Misappropriation of a trade secret, under New York law²¹, requires a plaintiff to show that (1) a trade secret existed; (2) the secret was communicated in confidence by plaintiff to defendant; (3) defendant used the secret in breach of that confidence; (4) and the defendant's use was to the plaintiff's detriment. Heyman v. A.R. Winarick, Inc., 325 F.2d 584 (2d Cir. 1963); Sublime Products, Inc. v. Gerber Products Inc., 579 F.Supp. 248 (SDNY 1984).

Jerome's proprietary manufacturing process for Unithroid is a trade secret. Jerome communicated that trade secret in confidence to FDA in Unithroid's NDA (as it was legally required to do, confident in the knowledge that FDA had an unequivocal legally duty to keep Jerome's trade secrets confidential). Without notice to, or permission from, Jerome and against Jerome's demands after discovering the law violation, FDA divulged Jerome's manufacturing information to the world on www.fda.gov. The disclosure of Jerome's trade secrets has enabled Jerome's competitors to use Jerome's trade secrets for their own competitive advantage, a change in economic circumstances adverse to Jerome that would not have occurred but for FDA's unlawful disclosure of those trade secrets.

²¹ Jerome is located in New York and the tortious injury was felt in New York. Thus, New York law applies. See, e.g. Hercules & Co. v. Shama Restaurant, 566 A.2d 31, 40 (D.C. 1989).

1. JEROME'S PROCESS TO CREATE STABLE, SAFE, AND EFFECTIVE LS IS A TRADE SECRET

A trade secret is "any formula, pattern, device, or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it." Restatement of Torts § 757(b) (1939).²² Jerome's manufacturing processes for Unithroid™ are a valuable plan and process for making, preparing, and processing the drug Unithroid. As such, those processes are protectable as trade secrets. As stated by FDA in its 1997 Guidance, the LS industry has been plagued by an inability to manufacture a safe, stable, and potent orally administered LS drug since the 1950's. Indeed, since that time, manufacturers have been struggling to find a cost effective way to achieve a safe, stable, potent LS drug to no avail. Jerome expended considerable time, effort and expense to develop its stabilization process and has consistently held that trade secret in strictest confidence, cognizant of its great market potential for the company. Prior to FDA's unlawful disclosure (and to this day) Jerome has assiduously avoided disclosure of the trade secrets to third parties (with the exception of the FDA in Jerome's NDA). Jerome's owners entered into a confidentiality agreement with the only other person that knows the secret process, Jerome's scientist William Cardone, forbidding disclosure of the secrets. The trade secrets were (until FDA's posting of them on the web) unknown in the industry and could not have been discovered through reverse-engineering of the final product.

2. JEROME COMMUNICATED ITS TRADE SECRETS TO FDA IN CONFIDENCE

Jerome reasonably expected that FDA would abide by federal law, 21 C.F.R. § 314.430; the FDCA, 21 U.S.C. § 331(j); and the Federal Trade Secrets Act, 18 U.S.C. § 1905, by holding

²² New York follows the Restatement of Torts (First) for its trade secret law.²² E.g., FMC Corp. v. Taiwan Tainan Giant Industrial Co., Ltd., 730 F.2d 61, 63 (2d Cir. 1984).

Jerome's trade secrets in strictest confidence and not divulging them to any member of the public. When a party gains a trade secret from another in a confidential relationship the receiving party has a fiduciary duty not to use the trade secret to the supplying party's detriment. Heyman v. A.R. Winarick Inc., 325 F.2d 584, 591 (2d Cir. 1963) citing Franke v. Wiltschek, 209 F.2d 493, 495 (2d Cir. 1953)(citations omitted). FDA requires that trade secrets related to the production of a new drug be divulged to the agency. The legal necessity for trade secret submission creates an undeniable confidential relationship between the FDA and the applicant. 21 U.S.C. § 355 (b)(1)(D) (Application must contain "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug"). The FDCA prohibits the disclosure of trade secrets obtained by the agency during the course of its review of an NDA, making the release of such secrets a criminal offense. 21 U.S.C.A. § 331(j). FDA's regulations likewise prohibit the disclosure of trade secrets, including manufacturing methods, that are a part of a NDA:

(g) The following data and information in an application or abbreviated application are not available for public disclosure unless they have been previously disclosed to the public as set forth in §20.81 of this chapter or they relate to a produce or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under § 20.61 of this chapter:

(1) manufacturing methods or processes, including quality control procedures.

21 C.F.R. § 314.430(g). FDA is thus under a clear legal duty to protect the confidence of trade secrets imparted to the agency during its NDA review process. 21 U.S.C.A. § 331(j) and 21 C.F.R. § 314.430.

3. FDA DISCLOSED JEROME'S TRADE SECRETS, BREACHING ITS CONFIDENCE

The day after approving Unithroid's NDA, FDA posted Jerome's trade secrets on the world wide web at www.fda.gov without serving Jerome advance notice or obtaining Jerome's

consent for that action. Federal courts have repeatedly held that “posting works to the Internet makes them ‘generally known’ at least to the relevant people interested in [that webpage or website].” Religious Technology Center v. Lerma, 908 F.Supp. 1362, 1368 (E.D.Va. 1995) citing Religious Technology Center v. Netcom On-Line Communication Services, Inc., 907 F.Supp. 1361 (N.D.Cal. 1995). “Once a trade secret is posted on the Internet, it is effectively part of the public domain, impossible to retrieve.” Lerma, supra. The person who originally posted the trade secret on the Internet is liable for trade secret misappropriation. Id.

When Jerome demanded that FDA remove Jerome’s trade secrets from the internet, FDA—having already breached its legal duty—did not act immediately to delete the publication. Instead, FDA refused to remove the information, against Jerome’s protests, for an entire month (that after it had already left the information on its website for four prior months). Jerome placed numerous phone calls and sent repeated letters to FDA before the agency finally removed all of Jerome’s trade secrets, a full five months after FDA’s original unlawful publication on www.fda.gov.

4. FDA’S DISCLOSURE OF JEROME’S TRADE SECRET GIVES JEROME’S COMPETITORS THE MANUFACTURING PROCESS FOR A SAFE, STABLE, AND POTENT LS DRUG

Jerome’s competitors can use Jerome’s trade secrets to their economic advantage. The secrets enable them to obtain FDA’s approval of their NDAs and ANDAs for levothyroxine sodium products by replicating the trade secrets, or closely mimicking Jerome’s process, in their own applications. FDA’s disclosure of Jerome’s trade secrets has thus not only denied Jerome the substantial economic benefit of its invention but it has also denied Jerome a period of de facto exclusivity in the market where it could have capitalized on the invention to seize a far

greater market share than the comparatively small share it now has. Jerome's loss of market exclusivity due to FDA's misappropriation has cost Jerome an estimated \$1,345,316,242.

FDA has no sound defense for its misappropriation of Jerome's trade secrets. The posting was not a "discretionary act."²³ FDA's duty to hold confidential all trade secrets submitted with a NDA is unequivocal and mandatory from the moment it receives the NDA and for all time thereafter. 21 U.S.C.A. § 331(j); See also 21 C.F.R. § 314.430. FDA employees are required, on pain of criminal sanction, to keep all trade secrets confidential. Id. FDA's posting of Jerome's trade secrets was thus a clear tortious misappropriation for which the United States is liable under the Federal Tort Claims Act.

B. FDA BREACHED ITS CONFIDENTIAL RELATIONSHIP WITH JEROME

FDA's disclosure of Jerome's confidential and trade secret manufacturing information breached the confidential relationship between the agency and Jerome. The common law breach of confidence theory is essentially the same as misappropriation of a trade secret, except that the breach of confidence theory requires only that the information not be generally known, a broader concept than trade secret. E.I. du Pont de Nemours Powder Co. v. Masland, 244 U.S. 100, 102 (1917) (Supreme Court rejected trade secret protection for plaintiff but stated that the breach of confidence issue remained for the Court to consider).

"A confidential or fiduciary relationship exists between parties 'where the parties do not deal on equal terms and one trust and relies on the other.'" McGhan v. Ebersol, 608 F.Supp. 277, 285 (S.D.N.Y. 1985) citing Sachs v. Cluett, Peabody & Co., 265 A.D. 497, 39 N.Y.S.2d 853, 856 (1st Dept.) aff'd 291 N.Y. 772, 53 N.E.2d 241 (1944). The nature of the relationship

²³ To be discretionary, the act or omission must have been "made while exercising due care, in the execution of a statute or regulation or performance or the failure to exercise or perform a discretionary function or duty on the part of a federal agency or an employee of the government, whether or not the discretion involved be abused." 28 U.S.C. § 2680; See U.S. v. Gaubert, 499 U.S. 315 (1991).

(the degree of trust) is the key element to a breach of confidence claim. "Actionable claims for breach of confidential and fiduciary relationships are centered on breach of an agreement between parties, or breach of trust they place in each other because of the nature of their relationship." Walker v. Time Life Films, Inc., 615 F.Supp. 430, 440 (S.D.N.Y. 1985) citing Smith v. Weinstein, 578 F.Supp. 1297, 1302 (S.D.N.Y.), aff'd mem. 738 F.2d 419 (2d Cir. 1984).

As discussed above, FDA's NDA process requires that an applicant enter into a confidential relationship with the agency. An applicant must reveal confidential information to the agency to obtain FDA pre-market drug approval. Webb, supra, at 102-103. As the courts have recognized,

If citizens fear uncontrolled disclosure of the trade secrets, tips, and other confidential data the government asks them to provide, they will be less willing to cooperate in the government's efforts to collect the data ... The Supreme Court recently suggested that the government has particularly extensive power to control the disclosure of sensitive information within its custody, and that the government may sanction its employees where 'the mishandling of sensitive information leads to its dissemination.'

U.S. v. Wallington, 889 F.2d 573 (5th Cir. 1989) citing The Florida Star v. B.J.F., 491 U.S. 524, 109 S.Ct. 2603, 2609, 105 L.Ed.2d 443 (1989) (citation omitted).

FDA and NDA applicants are not on equal terms. FDA's will has the force of law behind it and imposes an absolute barrier to market entry unless an NDA applicant supplies FDA with information the agency requires for grant of the application. That required information includes trade secrets on the drug's manufacture, stability, safety, and efficacy. 21 U.S.C.A. § 355. As an NDA applicant, Jerome was required to reveal confidences to the agency. Id. Jerome reasonably relied on FDA's duty to keep its confidential and trade secret manufacturing information from the public and reasonably entrusted FDA with fulfillment of that legal duty. FDA breached that trust, violated the law, abused its discretion, and abused its confidential relationship with Jerome

when FDA posted Jerome's confidential and trade secret manufacturing information on the worldwide web.

**V. FDA TOOK JEROME'S PROPERTY RIGHTS WITHOUT
DUE PROCESS OF LAW**

The Fifth Amendment states that no person "may be deprived of life, liberty, or property without due process of law." U.S. Const. amend V. The Constitution requires that due process be afforded before an individual is deprived of property. Eli Lilly and Company v. Environmental Protection Agency, 615 F. Supp. 811, 819 (S.D.In. 1985)(emphasis added). The Due Process Clause involves a substantive and a procedural component. Daniels v. Williams, 474 U.S. 327, 334 (1986). Procedural due process requires "notice and an opportunity to be heard before the government deprives [an individual] of property." United States v. James Daniel Good Real Property et al., 510 U.S. 43, 48 (1993) (emphasis added). Substantive due process bars certain arbitrary government actions, "regardless of the fairness of the procedures used to implement them." Daniels, supra at 334. FDA has violated Jerome's substantive and procedural due process rights, arbitrarily depriving Jerome of its trade secret exclusivity, a fundamental property right, without any advance notice or opportunity to be heard.

**A. FDA FAILED TO NOTIFY JEROME IN ADVANCE AND GIVE IT AN
OPPORTUNITY TO OBJECT BEFORE POSTING ITS PROPERTY ON
THE INTERNET**

"Consideration of what procedures due process may require under any given set of circumstances must begin with a determination of the precise nature of the government function involved as well as of the private interest that has been affected by government action." Cafeteria & Restaurant Workers v. McElroy, 367 U.S. 886, 895 (1963). At a minimum, procedural due process requires "adequate notice and an opportunity to be heard at a meaningful time and in a meaningful manner." Boddie v. Connecticut, 401 U.S. 371, 378 (1971).

Jerome's trade secret is a core property interest protected by procedural due process. See, e.g. Zotos International, Inc. v. Kennedy, 460 F. Supp. 268 (D.C. 1978). By divulging Jerome's trade secrets to the world on FDA's website, the agency deprived Jerome of its property interest without any advance notice or opportunity to be heard. The Supreme Court has stated,

the right to exclude others is generally 'one of the most essential sticks in the bundle of rights that are commonly referred to as property.'...With respect to a trade secret, the right to exclude others is central to the very definition of the property interest. Once the data that constitutes a trade secret is disclosed to others, or others are allowed to use that data, the holder of the trade secret has lost his property interest in the data.

Ruckelshaus v. Monsanto Co., *supra*, at 1011-1012 citing Kaiser Aetna, *supra*, at 176.

Jerome's trade secrets were of significant value in an industry of more than \$630 million in U.S. sales per year. See Exhibit 5 at 2. Jerome's trade secret value was due in no small measure to the immediate market exclusivity Jerome would have experienced had FDA kept Jerome's trade secrets confidential. FDA had erected a formidable market barrier to entry and remaining in the market. It did so by forbidding drug companies from entering the levothyroxine sodium market without an NDA or ANDA and requiring companies that were already in that market to submit NDAs by August 2001. When FDA published Jerome's trade secrets on the World Wide Web, it substantially reduced, if not completely eliminated, the economic value of Jerome's trade secret. It did so without Jerome's permission, as well as without any notice to Jerome or opportunity for Jerome to be heard.

In Eli Lilly & Co. v. EPA, cited *supra*, the plaintiff sued EPA for issuing and maintaining the registrations of certain pesticide products of a competing company in Lilly's market. In issuing and maintaining the competitor's registrations, EPA considered various health, safety, and efficacy data submitted by Eli Lilly. Lilly was not compensated for this information by EPA or the competing company. The court found that EPA's use of Lilly's data for a competitor's

application without the company's permission constituted a deprivation of Eli Lilly's property rights without due process of law under the Fifth Amendment. As in Lilly, FDA's publication of Jerome's trade secrets violated 21 USC § 331(j)²⁴ and the company's procedural due process rights.

B. JEROME'S SUBSTANTIVE DUE PROCESS RIGHTS WERE VIOLATED BY FDA'S ACTIONS

Substantive due process bars certain government actions regardless of the fairness of the procedures used to implement those actions. See, e.g., Daniels, supra, at 337. To establish a substantive due process claim, a plaintiff must prove that the government's action was clearly arbitrary and unreasonable, having no substantial relation to the public health, safety, morals, or general welfare. See Village of Euclid v. Ambler Realty Co., 272 U.S. 365, 395 (1926). When FDA inexplicably and unreasonably posted Jerome's trade secrets on the Internet and did not remove them for nearly five months, it violated the company's substantive due process rights.

"A property interest that falls within the ambit of substantive due process may not be taken away by the state for reasons that are 'arbitrary, irrational, or tainted by improper motive...or by means of government conduct so egregious that it 'shocks the conscience.'" Nicholas v. Pennsylvania State University, 227 F.3d 133, 139 (3d Cir. 2000). A property interest qualifies for substantive due process protection depends if it is "fundamental" under the Constitution. See, Regents of University of Michigan v. Ewing, 474 U.S. 214, 229 (1985) (Powell, J. concurring)). Trade secrets qualify as a fundamental right, as "property interests in trade secrets have been recognized for over a century by English and American courts of equity." Zotos International v. Kennedy, 460 F. Supp. 268, 272 (D.C. 1978). Trade secrets have also been recognized as a property interest within the scope of the Due Process Clause of the Fifth

²⁴ It also violates FDA regulation 21 C.F.R. § 314.430.

Amendment. Id. at 273 (procedural due process claim at issue). Thus, just as land ownership is “a fundamental property interest dating back to the foundation of the American colonies” (Homar v. Gilbert, 63 F. Supp. 2d 559, 557 (M.D. Pa. 1999), intellectual property ownership dates back just as far and should be accorded the same protection. See Copyright Act of 1790, 1 Stat. 124 (repealed 1831).

Jerome lost its fundamental property interest, its trade secret exclusivity, as a result of capricious government action. This violation occurred when FDA posted Jerome’s trade secrets for Unithroid™ on its website, www.fda.com, on August 22, 2000, the day after Unithroid’s NDA was approved. That action was arbitrary, irrational, and shocking to “the conscience.” See, Nicholas, 227 F.3d at 139. Jane Axelrad, the Associate Director for Policy for CDER, admitted that the posting was “a mistake.” That “mistake” occurred in the process of a New Drug Application, where FDA has an absolute statutory and fiduciary duty to guard pharmaceutical trade secrets. That “mistake” also sacrificed Jerome’s right to its intellectual property and imposes a lost opportunity cost upon the company in excess of \$1.3 billion.

When FDA published Jerome’s trade secrets on the Internet, it acted arbitrarily and capriciously, contrary to its statutory duties, and without any rational relation to the public good or general welfare. See Village of Euclid, 272 U.S. at 395. In doing so, it deprived Jerome of its fundamental property rights in its trade secret without due process of law. As such, FDA deprived Jerome of the substantive due process protection that was Jerome’s due.

VI. FDA’S DISCLOSURE OF JEROME’S CONFIDENTIAL AND TRADE SECRET INFORMATION VIOLATED THE APA

A. FDA ACTED NOT IN ACCORDANCE WITH THE LAW

Agency action that is contrary to law violates the APA. 5 U.S.C.A. § 706(2)(A). The federal Courts have found that when FDA discloses a trade secret (the very action that the trade

secret statutory provisions protect against), the agency acts arbitrarily, capriciously and unreasonably; it also acts contrary to law under 5 U.S.C. § 706(2)(A). Serono Labs, supra, at 3.

The Trade Secrets Act prevents the government from disclosing confidential information received in an official capacity. 18 U.S.C. § 1905. The Act in pertinent part provides:

Whoever, being an officer or employee of the United States or of any department or agency thereof, ... publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; or permits any income return or copy thereof or any book containing any abstract or particulars thereof to be seen or examined by any person except as provided by law; shall be fined not more than \$ 1,000, or imprisoned not more than one year, or both; and shall be removed from office or employment.

18 U.S.C. § 1905. The Trade Secrets Act is a criminal statute, providing sanctions against violators, but does not convey or imply a private right of action. Chrysler Corp. v. Brown, 441 U.S. 281, 317 (1979); MegaPulse v. Lewis, 672 F.2d 959, 966 (D.C. Cir. 1982). Nevertheless, Courts have held that "any disclosure that violates § 1905 of the Trade Secrets Act is 'not in accordance with law'" within the meaning of section 10(a) the Administrative Procedure Act. Id. Thus, a violation of the Trade Secrets Act is reviewable as a violation of the APA. Id.

In applying § 1905 the Court looks at factors such as whether the disclosure would significantly aid the agency in performing functions, whether the disclosure would harm producers and the public generally, and whether alternatives to full disclosure could serve the public interest. Doctors Hospital of Sarasota, Inc. v. Califano, 455 F. Supp. 476 (M. Fla. 1978). In this case none of the factors weigh in FDA's favor. The unauthorized disclosure of Jerome's trade secrets does not aid FDA's functioning; in fact, it harms FDA by calling into question the confidential relationship upon which FDA depends for full disclosures of manufacturing

procedures, processes, and formulas in NDAs, disclosures it must have to evaluate drug safety and efficacy. The disclosure has substantially and irreparably harmed Jerome and has called into question the integrity of FDA's drug approval process. If left uncompensated and unpunished, the wrong may produce a significant disincentive for companies to disclose trade secrets in future NDAs, contrary to the public interest in the efficient provision of safe and effective drugs to the market.

FDA's disclosure of Jerome's trade secrets also violates the FDCA, 21 U.S.C. § 331(j), which states, in pertinent part, that:

The following acts are thereby prohibited... (j) The using by any person to his own advantage or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act [21 USCS §§ 301 et seq.], any information acquired under authority of section 505... [21 U.S.C.A. § ...355...], concerning any method or process which as a trade secret is entitled to protection;

Id. (2001). Violation of § 331 is a crime. 21 U.S.C.A. § 333 (a)(1) (“ Any person who violates a provision of section 301 [21 U.S.C. § 331] shall be imprisoned for not more than one year or fined not more than \$ 1,000, or both.”). Like the Trade Secrets Act a private party cannot enforce the FDCA. Nevertheless, an agency's violation of the FDCA is a violation of the APA as an act not in accordance with the law.

FDA defines a trade secret²⁵ as any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. 21 C.F.R. §

²⁵ Analyzing FDA's violation of the FDCA requires application of FDA's definition of a trade secret. FDA adopted the First Restatement's definition of a trade secret as its definition. 21 C.F.R. § 20.61; See also, Anderson v. DHHS, 907 F2d 936, 943 (10th Cir. 1990). The D.C. Circuit rejected FDA's definition of a trade secret as too broad when applied to the Freedom of Information Act exception for trade secrets. See, Anderson, supra, at 943-44 citing Public Citizen Health Research Group v. FDA, supra. The D.C. Circuit defined a trade secret under common law as “a secret, commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort.” Anderson, supra, at 944 citing PCHRG, supra, at 1288. Under the D.C. Circuit's definition there

20.61. To qualify as a trade secret, there must be a direct relationship between the trade secret and the productive process. 21 CFR § 20.61(a); see also Consumers Union v. Veterans Admin., 301 F. Supp. 796, 801 (S.D. N.Y. 1969) (distinguishing between data relating to processes and methods which relate to private innovation and are protected from disclosure, and safety and efficacy data which are in the public interest to disclose). Data and information submitted to FDA that meet the definition of a trade secret cannot be made available to the public. 21 CFR § 20.61(c); see also, Public Citizen Health Research Group v. FDA, 539 F. Supp. 1320, 1325 (D.D.C. 1982)(stating that once a document is determined to be a trade secret the document is exempt from disclosure). Thus, FDA has violated federal law by revealing a trade secret it obtained in an NDA application and thereby it has also violated the APA.

B. FDA'S DISCLOSURE OF JEROME'S TRADE SECRETS ON ITS WEBSITE AND FDA'S SUBSEQUENT FAILURE TO REMOVE THE SECRETS IMMEDIATELY WAS ARBITRARY AND CAPRICIOUS

A court may hold as unlawful and set aside agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. See 5 U.S.C. § 706 (2)(A) (2001). In reviewing arbitrary and capricious agency action under § 706 a court must "consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." Bowman Transportation Inc. v. Arkansas-Best Freight System, Inc., 419 U.S. 281, 286, 95 S.Ct. 438, 42 L.Ed. 447 (1974) citing Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 416 (1971). "The agency must articulate a 'rational connection between the facts found and the choice made.'" Bowman, *supra*, at 286 citing Burlington Truck Lines v. United States, 371 U.S. 156, 168 (1962).

can be no question but that the Jerome secrets FDA divulged to the public on the worldwide web were "trade secrets."

However, “[m]ore exacting scrutiny will be particularly useful [for the court when examining agency action] when for some reason the presumption of agency regularity (see, Overton Park, supra, at 415) is rebutted as where the agency has demonstrated undue bias towards a particular private interest (see e.g., Central Florida Enterprises, Inc. v. FCC, 598 F.2d 37 (1978)); where the agency has had a history of ‘ad hoc inconsistent judgments’ on a particular question (Local 777 v. NLRB, 603 F.2d 862, 869-971 (1978)); where the agency has arrived at an identical result after remand from a reviewing court for further explanation of reason (e.g., Food Marketing Inst. V. ICC, 1587 F.2d 1285, 1289-90 (1978)); or when an agency has departed from its consistent and longstanding precedents or policies (see, Office of Communication of United Church of Christ v. CAB, 590 F.2d 1062, 1068-1069 (1978)(citations omitted)).” Natural Resources Defense Council, Inc. v. SEC, 606 F.2d 1031, 1050, n.23 (1978).

FDA’s regulatory treatment of Unithroid is littered with “ad hoc inconsistent judgments.” FDA’s decision to publish Jerome’s trade secrets on its website was of course an action inconsistent with its statutory and regulatory obligations. Moreover, FDA’s failure to act immediately upon notification by Jerome that FDA had published Jerome’s trade secrets was totally inconsistent with the agency’s well understood statutory and regulatory duty to protect trade secrets. Jerome was forced to contact FDA multiple times, demanding FDA remove the trade secrets before FDA finally acted and completely removed the offending material. FDA’s actions, and failure to act, were clearly inconsistent with legal duty and have no reasoned basis. Thus, FDA’s disclosure of, and subsequent failure to remove, Jerome’s trade secrets was arbitrary and capricious in violation of the APA.

C. FDA’S JULY 2001 POLICY CHANGE CONCERNING THE SAFETY RISKS OF SYNTHROID WAS ARBITRARY AND CAPRICIOUS

FDA's decision to allow until August 14, 2001, for the filing of LS NDAs after initially requiring grant of pre-market approval for those NDAs by August 14, 2000, is unreasoned, unexplained, inexplicable, and arbitrary and capricious in light of FDA's public health determination that patients were at immediate risk of significant harm from unstable LS products then on the market and that new NDAs were therefore promptly required to achieve the LS drug stability needed. Having granted an application providing a stable, safe, and effective LS drug in Jerome's Unithroid (and having been served with notice that Jerome was ready, willing, and able to supply national demand for LS), FDA again acted arbitrarily and capriciously by favoring an unstable LS drug, Abbott's Synthroid, permitting Synthroid to be marketed for three years after its original August 14, 2000 deadline. Those actions are wholly inconsistent with FDA's stated objective of safeguarding the public from unstable, unsafe, and ineffective LS drugs.

Indeed, it was in April 2001 that FDA found Synthroid not reliably potent and stable. Exh. 10 at 7. It found that patients taking Synthroid had experienced "significant, unintended variations in their doses of levothyroxine sodium." Id. at 8. The agency reasoned that "because of the serious consequences of too much or too little circulating thyroxine, it is very important that patients receive the dose of levothyroxine sodium determined by their physicians to be optimal to replace the amount of hormone that would have been present naturally." Id.

With Unithroid's approval FDA had confirmed the existence of a safe and effective drug available for thyroid disease patients that had none of the risks of adverse reactions due to overdosing or under-dosing FDA found to have historically plagued Synthroid users. Id. at 6-8. After Unithroid's approval Jerome assured FDA in writing that Jerome had the ability to meet the LS demand of the U.S. population. Jerome offered to meet with FDA on that issue to discuss the matter further but FDA refused.

In July 2001, just three months from its complete rejection of Synthroid due to its public health risks, FDA issued the July Guidance stating:

Notwithstanding the fact that there are now two approved applications for orally administered levothyroxine sodium, FDA has determined that it will take time for the millions of patients taking unapproved products to switch to approved products, and for manufacturers of approved products to scale up their production and to introduce this increased production into the distribution chain.

Id. at 3. That announcement is wholly irrational in light of FDA's public interest findings and its knowledge that Jerome stood ready, willing and able to meet market demand with an FDA approved safe, stable, and effective LS product. FDA's decision to permit unstable Synthroid, an LS market leader, to continue to be sold denied Jerome a significant opportunity to increase its LS market share.

When an agency departs from policy in an unreasoned manner, particularly in a way that shows bias, it acts arbitrarily and capriciously. Natural Resources Defense Council, Inc., supra, 1050, n.23 citing Office of Communication of United Church of Christ v. CAB, supra, 1068-1069. Moreover, where the agency has made "ad hoc inconsistent judgments" on particular questions it has acted arbitrarily and capriciously. Id. citing Local 777, supra, 869-971. FDA's wholly irrational change in its LS grant timetable was arbitrary and capricious agency action in violation of the APA.

D. FDA'S DISPARATE TREATMENT OF LEVOXYL AND UNITHROID WAS ARBITRARY AND CAPRICIOUS

As of the filing of this Notice, FDA has approved one other orally administered LS drug, Levoxyl, manufactured by Jones Pharma. However, FDA did not require Levoxyl to meet the same regulatory requirements that Unithroid had to meet. Unithroid and Levoxyl's applications were not treated equally.

In an internal FDA memo FDA Division of Scientific Investigations Pharmacologist Dr. Michael F. Skelly recounted an audit of the analytical portions of two of Levoxyl's bioequivalence studies.²⁶ Exh. 13 at 1. In that memo, Dr. Skelly stated that FDA failed to inspect the clinical facilities where Levoxyl was studied. Dr. Skelly stated that Jones Pharma did not keep reserve samples of Levoxyl used in bioavailability testing in accordance with 21 C.F.R. § 320.38(b)(3).²⁶ He noted, because of the lack of reserve samples, "the identity of the test and reference drug products used in the studies cannot be verified." Id. at 2.²⁷ Failure to comply with § 320.38 is a significant violation of FDA's regulations, particularly for LS drugs.²⁸ Without verification that the sample tested is the same as the drug being approved, it is impossible to verify the bioavailability of the approved drug.²⁹ Furthermore, the requirement to have test samples and reference standards on hand for FDA's inspection is a continuing requirement. Id. at (e). FDA requires that the reserve sample be retained by the NDA applicant for at least five years after the date that the NDA is approved. Id.

²⁶ Study 338-02 "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine," and Study 338-04 "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Three Strengths of Levothyroxine (Levoxyl)." Exh. 13 at 1.

²⁶ 21 C.F.R. § 320.38(b)(3) requires an NDA applicant of a drug that is a "new formulation, new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing, [retain] a reserve sample of the test article and of the reference standard used to conduct an in vivo bioequivalence study comparing the test article to a marketed product (reference standard) that contains the same active drug ingredient or therapeutic moiety."

²⁷ In his discussion of Jones Pharma's failure to keep reference drugs, Dr. Skelly stated that the Department of Scientific Investigations "has not examined comparable records of clinical portions of bioequivalence studies for other levothyroxine NDAs." That statement is incorrect. Jerome's bioequivalence studies were examined by the same investigators as the Levoxyl studies, Dr. Skelly and Dr. C.T. Viswanathan. During Jerome's inspection, Jerome provided the inspectors with reserve samples of the drugs it used in its bioequivalence studies.

²⁸ In 1988 the House Subcommittee on Oversight and investigations launched an investigation into FDA's generic drug approval process. Hutt et al., "FDA Regulation and Promotion of Generic Drugs," Food and Drug Law (576-580,579 (Foundation Press, 1991). It found that some FDA employees had accepted bribes and some manufacturers conducted (and submitted) bioavailability and bioequivalence studies using the pioneer drug rather than their own generic products, and that significant discrepancies occurred in the testing and manufacture of some generic drugs. Id. at 579. By early 1991 five FDA employees had been convicted of bribery or perjury and eight generic drug companies had been found to have submitted applications to FDA containing fraudulent data. Id. at 580. In response to the fraudulent bioavailability and bioequivalence studies discovered FDA promulgated the requirement of retaining reserve samples. See 55 F.R. 47034 (1990); finalized at 58 F.R. 25927 (1993)

Moreover, in his memo Dr. Skelly stated that the bioavailability studies' incompleteness was exacerbated by software failure in Jones Pharma's information systems used to analyze the bioavailability studies. Id. As of the date of Dr. Skelly's memo, Jones Pharma had not evaluated the effect of the software errors on its analysis of the bioavailability study results. Thus, the results and analysis of Levoxyl's bioequivalency studies may be totally erroneous. In fact, Dr. Skelly recommended that the data from the bioequivalency studies not be accepted by FDA "unless and until it is shown that software failure did not affect [the] data." Id. at 3. There is no record in the Levoxyl NDA material on FDA's website that Jones Pharma's software failure was examined and the results of the bioequivalency studies verified.

By contrast to FDA's treatment of Levoxyl, allowing it to skip the requirements of § 320.38, Jerome was held to that strict standard. Jerome kept test and reference samples during its bioavailability testing, made them available for inspection, and continues to hold them available for FDA inspection in accordance with its on-going requirements. Jerome had reliable results showing Unithroid's bioavailability. FDA's failure to hold Jones Pharma to the same regulatory requirements as Jerome was arbitrary and capricious in violation of the APA.

IV. JEROME REQUESTS MONETARY DAMAGES FOR FDA'S WRONGFUL ACTS

FDA's disclosure of Jerome's confidential and trade secret manufacturing information was (1) a tortious misappropriation of trade secrets and (2) a breach of its confidential relationship with Jerome. The Federal Tort Claims Act requires the claimant to name a sum certain in its administrative notice. 28 U.S.C. § 2675(b).³⁰ Based on the independent economic

²⁹ Levoxyl's bioavailability is particularly significant because of the potency issues with LS drugs. Overdosing and underdosing have serious health consequences. Exh. 10 at 8.

³⁰ "Action under this section shall not be instituted for any sum in excess of the amount of the claim presented to the federal agency, except where the increased amount is based upon newly discovered evidence not reasonably discoverable at the time of presenting the claim to the federal agency, or upon allegation and proof of intervening facts, relating to the amount of the claim." Id.

assessment of damages attached hereto, Jerome's injury amounts to \$1,345,316,242. Exhibit 5 at 2 and 4.³¹

Jerome's injury is based on the assumption that Unithroid and Levoxyl would have shared 90% of the orally administered LS market had FDA fulfilled its statutory obligations. Id. That presumption is reasonable in light of the historic difficulty (documented in FDA's 1997 Notice) that drug companies have had in manufacturing a safe, stable and potent LS drug product. The assumption that Levoxyl and Unithroid would have divided the LS market for ten years without generics is reasonable, despite LS drugs' lack of exclusivity, because generic LS drugs would have to obtain ANDA approval. ANDA approval would be impossible without a generic-LS manufacturer making its own discovery of a manufacturing process for a safe, stable, and potent LS product. From LS's introduction in the 1950's until Jerome's discovery in 1990, drug manufacturers had failed to make that discovery despite every incentive to identify a safe, stable and cost effective form.

Other than from generics seeking ANDA approval, the principal source of competition for Unithroid and Levoxyl is Synthroid, the NDA for which is currently pending. However, FDA had previously rejected Synthroid in April of 2001, finding it not safe and effective, citing formulation and manufacturing problems. If FDA hadn't disclosed Jerome's confidential and trade secret information, it is reasonable to assume that Synthroid would not be competing with Unithroid and Levoxyl. As of April 2001, Synthroid's makers had failed to produce a formula and manufacturing process that was safe and stable.

Moreover, Synthroid's NDA currently pending before FDA can only be based on a "new" formulation and manufacturing process since its prior formulation and manufacturing

³¹ The United States is not liable for interest prior to judgment under the FTCA. Jerome's injury does not include pre-judgment interest. It does include, however, a real interest rate of 3% applied to Jerome's total revenue per year

process was so thoroughly rejected by the FDA in April of 2001. Jerome can only assume that with Jerome's confidential and trade secret information available to it, Abbott Laboratories (or its predecessor Knoll Laboratories) will be able to succeed in formulating a stable new LS drug.

Jerome's Petition for a Stay, filed simultaneous with this notice, asks FDA to stay approval of any NDA or ANDA for an orally administered LS drug that uses, relies on, or is based on Jerome's confidential and trade secret manufacturing information.³² If Jerome's FTCA Notice is unresolved at the agency level and Jerome files suit in federal court, in addition to its claims for relief for FDA's tortious acts, Jerome will seek a declaratory judgment on its APA claims, injunctive relief against the grant of pre-market approval to applicants that have used, relied on, or based their LS stability submissions on Jerome's trade secrets, and monetary relief for FDA's violation of Jerome's Fifth Amendment due process rights.

that it would have received absent the FDA's disclosure. Exhibit 5 at 2 and 4.

³² While Levoxyl's NDA was submitted to FDA prior to FDA's disclosure of Jerome's trade secrets, Jerome cannot be certain that Jerome's manufacturing processes were not part of an amendment after the disclosure but before Levoxyl's approval. Thus, in its petition, Jerome asks FDA to include Levoxyl in its review.

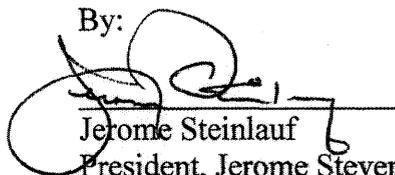
VII. CONCLUSION

Jerome hereby submits notice pursuant to the FTCA that FDA is liable for the misappropriation of Jerome's trade secrets and for breaching its confidential relationship with Jerome. FDA is also liable for violating Jerome's Fifth Amendment Due Process Rights and for violating the APA. In restitution of its tort claims, Jerome seeks \$1,345,316,242 in damages.

Sincerely,

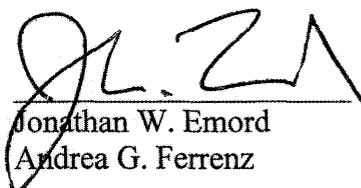
JEROME STEVENS
PHARMACEUTICALS

By:



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Date Submitted: March 22, 2002

Exhibit 1

Exhibit 2

This exhibit has not been included in accordance with instructions from the Dockets Management Branch and to avoid risk of unauthorized disclosure. The exhibit contains information protected from disclosure by the Trade Secrets Act, 18 U.S.C.A. § 1905, the Food, Drug and Cosmetic Act, 21 U.S.C.A. § 331(j), FDA's regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4).

Exhibit 3



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US Top 10 Products Ranked on Total Dispensed Prescriptions

January 2000 - December 2000

Source: IMS HEALTH's National Prescription Audit Plus

The 10 most frequently dispensed prescription drugs in the US for the twelve months ending December 2000

Product	Total Dispensed Prescriptions (000)	%Growth (+/-)	%Market Share
Lipitor - Pfizer	48,791	29	2
Premarin - Wyeth-Ayerst	46,776	-2	2
Synthroid - Knoll	43,504	6	2
Hydrocodone/APAP - Watson	36,534	20	1
Prilosec - AstraZeneca	32,082	3	1
Norvasc - Pfizer	30,765	13	1
Glucophage - Bristol-Myers Squibb	27,424	21	1
Albuterol - Warrick	27,415	-8	1
Claritin - Schering	26,485	4	1
Zoloft - Pfizer	25,167	9	1

All data reported in thousands (000)

Channels covered: chainstores, independents, foodstores, mail order and long term care facilities.

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Exhibit 4

DA ALK PAPER

*Food and Drug Administration
5. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

DA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

00-36
August 22, 2000

Print Media: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES FIRST NDA FOR LEVOTHYROXINE SODIUM

FDA today approved the first NDA for the thyroid hormone replacement drug, levothyroxine sodium (Unithroid) for use in adults and children.

In children, thyroid hormones are essential for normal physical growth and intellectual development. They are also involved in the regulation of a wide range of metabolic processes within the body in all age groups. Hypothyroidism, or low levels of thyroid hormone, may be due to a birth defect (e.g. partial or complete absence of the thyroid gland) or it may occur later in life due, for example, to thyroiditis, goiter, or surgical removal of the thyroid gland.

Symptoms of hypothyroidism include poor growth in children and, in those born with this disorder, impaired intellectual development if this disorder is not promptly and adequately treated. Symptoms of hypothyroidism in children and adults include fatigue, cold intolerance, dry skin, lethargy and weight gain.

Levothyroxine is identical to a natural thyroid hormone produced by the body and is most commonly used to return thyroid hormone levels to normal in patients with hypothyroidism. The dose of levothyroxine for replacement or supplemental therapy in patients with hypothyroidism must be individualized based on patient response. Patients taking levothyroxine as replacement must be monitored with blood tests at regular intervals to determine that thyroid hormone levels are within the normal range, to assure patient safety, and to help guide dose adjustments.

During initiation of replacement therapy with levothyroxine, blood tests are usually performed every six to eight weeks in adults to aid in dose adjustment. Once the optimal replacement dose of levothyroxine for an individual adult patient is determined, blood tests are usually done less frequently; e.g., every six to twelve months. Infants and children are usually begun on full levothyroxine replacement doses and the frequency of monitoring of blood tests, growth and intellectual development is age-dependent.

Side effects from levothyroxine are usually due to over-dosage and include nervousness, weight loss,

hycardia (rapid heart beat), irritability, and anxiety.

though oral levothyroxine drugs products have been marketed in the United States since the 1950's, the approval of Unithroid represents the first time that a single ingredient oral levothyroxine product has been approved by the FDA.

the August 14, 1997 Federal Register, FDA announced that orally administered drug products containing levothyroxine sodium are new drugs. The unapproved thyroid hormone replacement products that have been on the market have been associated with stability and potency problems. These problems have resulted in product recalls and have the potential to cause serious health consequences to the public.

To address these concerns, the agency announced that after August 14, 2001, any orally administered levothyroxine drug product must be the subject of an approved New Drug Application. If there is no such approved application, the product will be subject to regulatory action as an unapproved new drug. With the approval today of Unithroid, patients and physicians will now have available to them an oral levothyroxine sodium drug product that has been determined to be safe and effective by the FDA and that also meets FDA standards for manufacturing processes, purity, potency, and stability.

Unithroid is manufactured and distributed by Jerome Stevens Pharmaceuticals of Bohemia, NY.

For more information on this topic, see the Center for Drug Evaluation and Research's [Unithroid Information Page](#).

[FDA News Page](#) | [FDA Home Page](#)

Office of Public Affairs

Hypertext uploaded by [jch](#) 2000-AUG-22.

Exhibit 5

ECONOMIC LOSS ANALYSIS FOR JEROME STEVENS PHARMACEUTICALS FROM FDA PUBLICATION OF JEROME'S CONFIDENTIAL AND TRADE SECRET MANUFACTURING INFORMATION

I have been asked to compute the loss to Jerome Stevens Pharmaceuticals (hereinafter "Stevens") caused by the decision of the Food and Drug Administration to publish on the FDA website Stevens' confidential and trade secret information regarding its manufacturing process. With the disclosure of Stevens' confidential and trade secret information, competitors may use those secrets to obtain FDA approval to enter the levothyroxine sodium market, thus causing harm to Stevens. Competitors may use Stevens' manufacturing information in New Drug Applications, to obtain approval as brand name drugs, or may use them in Abbreviated New Drug Applications, to obtain approval as generic drugs. They may use the information directly by duplicating Stevens' manufacturing process or indirectly by learning from it and developing a different process based upon it.

I have computed an estimate of Stevens' economic damages. My calculation is based in large part on a contract between Stevens and its partner, Watson Labs. Entered into before FDA's publication of Stevens' confidential and trade secret information on the worldwide web, the contract is based on mutually acceptable forecasts of the market value attainable from FDA approval of the Stevens' NDA for orally administered levothyroxine sodium. That contract was a business document prepared in the ordinary course and is of a kind generally accepted among economists for the analysis of damages and similar issues. David P. Kaplan, "The Nuts and Bolts of Antitrust Analysis: Some Thoughts On How To Develop the Facts," in *Economic Inputs, Legal Outputs: The Role of Economists in Modern Antitrust*, (Fred McChesney, ed., 1996).

There are three relevant parts to the Watson Labs contract. First is an item called "Additional Payments" which is a quarterly payment from Watson to Stevens. The amount of this payment depends on the number and type of other sellers of levothyroxine sodium in the market. The second is an item called "Royalties on Net Sales." This sets forth a royalty schedule for payments from Watson to Stevens based on Watson's sales. Third is a set of transfer prices. These represent approximate manufacturing and shipping costs to Stevens, recovered as transfer payments from Watson, and so do not enter directly into the analysis. Since those transfer prices include all of Stevens' costs, costs are not separately deducted from the total revenue figures derived below.

In performing my analysis, I make the following assumptions;

1. Absent the FDA's error in publishing Stevens' confidential and trade secret information, Watson (Stevens' partner) and Jones Pharmaceuticals (the other approved seller) would have split 90% of the market between them.
2. The market would have grown at a real (physical) rate of 13% per year, based on the existence of many potential users who do not currently use the product. This is a conservative estimate; for 2000-2001 the market actually grew 27%.

3. I use a real discount rate of 3%, which is consistent with historical values of the real interest rate.

My calculations are set forth in the attached tables. The real interest rate is generally considered to be about 3% or less; see, for example, William Poole, "Are Real Interest Rates Too High?," speech before Money Marketeers of New York University, New York City, September 21, 1999, available online at <http://www.stls.frb.org/general/speeches/990921.html>. The calculations are based on standard present value formulas. These are discussed, for example, in Michael L. Brookshire and Stan V. Smith, *Economic/Hedonic Damages*, Anderson Publishing Company, Cincinnati, 1990, pp. 33-43. This also suggests a real interest rate of about 3%.

Column 1 represents the annual "Additional Payment." This is \$10,000,000 per quarter (\$40,000,000 per year) if no other producers of levothyroxine sodium are approved, and \$2,500,000 per quarter (\$10,000,000 per year) if one other producer other than Knoll Pharmaceutical is approved. Since it appears that only Jones would have been approved, I allow for a \$10,000,000 annual payment. This does not change annually.

Column 2 is the total revenue that Watson would have earned. This is based on an extrapolation from a report from IMS Health, a market research company whose empirical data and analyses are generally accepted, and are relied upon by the FDA. Sales in 2001 were \$630,000,000. I assume that Watson and Jones would have split 90% of this market, with the rest going to small sellers. On this basis, Watson's sales would be \$283,000,000 in 2001. I also assume a real increase in sales of 13% per year. I do not include any adjustment for inflation or for price changes.

Column 3 represents the royalty payment from Watson to Stevens on the first \$100,000,000 of sales, based on the formula: 15% of the first \$25,000,000, 20% of the next \$25,000,000, and 25% of the next \$50,000,000. The total of these amounts is \$21,250,000, and this does not change annually.

Column 4 is a royalty of 30% on sales above \$100,000,000, from column 2, as specified in the contract.

Column 5 is total revenue each year for Stevens, the sum of columns 1, 3, and 4.

Column 6 is the present value of the entries in column 5. Since I did not allow for any inflation in the earlier calculations, I do not adjust for any inflation here. In computing this column, I have used an interest rate of 3%. The 3% is approximately the historic real rate of interest, and is theoretically preferred.

Column 7 is the cumulative value of the entries in column six. This is the basis for any damage payment. The ten year figure (\$1,345,316,242) is appropriate since there is no reason to expect any major change in the market over that time period.

Paul H. Rubin

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¹ A complete copy of my CV is attached to this report.

Damages to Jerome Stevens Pharmaceuticals, 3% Discount Rate

Year	1. Annual Additional payment	2. Total Revenue, Watson	3. Royalties on Sales below 100,000,000	4. Royalties on Sales above 100,000,000	5. Total Revenue, Stevens	6. Present Value of total revenue, 3% interest rate	7. Cumulative total revenue
1	\$10,000,000.00	\$283,000,000.00	\$21,250,000.00	\$54,900,000.00	\$86,150,000.00	\$86,150,000.00	\$86,150,000.00
2	\$10,000,000.00	\$319,790,000.00	\$21,250,000.00	\$65,937,000.00	\$97,187,000.00	\$94,356,310.68	\$180,506,310.68
3	\$10,000,000.00	\$361,362,700.00	\$21,250,000.00	\$78,408,810.00	\$109,658,810.00	\$103,363,945.71	\$283,870,256.39
4	\$10,000,000.00	\$408,339,851.00	\$21,250,000.00	\$92,501,955.30	\$123,751,955.30	\$113,250,569.72	\$397,120,826.11
5	\$10,000,000.00	\$461,424,031.63	\$21,250,000.00	\$108,427,209.49	\$139,677,209.49	\$124,101,391.52	\$521,222,217.63
6	\$10,000,000.00	\$521,409,155.74	\$21,250,000.00	\$126,422,746.72	\$157,672,746.72	\$136,009,896.38	\$657,232,114.01
7	\$10,000,000.00	\$589,192,345.99	\$21,250,000.00	\$146,757,703.80	\$178,007,703.80	\$149,078,649.50	\$806,310,763.51
8	\$10,000,000.00	\$665,787,350.97	\$21,250,000.00	\$169,736,205.29	\$200,986,205.29	\$163,420,177.42	\$969,730,940.92
9	\$10,000,000.00	\$752,339,706.59	\$21,250,000.00	\$195,701,911.98	\$226,951,911.98	\$179,157,935.06	\$1,148,888,875.99
10	\$10,000,000.00	\$850,143,868.45	\$21,250,000.00	\$225,043,160.53	\$256,293,160.53	\$196,427,366.62	\$1,345,316,242.60
							Total

PAUL H. RUBIN

March 1, 2002

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EDUCATION

- Ph.D., Economics, Purdue University, 1970
- B.A., University of Cincinnati, 1963 (Honors)

PROFESSIONAL EXPERIENCE

ACADEMIC

- Emory University: Professor of Economics and Law beginning 1999; Professor of Economics, 1991-1999; Acting Chair, Economics, 1993-94.
- Adjunct Professor: VPI, 1984; George Washington University Law Center, 1985-89.
- Baruch College and the Graduate Center, CUNY: Professor, 1982-83.
- University of Georgia: Assistant, Associate and Full Professor of Economics, 1968-82.

NONACADEMIC

- Glassman-Oliver Economic Consultants: Vice President, 1987-1991.
- U.S. Consumer Product Safety Commission: Chief Economist, 1985-87 (Senior Executive Service).
- Federal Trade Commission: Director of Advertising Economics, 1983-85.
- President's Council of Economic Advisers: Senior Staff Economist, 1981-82.

ADDITIONAL PROFESSIONAL AFFILIATIONS

- Senior Fellow, Progress and Freedom Foundation.
- Adjunct Scholar: American Enterprise Institute; Georgia Public Policy Foundation; Cato Institute, 1992-1998.
- Editor In Chief: *Managerial and Decision Economics* since 1994.

RESEARCH AND TEACHING AREAS

Law and Economics (Economics Departments, Law Schools, and Practicing Attorneys); Industrial Organization and Antitrust; Transactions Cost Economics; Government and Business (Economics and MBA Students); Public Choice; Economics of Advertising and Safety; Regulation and Cost-Benefit Analysis; Price Theory; Law in Post-Communist Economies; Biological Evolution and Economics.

PROFESSIONAL RECOGNITION

- Over 1400 citations to published work in *Social Science Citation Index*; about 60-75 per year.
 - “Why Is the Common Law Efficient?” *Journal of Legal Studies*, 1977, about 300 citations; Reprinted eight times, in English, Spanish and French.
 - “Self Interest, Ideology and Logrolling in Congressional Voting,” *Journal of Law and Economics*, 1979, with James B. Kau , over 175 citations; reprinted.
 - “The Theory of the Firm and the Structure of the Franchise Contract,” *Journal of Law and Economics*, 1978, over 150 citations; reprinted.
- Listed in *Who's Who in Economics, A Biographical Dictionary of Major Economists*, Second Edition, edited by Mark Blaug, Cambridge: MIT Press, 1986; Third Edition, edited by Simon James and Mark Blaug, Hants, UK: Edgar Elgar Publishing, Limited, 1998. These volumes include the 1000 most cited living and 400 deceased economists. Living economists citations determined from the *Social Sciences Citation Index*.
- Listed in: *Who's Who in America, Who's Who in the World, Who's Who in the East, Who's Who in the South and Southwest, Who's Who in Finance and Industry, Who's Who in Science and Engineering, Dictionary of International Biography; Men of Achievement; Heritage Guide to Public Policy Experts; Cato Policy Experts; FACSNET Economic Experts*.
- Grants and Fellowships: Progress and Freedom Foundation, 2000-2001; Emory University International Travel Fund, 1998; 2000; Emory University Research Committee, 1997; William H. Donner Foundation, 1997-98; Pfizer, 1997; IRIS (University of Maryland, funded by USAID), 1992-93; Paul Oreffice Fund, AEI, 1993; Liberty Fund, 1979; CUNY, 1983.
- Fellow, Public Choice Society
- Testified before Congress three times
- Member, Institute of Justice task force on “Consumer Freedom”
- Asked to write entries for *Encyclopedia of Law and Economics, New Palgrave Dictionary of Economics and the Law*, and *Encyclopedia of Public Choice*.
- Senior lecturer, World Bank Conference on Private Sector Development, Trest, Czech Republic, November 1994.
- First Vice-President, Southern Economics Association, 1994-1996
- Vice-President, Georgia Chapter, National Association of Scholars, 1994-2001.
- Chairman's Award, Consumer Product Safety Commission, 1987.
- *Managing Business Transactions*, 1990; paperback, 1993
 - Reviews: *Journal of Economic Literature*, June, 1992, by David Kaserman, 900-1; *Southern Economic Journal*, July, 1992, by Dwight Lee, 131-132; *Managerial and Decision Economics*, January, 1993, by Gregory Dow, 91-93; *Across the Board*, January, 1991, by Shlomo Maital; *Booklist*, November, 1990; *Journal of Business Communications*, 1993, by Donald P. Rogers, p. 84-85; *Sloan Management Review*, Winter, 1991; *Personal Selling Power*, March, 1991; *Manageris* (French), 1994, by Bernard Sinclair-Desgagne.
 - Several course adoptions; selected by the Executive Book Club.
 - Guest editor, special issue of *Managerial and Decision Economics*, March 1993, stimulated by *Managing Business Transactions*.
- *Tort Reform by Contract*, reviewed, *Journal of Legal Economics*, July 1998, by Thomas Ireland, 96-98.

PUBLICATIONS

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Written:

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2. *Business Firms and the Common Law*, Praeger, 1983
3. *Managing Business Transactions: Controlling the Costs of Coordinating, Communicating, and Decision Making*, Free Press, Foreword by Oliver Williamson, 1990; paperback, 1993.
4. *Tort Reform by Contract*, American Enterprise Institute, 1993.
5. *Promises, Promises: Contracts in Russia and Other Post-Communist Economies*, Shaftesbury Papers (No. 11), Edward Elgar and the Locke Institute, 1998.
6. "Darwinian Politics: The Evolutionary Origins of Freedom," Rutgers University Press, Rutgers Series in Human Evolution, forthcoming, 2002.
7. *Privacy and the Commercial Use of Personal Information*, Kluwer Academic Publishers and Progress and Freedom Foundation, foreword by Senator Orin Hatch, with Thomas Lenard, 2001.

Edited:

1. *Evolutionary Models in Economics and Law*, (Central paper by Jack Hirshleifer), Vol. 4 of *Research in Law and Economics*, 1982.
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OTHER PROFESSIONAL ACTIVITIES

PARTICIPATION IN PROFESSIONAL MEETINGS

- American Association of Law Schools, 1985.
- American Economics Association/Allied Social Science Associations, 1979, 1980, 1981, 1984, 1993, 1994, 1995, 1996, 1997, 1998, 1999.
- American Law and Economics Association, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2001.
- Association for Politics and the Life Sciences, 1999.
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- Econometric Society, 1970, 1971, 1974, 1975, 1977, 1978; European Meetings, 1978.
- European Law and Economics Association, 1993, 2000.
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- Southern Economic Association, 1971, 1976, 1977, 1978, 1979, 1980, 1981, 1984, 1985, 1987, 1991, 1993, 1994, 1995, 1996, 1997, 1998.
- Southern Political Science Association, Invited Panel, 1998.
- Western Economic Association, 1974, 1975, 1984, 1985, 1988, 1996, 1997, 2001.

CONFERENCE ORGANIZED

“Economics of Consumer Protection,” Georgetown University, Continuing Legal Education, 1985.

INVITED PRESENTATIONS, CONFERENCES AND CONGRESSIONAL TESTIMONY

Presentations at Universities

Arizona State University, 2000; Auburn University, 1978, 1996; Berkeley, 1984; Boston University, 1984; Carnegie-Mellon, 1982; Case-Western Reserve University, 1986; CIRANO (Montreal), 1996; City University of New York, Graduate Center, 2001; Clemson University, 1993; Columbia University, 1998; Cornell University, 1998; Duke University, 1981; Emory University, 1981; Florida State University, 1998; George Mason University, 1983, 1985, 1989, 1990, 1992, 1993, 1994, 1995, 1997, 1998; Harvard University, 1993, 1995; Hoover Institution, 1983; Lund University (Sweden), 1992; Montana State University, 1998; McMaster University, 1983; New York University, 1998, 2001; Northwestern University, 2000; Purdue University, 1991; Stanford University, 1995; Texas A & M, 1985; University of California at Los Angeles, 2001; University of Chicago, 1978, 1979; University of Florida, 1989; University of Georgia, 1996; University of Kansas, 1995; University of Miami, 1979; University of Michigan, 1987; University of Pennsylvania, 1993; University of Southern California, 2001; University of Toronto, 1984, 1995; Virginia Polytechnic Institute, 1983; Washington University, 1991, 1993; Western Ontario, 1984; York University, 1984.

Non-Academic Presentations

Federal Trade Commission, 1983; Cato Institute, 1985, 1990, 1991; U.S. Department of Justice, Antitrust Division, 1986, 1988, 1995; National Association of Business Economists, 1988; Brookings Institution, 1986; American Medical Writers-Pharmaceutical Advertising Association, 1986; National Library of Medicine, 1986; American National Standards Institute, 1986; Jefferson Society, 1986; Drug Information Association, 1991; U.S. Commodities Futures Trading Commission, 1991, Distinguished Speaker, 1992; U.S. Chamber of Commerce, Washington, 1991; Milken Institute, 1992; Food and Drug Law Institute, 1992; Institute for International Research, 1992; Heritage Foundation, 1992; American Enterprise Institute, 1992, 1993, 1994, 1995; Coalition of Healthcare Communicators, 1992; Independent Institute, 1993, 1994; Political Economy Research Center, 1994; Ad-Hoc Committee on Pharmaceutical Economics, 1997; Employer's Managed Health Care Association, 1999; Mercatus Center (Capitol Hill), April, 2000; August, 2000; September 2000.

Invited Conference Attendance

Economics of Regulated Utilities, University of Chicago, 1975; Legal Institute for Economists, University of Miami, 1977; Private Alternatives to the Judicial System, University of Miami, 1978; Toward Liberty, VPI, 1978; Evolutionary Theory in Law and Economics, University of Miami, 1980; Guest, Nutter Memorial Lecture, Hoover Institution, 1981; Regulatory Authorities, Corporate Privacy, and the Corporate Attorney, Emory University, 1981; Carnegie Conference on Political Economy, Pittsburgh, 1982, 1983, 1984; Constitutional Economics, Heritage Foundation, 1982; Perspectives on Entrepreneurship, Political Economy Research Center, Denver, 1984; Critical Issues in Tort Law Reform, Yale, 1984; Valuing Health Risks, National Academy of Sciences, 1987; The Calculus of Consent After 20 Years, Santa Cruz, 1988; Political Economy Forum, Political Economy Research Center, Bozeman, Montana, 1990, 1998; Malpractice Reform, American Enterprise Institute, 1992; Health Care Policy and Regulation Workshop, Rutgers, 1994; Franchising, University of Michigan, 1994; Workshop on the Evolution of Utilities and Utility Functions, University College, London, 1997; Evolution and Legal Theory, Georgetown University, 1999; Liberty Fund Conference on "Common Law, Merchant Law, and Democratic Legislation," Berkeley, 2001; Gruter Institute, Squaw Valley, 2001; AEI-Brookings Joint Center for Regulatory Studies, "Constitutional Issues in Information Privacy," 2001.

Congressional Testimony

- Committee on Government Operations, U.S. House of Representatives, "All-Terrain Vehicle Settlement," January 28, 1988.
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- Committee on Energy and Commerce, Subcommittee on Commerce, Trade, and Consumer Protection, "Privacy in the Commercial World," March 1, 2001, available at <http://www.house.gov/commerce/hearings/0301200143/Rubin66.htm>.

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Baruch College, CUNY; Brigham Young University; Cornell University; George Mason University; George Washington University; Florida State University; Pennsylvania State University at Erie; State University of New York at Binghamton; University of Alabama; University of Kansas; University of Southern California; University of Minnesota; Vanderbilt University.

DOCTORAL COMMITTEES CHAIRED:

Susan Griffin, Emory, 1994, (Center for Disease Control); Todd Merolla, Emory, 1995; Kristine Principe, Emory, 1996; Raymond Atkins, Emory, 1998 (J.D., George Mason; Covington and Burling); John Yun, Emory, 1999 (Federal Trade Commission); Kari Jones, Emory, 1999 (University of Georgia); David Prince, 2000 (J.D., University of Michigan; Simpson Thacher & Bartlett); Jin Wang, Emory, 2001, (China Jingtai Securities, Beijing, China); Joanna Mehlhop Shepherd, 2001, (Clemson).

EDITORIAL

Editor-in-Chief

Managerial and Decision Economics, since 1994; editor, Special issue, "Transactions Costs and Management," 1993.

Editorial Boards

Public Choice; Regulation; Journal of Bioeconomics; Journal of Research in Pharmaceutical Economics; Journal of Real Estate Finance and Economics.

Referee

National Science Foundation; Research Council of Canada; *American Economic Review; American Journal of Political Science; American Law and Economics Review; American Political Science Review; Annals of Regional Science; Cato Journal; Contemporary Policy Issues; Eastern Economic Journal; Economic Inquiry; Economic Journal; Economics of Governance; Emory University Law Review; European Journal of Law and Economics; International Regional Science Review; International Review of Law and Economics; Journal of Corporate Finance; Journal of Economic Behavior and Organization; Journal of Economics and Business; Journal of Economics and Finance; Journal of Labor Research; Journal of Law and Economics; Journal of Law, Economics, and Organization; Journal of Legal Studies; Journal of Marketing; Journal of Political Economy; Journal of Public Economics; Journal of Real Estate Finance and Economics; Journal of Social and Biological Structures; Journal of the American Real Estate and Urban Economics Association; Managerial and Decision Economics; National Tax Journal; Politics and the Life Sciences; Public Choice; Public Finance Quarterly; Quarterly Journal of Economics; Review of Regional Studies; Social Science Quarterly; Southern Economic Journal; Marketing and Public Policy Conference, 1995.*

CONSULTING

ANTITRUST, INCLUDING MERGERS AND ACQUISITIONS

Appelton Papers; ARCO; Barclays Bank and Visa; Broadcast Music Inc.; Browning-Ferris Industries; Campbells; Coca-Cola Bottling Company of the Southwest; College Football Association; Columbian Chemical Company; Dresser Industries; First Hawaiian; Georgia-Pacific; General Motors; Juki; Kodak and Fuqua; Levi Strauss; McKesson; National Soft Drink Association; Nederlander; *Newsday*; *Olivetti*; Professional Golfers Association; Real estate industry, market definition; Regional Bell Operating Companies; Roppe; Sara Lee; Scripps; SmithKline-Beckman; Southern Natural Gas; Thomson; United Airlines; West Point Pepperell.

OTHER MATTERS

Alamo Car Rental; Cemex; Ciba-Geigy; Dial Corp; Drug Emporium; Emerson Electric; for Hernando de Soto, on property rights in the informal sector of the Peruvian economy, cited in *The Other Path*; Ford Motor Company; National Propane Gas Association; Pfizer; Physicians Weight Loss; R.J. Reynolds, on advertising matters; Hedonic damages, several cases; U.S. Sentencing Commission; Texans Against Censorship, Inc.

TESTIMONY

- In the U. S. District Court, Eastern District of Texas, on lawyer advertising, for Texans Against Censorship, Inc., 1995.
- For defendants in tort liability litigation, criticizing use of "hedonic" damages.
- For the New York Power Authority, before the Nuclear Regulatory Commission on costs and benefits of the Indian Point Nuclear Reactor, 1983.
- For the Pharmaceutical Manufacturers Association, before the Health Committee of the Georgia Senate, on bills to regulate pharmaceutical prices, 1994; 1995.
- Before the Food and Drug Administration, on direct-to-consumer promotion of pharmaceuticals, sponsored by the Progress and Freedom Foundation, 1995.
- For the State on New Mexico, regarding taxation of franchising, in an administrative proceeding.

AFFIDAVITS FILED

- Airline Antitrust Litigation, regarding the value of the settlement; cited favorably and found "credible" in *Order* of Marvin H. Shoob, Senior U.S. District Court Judge, 1992
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- For Hoechst Celanese Corporation, in the class action regarding polybutylene plumbing, in Chancery Court for Obion County, Tennessee, regarding the fairness of the \$950 million settlement.
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- Folkerts et al. v. Illinois Bell Telephone Company and Todt et al. v. Ameritech, class action suits regarding "inside wire", on the fairness of the settlements. (There are no decision as yet in these matters; I had previously worked on liability and damage issues for plaintiffs.)
- Eller Media v. City of Milwaukee, for Eller Media on the effects of advertising on smoking in First Amendment suit regarding City of Milwaukee ordinance restricting tobacco advertising on billboards. Settled.
- Julian M. Whitaker, M.D. v. Donna E. Shalala, Secretary, regarding first amendment issues in the labeling of Saw Palmetto, a dietary supplement, June 8, 2000

Exhibit 6

This exhibit has not been included in accordance with instructions from the Dockets Management Branch and to avoid risk of unauthorized disclosure. The exhibit contains information protected from disclosure by the Trade Secrets Act, 18 U.S.C.A. § 1905, the Food, Drug and Cosmetic Act, 21 U.S.C.A. § 331(j), FDA's regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4).

Exhibit 7

This exhibit has not been included in accordance with instructions from the Dockets Management Branch and to avoid risk of unauthorized disclosure. The exhibit contains information protected from disclosure by the Trade Secrets Act, 18 U.S.C.A. § 1905, the Food, Drug and Cosmetic Act, 21 U.S.C.A. § 331(j), FDA's regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4).

Exhibit 8

This exhibit has not been included in accordance with instructions from the Dockets Management Branch and to avoid risk of unauthorized disclosure. The exhibit contains information protected from disclosure by the Trade Secrets Act, 18 U.S.C.A. § 1905, the Food, Drug and Cosmetic Act, 21 U.S.C.A. § 331(j), FDA's regulations, 21 C.F.R. §314.430, and the Freedom of Information Act (FOIA), 5 U.S.C. § 552(b)(4).

Exhibit 9

Drug Formulation

Is the composition of each strength tablet similar?

Each strength tablet is proportionally similar in its active and inactive ingredients, but quantitatively different in the amounts of levothyroxine and color additives. The levothyroxine [] is formulated with increasing amounts of levothyroxine sodium, USP, [], for each of the respective tablet strengths. Unithroid® tablets will be packaged in 100 and 1000 count containers for each of the eleven to-be-marketed strengths ranging from 25 mcg to 300 mcg per tablet.

Components and Composition			
Component	Amount Per Tablet	Component	Amount Per Tablet
25 mcg Tablet		125 mcg Tablet	
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Yellow #6 Aluminum Lake	0.0250 mg	Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Yellow #6 Aluminum Lake FD&C Red #40 Aluminum Lake FD&C Blue #1 Aluminum Lake	0.1250 mg
50 mcg Tablet		150 mcg Tablet	
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF	0.0500 mg	Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #2 Aluminum Lake	0.1500 mg
75 mcg Tablet		175 mcg Tablet	
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #2 Aluminum Lake FD&C Red #40 Aluminum Lake	0.0750 mg	Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #1 Aluminum Lake D&C Red #27 Aluminum Lake	0.1750 mg
88 mcg Tablet		200 mcg Tablet	
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Yellow #6 Aluminum Lake FD&C Blue #1 Aluminum Lake	0.0880 mg	Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Red #40 Aluminum Lake	0.2000 mg
100 mcg Tablet		300 mcg Tablet	
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Yellow #6 Aluminum Lake	0.1000 mg	Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Blue #1 Aluminum Lake FD&C Yellow #6 Aluminum Lake	0.3000 mg
112 mcg Tablet			
Levothyroxine [] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Red #27 Aluminum Lake	0.1120 mg		

D&C Red #27 Aluminum Lake	
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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Levothyroxine Sodium

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader

Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)

HFD#510

Review Completion Date: May 24, 2000

Review number: 1

NDA NUMBER: NDA 21-210

Serial number/date/type of submission: Initial NDA/ October 21, 1999

Information to sponsor: Yes (X) No () (class labeling)

Sponsor (or agent): Jerome Stevens Pharmaceuticals, Inc.; 60 DaVinci Drive; Bohemia, NY 11716

DRUG

Generic Name: levothyroxine, sodium tablets, USP

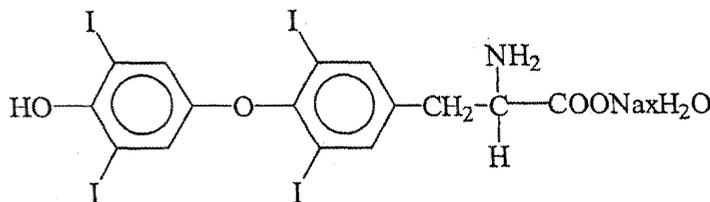
Trade Name: Unithroid® Tablets

Chemical Name: Sodium L-3,3',5,5'-tetraiodothyronine (T₄)

CAS Registry Number: CAS-254-16-65-3 [hydrate]; CAS-55-03-8 [anhydrous]; CAS-51-48-9 [L-thyroxine]

Molecular Formula/ Molecular Weight: C₁₅H₁₀I₄NNaO₄xH₂O; 798.86

Structure:



Relevant INDs/NDAs/DMFs: None cited

Drug Class: synthetic thyroid hormone.

Indication: Replacement therapy for diminished or absent thyroid function.

Clinical formulation: Tablets available as 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 • g Levothyroxine.

Exact formulation varies for each tablet due to amount of Levothyroxine[]. Inactive ingredients include:

Lactose, NF []

Microcrystalline Cellulose, NF []

Sodium Starch Glycolate, NF []

Magnesium Stearate, NF []

Colloidal Silicon dioxide, NF []

Each tablet size contains FD&C or D&C "Lake" dyes to clearly differentiate dosage.

Route of administration: Oral

Proposed clinical protocol or Use: Thyroid hormone replacement therapy. Dose is titrated. Tablets available as 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 • g Levothyroxine.

Previous clinical experience: Extensive clinical use. Currently marketed as Levotheroid Tablets (Forest), Levoxyl Tablets (Jones Medical Industries), Synthroid Injection and Synthroid Tablets (Knoll Pharmaceutical).

INTRODUCTION AND DRUG HISTORY: Levothyroxine has been marketed extensively for many years as both tablets and injection. The indication is for replacement therapy for diminished or absent thyroid function. One problem with currently marketed formulations is a lack of stability and batch to batch reliability. Under FR August 14, 1997 (volume 62, Number 157) it is defined that the current products will be branded as mislabeled in August of 2000 and removed from the market. Thus, there is need for a new NDA submission to provide for a continued source for therapy.

Studies reviewed within this submission: No preclinical data were submitted with this NDA. In pre-NDA discussions, it was indicated that the sponsor need only submit appropriate literature to cover labeling issues in the preclinical sections.

OVERALL SUMMARY AND EVALUATION:

Introduction: Levothyroxine has been marketed extensively for many years as both tablets and injection. The indication is for replacement therapy for diminished or absent thyroid function. For such replacement use with a naturally occurring essential hormone, there is little intrinsic risk. Potential problems may arise with inappropriate dosing. However, the extensive past human experience suggests that proper monitoring can keep this to a minimum.

Safety Evaluation: There are no preclinical safety issues with this product if proper replacement dosing is performed and stability of the product is appropriate.

Conclusions: Pharmacology recommends approval of this product. The Division has proposed that there be a class label for this product and recommendations for the preclinical sections are proposed below.

COMMUNICATION REVIEW:

Labeling Review (NDA):

Since there were no preclinical studies submitted and neither carcinogenicity, mutagenicity fertility nor reproduction studies have been performed, the preclinical sections do not require any specific animal data to be discussed and standard labeling as proposed in 21 CFR 201.57 are appropriate. There are several versions of labels listed in the appendix to this report for products already on the market, all of which are generally acceptable.

There is one issue this reviewer has with the pregnancy category. Some currently marketed versions refer to safety demonstrated in human studies and claim to be a category A. Actually, all currently marketed products list a pregnancy category A whether they refer to human data or not (see appendix for text of currently marketed products). This sponsor has not provided any reference to human data in the pharm/tox section of the NDA. Technically, in order for a product to be given a category A, there must be human data from well-controlled clinical trials. In addition, there are no animal data presented to support a category B (i.e., no findings in animal studies, no human studies performed) as defined by the CFR. With currently available

information, the pregnancy category should technically be category C. This may cause considerable confusion for several reasons:

1. Since long-time past labeling used category A, a switch to category C might imply that the newly approved products are somehow less safe than the currently marketed products when, indeed, they should be safer given stability considerations.
2. Current clinical practice is to maintain dosing of thyroid hormone during pregnancy. Current labeling for all products recommends that there be monitoring to prevent hypothyroidism in pregnant women. Such practice would seem at odds with a category C listing. This reviewer believes it is necessary to include information on current accepted practice in the label.
3. A category C listing might suggest to some patients that they should discontinue dosing during pregnancy. This would not be appropriate according to current clinical practice.

Based on current clinical practice and the above reasons, this reviewer believes that a category A is still appropriate even though this would be at variance with technical definitions listed in the CFR. The synthroid label has a rather extensive and (if supported by data) informative section on treatment during pregnancy. However, in the absence of human data presented by individual sponsors for the new NDA products, a more general approach to labeling is necessary. A class label for thyroid hormones is being developed by the Division. This reviewer recommends that the proposed wording of the class label for thyroxines be presented to the sponsor when it is completed.

RECOMMENDATIONS:

Internal comments: Pharmacology recommends approval of Unithroid• Tablets. The Division has proposed that there be a class label for this product and this should be communicated to the sponsor when it is finalized by the Division.

External Recommendations (to sponsor): Communicate labeling as listed above.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP

PENDIX: CURRENT PRECLINICAL LABELING FOR PRODUCTS LISTED IN THE PDR

Forest Pharmaceuticals Levothyroid tablets:

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY--A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients on thyroid for established indications should not discontinue therapy. No confirmatory long-term studies in animals have been performed to evaluate carcinogenic potential, mutagenicity, or impairment of fertility in either males or females.

PREGNANCY-CATEGORY A--Thyroid hormones do not readily cross the placental barrier. The clinical experience to date does not indicate any adverse effect on fetuses when thyroid

hormones are administered to pregnant women. On the basis of current knowledge, thyroid replacement therapy to hypothyroid women should not be discontinued during pregnancy.

NURSING MOTHERS--Minimal amounts of thyroid hormones are excreted in human milk. Thyroid is not associated with serious adverse reactions and does not have a known tumorigenic potential. However, caution should be exercised when thyroid is administered to a nursing woman.

Jones Medical Industries Levoxyl Tablets:

Carcinogenesis, Mutagenesis, and Impairment of Fertility-- A reportedly apparent association between prolonged thyroid therapy and breast cancer has not been confirmed and patients taking LEVOXYL for established indications should not discontinue therapy. There are no data suggesting that L-T₄ is mutagenic or impairs fertility; such studies in animals over the long term have not been performed.

Pregnancy--Category A-- Thyroid hormones do not readily cross the placental barrier. Clinical experience to date does not indicate any adverse effect on fetuses when thyroid hormones are administered to pregnant women. On the basis of current knowledge, LEVOXYL replacement therapy to hypothyroid women should not be discontinued during pregnancy. During pregnancy, LEVOXYL requirements may increase; dosage should be guided by periodic measurements of serum TSH concentration.

Nursing Mothers-- Some thyroid hormone is excreted in human milk but this is usually insufficient for hypothyroid nursing neonates. L-T₄ taken by nursing mothers is not associated with serious adverse reactions and does not have a known tumorigenic potential; properly indicated LEVOXYL therapy should be continued.

Knoll Pharmaceutical Co. Synthroid (same for tablets and injection)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Although animal studies to determine the mutagenic or carcinogenic potential of thyroid hormones have not been performed, synthetic T₄ is identical to that produced by the human thyroid gland. A reported association between prolonged thyroid hormone therapy and breast cancer has not been confirmed and patients receiving levothyroxine sodium for established indications should not discontinue therapy.

Pregnancy: Pregnancy Category A. Studies in pregnant women have not shown that levothyroxine sodium increases the risk of fetal abnormalities if administered during pregnancy. If levothyroxine sodium is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, levothyroxine sodium should be used during pregnancy only if clearly needed.

Thyroid hormones cross the placental barrier to some extent. T₄ levels in the cord blood of athyroid fetuses have been shown to be about one-third of maternal levels. Nevertheless, maternal-fetal transfer of T₄ may not prevent *in utero* hypothyroidism.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion and preeclampsia, and has been reported to have an adverse effect on fetal and childhood development. On the basis of current knowledge, SYNTHROID® (levothyroxine sodium, USP) should therefore not be discontinued during pregnancy, and hypothyroidism diagnosed during pregnancy should be treated. Studies have shown that during pregnancy T₄ concentrations may decrease and TSH concentrations may increase to values outside normal ranges. Postpartum values are similar to preconception values. Elevations in TSH may occur as early as 4 weeks gestation.

Pregnant women who are maintained on SYNTHROID should have their TSH measured periodically. An elevated TSH should be corrected by an increase in SYNTHROID dose. After pregnancy, the dose can be decreased to the optimal preconception dose.

Nursing Mothers: Minimal amounts of thyroid hormones are excreted in human milk. Thyroid hormones are not associated with serious adverse reactions and do not have known tumorigenic potential. While caution should be exercised when SYNTHROID is administered to a nursing woman, adequate replacement doses of levothyroxine sodium are generally needed to maintain normal lactation.

Exhibit 10



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 26 2001

Mr. Gary D. Dolch
Dr. Melvin K. Spigelman
Mr. Jeffrey A. Staffa
Knoll Pharmaceutical Company
3000 Continental Drive North
Mt. Olive, NJ 07828-1234

Re: Docket No. 97N-0314/CP2

Dear Messrs. Dolch and Staffa and Dr. Spigelman:

This responds to your citizen petition concerning Synthroid dated December 15, 1997, and supplemented on May 29, 1998, November 17, 1999, and December 18, 2000. The agency has relied on trade secret and confidential commercial information belonging to Knoll in preparing its response. This information has been placed in a confidential appendix that will not be placed in the public docket with this letter.

On August 14, 1997, the Food and Drug Administration (FDA) published a *Federal Register* notice announcing that orally administered levothyroxine sodium drug products are new drugs and require approved applications as a condition of marketing (62 FR 43535) (1997 notice).¹ While that notice announced FDA's conclusions about the currently marketed levothyroxine sodium products as a class, it provided that if the manufacturer of a particular orally administered drug product containing levothyroxine sodium contends that the drug product is not subject to the new drug requirements of the Federal Food, Drug, and Cosmetic Act (the Act), this claim should be submitted in the form of a citizen petition under 21 CFR 10.30.

Your petition requests that FDA issue an order determining that Synthroid brand orally administered levothyroxine sodium USP is generally recognized as safe and effective (GRAS/E) for the treatment of hypothyroidism² and for thyroid cancer³ within the meaning of section 201(p) of the Act (21 U.S.C. section 321(p)) and, therefore, not subject to regulation as

¹ The 1997 notice provided that manufacturers who were marketing levothyroxine sodium products on or before August 14, 1997, could continue to market their products without approved applications until August 14, 2000. A subsequent *Federal Register* notice extended this date to August 14, 2001 (65 FR 24488; April 26, 2000).

² Specifically, the petition requests GRAS/E status for Synthroid as "replacement or supplemental therapy in patients of any age or state (including pregnancy) with hypothyroidism of any etiology except transient hypothyroidism during the recovery phase of subacute thyroiditis; primary hypothyroidism resulting from thyroid dysfunction, primary atrophy, or partial or total absence of the thyroid gland, or from the effects of surgery, radiation or drugs, with or without the presence of goiter, including subclinical hypothyroidism; secondary (pituitary) hypothyroidism; and tertiary (hypothalamic) hypothyroidism" (Petition at 1-2).

³ A supplement to the petition dated May 29, 1998, asked FDA to rule that Synthroid is GRAS/E "[a]s a pituitary TSH suppressant in conjunction with surgery and/or radioactive iodine therapy in the management of differentiated (papillary or follicular) carcinoma of the thyroid" (Supplement at 2).

a new drug. You ask FDA to rule that Synthroid may legally be marketed without an approved application. You also ask that FDA waive the requirements of 21 CFR 314.126 for adequate and well-controlled studies to the extent necessary to accept the studies submitted with the petition as substantial evidence of effectiveness. The 1997 notice stated that "no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective" (62 FR 43535 at 43538). You argue that this conclusion "misconceives the applicable law and is factually wrong as to Synthroid" (Petition at 3).

For the reasons discussed below, your petition is denied.

I FDA Has the Authority To Declare Synthroid a New Drug

Under section 201(p) of the Act, a drug product is classified as a new drug unless its manufacturer can show that (1) its composition is such that the drug product is "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" and (2) it has "been used to a material extent" and "for a material time under such conditions." Based on our review of available evidence, you have not satisfied FDA that both of these conditions have been met for Synthroid.

You argue that "section 201(p) of the FDCA [the Act] has to do with general recognition of safety and efficacy, as demonstrated in published studies, not with general recognition of manufacturing quality" (Petition at 3). However, the definition of "new drug" refers to drug products, not active ingredients. Only drug products, not active ingredients, can be evaluated under "the conditions of use . . . suggested in the labeling" as the statute requires. Moreover, there is nothing in the statutory definition of "new drug" at section 201(p) of the Act that limits FDA's legitimate areas of inquiry to only certain kinds of information about a drug product's safety or effectiveness. Rather, as the Supreme Court held in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973), "the reach of scientific inquiry under both § 505(d) and § 201(p) is precisely the same." Just as § 505(d)(3) requires FDA to refuse to approve an application where "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity," so too can inadequate manufacturing and controls defeat a drug's GRAS/E status. Even if an active ingredient has been previously approved as safe and effective in another drug product, a drug product is considered a "new drug" if the particular formulation of active and inactive ingredients has not previously been approved or has not been found to be GRAS/E. See *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983) (holding that "new drug" refers to a finished drug product, not an active ingredient). Your suggestion

that FDA is limited in determining if a drug product is a "new drug" to consulting published studies for evidence of safety or effectiveness has no basis in law and is contrary to the broad remedial purposes of the Act. The definition of "new drug" must be liberally construed in order to effectuate the policy of the statute, which is the protection of public health and safety (*United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). Furthermore, "Congress' exclusion of 'generally recognized' drug products from the definition of a 'new drug' is a very narrow one . . ." (*Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795, 802-803 (2d Cir. 1980)). See also "Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications" (65 FR 12999, 13002; March 10, 2000) (Congress recognized that PET drugs are new drugs because variations in manufacturing procedures can significantly affect identity, strength, quality, and purity).

You argue that "while FDA has ample authority to deal with stability, potency, and other manufacturing issues under other sections of the Act, including section 501 and regulations issued pursuant thereto, it lacks authority to import these issues into the definition of 'new drug'" (Petition at 3). This argument implies that because the FDA could bring an action under the adulteration provision of the Act, and has in the past dealt with deficiencies in current good manufacturing practice for levothyroxine sodium products as a compliance matter, it is precluded from bringing an action under the Act's new drug provisions. To the contrary, FDA is not required to choose between finding current good manufacturing practice violations and finding that a drug is a "new drug" that requires an approved application to be legally marketed. As the court in *United States v. Baxter Healthcare Corp.*, 901 F.2d 1401 (1990) stated:

Much of Baxter's argument appears to rest on the inaccurate view that the courts may not allow federal agencies to use more rigorous methods of enforcement of a statutory scheme when less rigorous methods would also be allowable under the statute. The fact that some of FDA's goals could be accomplished through the enforcement of "good manufacturing practices" standards does not mean that the FDA may not use its authority under Section 507(a) [now section 505] (901 F.2d at 1409)

See also *United States v. Premo Pharmaceutical Labs, Inc.*, 511 F. Supp. 958, 976 (D.N.J. 1981) (holding that postmarketing enforcement tools are not an adequate substitute for the drug application review process in protecting public health).

Moreover, FDA's regulations make clear that a contention that a drug product is GRAS/E under section 201(p) must be "supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application" (21 CFR 314.200(e)(1)). Given this provision, just as a drug product application must be supported by

data showing consistency, potency, and stability, so must a contention that a drug product is GRAS/E. See 21 U.S.C. 505(d)(3); 21 CFR 314.125(b)(1) (authorizing FDA to refuse to approve an application where methods of manufacture, facilities and controls are inadequate to preserve identity, strength, quality and purity).

The fact that the Agency issued its notice on a class-wide basis does not change the fact that it is a particular formulation, not an active ingredient, for which an approved application or a GRAS/E showing is required. FDA's notice stated the Agency's willingness to rely on published literature in place of clinical studies performed by the sponsor to support one requirement for approval, but did not indicate that published literature alone would be sufficient to support a finding that any particular product is safe and effective under the conditions of use prescribed in its labeling. To the contrary, because the potency and stability problem with levothyroxine sodium was found to be class-wide, the Agency adopted a procedure that addresses the problem on a class basis by declaring that all oral levothyroxine sodium drug products are new drugs that require approved applications to be legally marketed. FDA's class-wide approach, however, does not give companies license to establish the safety and effectiveness of their drug products by showing the safety and effectiveness of the active ingredient alone. Applications are approved for drug products, not for drug ingredients. A company seeking to show that a drug product is GRAS/E cannot rely solely on literature establishing the safety or effectiveness of its active ingredient. It must show that its *product* as currently formulated is GRAS/E for the labeled indication. Given the documented history of potency and stability problems, and the dangers of under- and over-dosing, a GRAS/E showing for a levothyroxine sodium product would necessarily include a showing of consistent potency and stability. As discussed above, FDA has ample authority under the Act to take this approach.

II. Synthroid Cannot Be Generally Recognized as Safe and Effective Because It Is of No Fixed Composition

Although FDA has documented potency and stability problems for marketed levothyroxine sodium products as a class, the difficulties in finding Synthroid to be GRAS/E are compounded by the fact that its formula has been changed numerous times throughout its marketing history. A new drug is defined as a drug "the *composition* of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof" or which, if so recognized "has not . . . been used to a material extent or for a material time" (21 U.S.C. 321(p) (*Emphasis added*)). To be generally recognized as safe and effective, there must be *some* consistent drug product for experts to recognize. In the case of Synthroid, there is no such consistent product because the composition of Synthroid has been changed repeatedly.

Synthroid tablets have been manufactured using an overage⁴ of the active ingredient that has ranged in size over the last 35 years. In addition to overage changes, FDA is aware of several other changes made to the composition of Synthroid since 1981.⁵

- Synthroid was reformulated in 1981.
- In 1983, an excipient was added to the 50 microgram (mcg) tablet.
- In February 1989, the dye for the 112 mcg tablet was changed.
- In August 1989, dyes for the 100 mcg tablet and the 300 mcg tablet were changed.
- In 1991, an excipient was removed from the 50 mcg tablet.

In support of its characterization of Synthroid as the "quintessential 'old drug,'" the petition states that "the current Synthroid formulation has been *fundamentally* unchanged since 1982"⁶ (Petition at 13, *emphasis added*). However, two formulations that are only basically the same are not the same drug product. "[T]he composition of the drug *is* relevant to the determination of new drug status. It is the particular composition of the drug which must be generally recognized as safe and effective in order to take the drug out of the statute" (*United States v. An Article of Drug . . . Atropine Sulfate*, No. CA3-85-1662-R (N.D. Texas, 1987), *aff'd*, 843 F.2d 860 (5th Cir. 1988)). Studies conducted on an old formulation have been held to be "an inadequate basis for drawing conclusions" about a subsequent formulation (*United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409, 414 (3rd Cir. 1989)). For this reason, FDA regulations specify: "For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigations" (21 CFR 314.126(d)). Because the formulation of Synthroid has been repeatedly changed, the published literature

⁴ An overage is the amount of active ingredient above 100% of the product's labeled potency at the time the finished product is tested for release. Such an overage is intended to compensate for potential loss of active ingredient by degradation while the product is stored and thus permit an extended shelf life for a product with a poor stability profile.

⁵ These are the changes the Agency is aware of through inspections and from documents submitted by the manufacturer. Because manufacturers of products marketed without approved applications are not required to seek permission to make formulation changes, there may be additional changes which have not been disclosed to the Agency.

⁶ The petition also states that "[t]he only formulation change made [between 1982 and December 15, 1997] was the temporary replacement in one Synthroid strength of one of the excipients removed as part of the 1982 reformulation; that excipient was again removed in 1991" (Petition footnote 94).

submitted in support of Knoll's petition is an inadequate basis to draw conclusions about the potency and stability of its existing formulation. It should also be noted that had Knoll been marketing Synthroid under an NDA, it would have been required to obtain preapproval from FDA before making formulation changes (see 21 U.S.C. § 356a as implemented in the guidance for industry on *Changes to an Approved NDA or ANDA* (November 1999)). FDA has cited manufacturers of approved products for marketing an unapproved new drug when they make changes that require FDA preapproval without having obtained such preapproval.⁷ If an approved product becomes an unapproved new drug under these circumstances, then certainly the changes that have been made to Synthroid reinforce its "new drug" status. Only a drug product of a precise composition is approved in an NDA. Similarly, it can only be a drug product of a precise composition about which there might be general recognition of safety and effectiveness. See generally *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983) (differences in excipients may affect the safety and effectiveness of drug products; a product (not merely its active ingredient) is a new drug until the product no longer meets the definition of new drug).

III. Synthroid Has a History of Problems

You assert that Synthroid has a "long history of careful and consistent manufacture, resulting in a reliably stable and potent levothyroxine sodium drug" (Petition at 3). In fact, Synthroid has a long history of manufacturing problems as discussed below. In August 1989, Knoll⁸ initiated a recall of 21 lots of Synthroid tablets in unit dose packaging because of a decrease in potency during stability studies.

In February 1991, 26 lots of Synthroid tablets packaged in hospital unit dose blister packs in strengths of 50, 75, 100, 112, 125, 150, 200, and 300 mcg were recalled because of subpotency. In an April 1991 inspection of the Synthroid manufacturing facility, FDA cited the firm for two deviations from current good manufacturing practices: inadequate validation of a blender and failure to monitor adequately the humidity and temperature in the manufacturing area. The inspector recorded the following observation on the FDA Form 483 issued to the firm:

"The humidity and temperature in the firm's manufacturing area are not monitored at a continuous basis. A drum with a subplot product . . . waiting to be mixed in the [name] mixer was observed uncovered and the product exposed to the ambient. Also the [described] blender with various sublots products, but not all the sublots required for

⁷ See, e.g., Warning Letter to Elder Pharmaceuticals from FDA's Cincinnati District, August 21, 1991.

⁸ Knoll acquired Synthroid from Boots Company PLC in 1995. Petition at 7. To avoid confusion, we refer to Knoll as the manufacturer of Synthroid regardless of the time period being discussed.

the blending step, was observed opened causing long exposure of the product to the ambient."

This inspection also revealed consumer complaints that Synthroid tablets lacked therapeutic effect. Synthroid tablets were recalled again in June 1991. Fifteen lots of Synthroid tablets in 100 and 1,000 tablet bottles in strengths of 25, 50, and 75 mcg were recalled because the lots were found to be subpotent during stability studies or their potency could not be assured through the expiration date.

FDA inspected the Synthroid facility again from October through December, 1992, because the Agency had observed an increase in the frequency of complaints concerning Synthroid. Knoll received 27 complaints in 1991 and 33 complaints in 1992 questioning the potency of Synthroid tablets. FDA's inspection recorded nine observations of failure to follow current good manufacturing practices, briefly summarized below. Knoll lacked adequate production and process control procedures to ensure batch-to-batch uniformity and homogeneity of Synthroid 25, 50, 75, and 100 mcg tablets. FDA also found that the firm had continued to manufacture and distribute low dosage Synthroid tablets during 1990, 1991, and 1992. The firm had failed to identify the causes for the stability failures that resulted in the recall of 21 lots of Synthroid tablets in August 1989, 26 lots in February 1991, and 13 lots in June 1991. The firm had failed to identify the causes for the potency or content uniformity failure of 46 lots of Synthroid tablets manufactured from 1990 through 1992 that it destroyed. The firm had failed to properly investigate in-process failures. The firm had failed to conduct adequate stability studies. The firm had not validated a variety of changes to the formulation and manufacturing processes for Synthroid.

In January 1994, FDA inspected the Shreveport, Louisiana, facility where stability testing of Synthroid was conducted and found that Knoll failed to assay some lots of Synthroid for stability at the interval required by the firm's protocol. In November 1998, Knoll recalled 18 lots of Synthroid tablets in 88, 100, 150, 175 mcg strengths because potency could not be assured through the expiration date.

The history of potency failures discussed above indicates that Synthroid has not been reliably potent and stable. Furthermore, Knoll's use of an overage that has not remained consistent over the years suggests that Synthroid has stability, potency, and consistency problems. Although you claim that Synthroid has been carefully manufactured, the violations of current good manufacturing practices discussed above indicate that Knoll has not always manufactured Synthroid in accordance with current standards for pharmaceutical manufacturing.

IV. Patients Need a Precise Dose of Levothyroxine Sodium

The effect of changes to Synthroid's formulation and Knoll's distribution of low potency

tablets is that patients taking Synthroid have experienced significant, unintended variations in their doses of levothyroxine sodium. As discussed below, these variations are not conducive to proper control of hypothyroidism.

Levothyroxine sodium is used as replacement therapy when endogenous thyroid hormone production is deficient or absent. The goal of thyroid replacement therapy is to replace the same amount of thyroid hormone that would have been present naturally. This amount differs from patient to patient. When a patient is newly diagnosed as needing replacement hormone, he or she is given an initial estimated dosage. In most patients, the response to treatment is assessed by the measurement of serum levels of thyroid stimulating hormone (TSH). The dosage of replacement therapy is increased in gradual increments until the TSH test indicates the correct maintenance dosage has been achieved. In order to allow for fine adjustments of dose, which are necessary due to levothyroxine sodium's narrow therapeutic range, levothyroxine sodium products are marketed in an unusually large number of dosage strengths. Synthroid, for example, comes in 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg strengths.

Superpotent tablets of levothyroxine sodium pose safety risks. Patients who inadvertently receive more levothyroxine than is necessary to control their condition may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can contribute to osteoporosis. Subpotent tablets of levothyroxine sodium are not adequately effective and, therefore, also pose safety risks. Patients inadvertently receiving less than their proper dose may experience such symptoms as fatigue, lethargy, sleepiness, mental impairment, depression, cold intolerance, hair loss, hoarseness, weight gain, constipation, decreased appetite, dry skin, increased perspiration, arthralgia, menstrual disturbances, and paresthesias. Because of the serious consequences of too much or too little circulating thyroxine, it is very important that patients receive the dose of levothyroxine sodium determined by their physicians to be optimal to replace the amount of hormone that would have been present naturally.⁹

The physician's reliance on the results of a TSH test to establish the optimal amount of replacement therapy is undercut when patients do not get the correct dose when filling and refilling their carefully calculated prescriptions. When patients receive tablets that are filled with a product of unpredictable potency, therapy with levothyroxine sodium is neither safe nor effective. Hypothyroidism is a chronic condition, and therefore patients may take Synthroid for many years. If Synthroid continues to be marketed without an approved application, patients may be subject to future formulation changes that could affect the bioavailability of the product without notice or prior FDA approval.

⁹ The December 15, 1997, Petition itself states: "The availability of multiple dosage strengths and sensitive TSH assays enable physicians to monitor thyroid status with sufficient precision and accuracy to permit fine titration of replacement doses while minimizing the potential for thyrotoxicity" (Petition at 21, footnote 67).

Docket No. 97N-0314/CP2

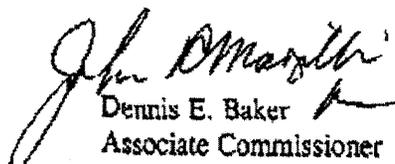
V. The Evidence Submitted with the Petition Does Not Demonstrate that Synthroid Is Generally Recognized as Safe and Effective

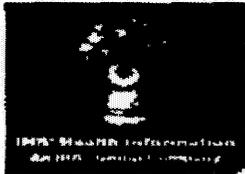
You present published studies and testimony from experts to demonstrate that Synthroid is generally recognized on the basis of these studies as safe and effective for the treatment of hypothyroidism and thyroid cancer. This evidence fails to address the potency and stability problems that impair the safety and effectiveness of Synthroid and does not address how changes in Synthroid's formulation undercut a finding that the marketed drug product (as currently formulated) has been marketed to a material extent and for a material time. Therefore, it does not establish that Synthroid is generally recognized as safe and effective. Given that manufacturing issues preclude a finding that Synthroid is generally recognized as safe and effective, FDA does not need to rule on your request to waive the requirements for adequate and well-controlled studies in making a GRAS/E finding.

VI. Conclusion

For the reasons discussed above, your request that FDA issue an order determining that Synthroid is generally recognized as safe and effective for the treatment of hypothyroidism and thyroid cancer is denied. FDA concludes that Synthroid is a new drug within the meaning of section 201(p) of the Act. It is, therefore, subject to section 505 of the Act and must comply with the provisions of the August 14, 1997, *Federal Register* notice, as amended in the *Federal Register* of April 26, 2000 (65 FR 24488).

Sincerely yours,

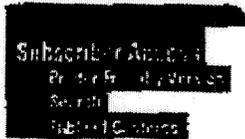

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs



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WARN 08/20/91 ELDER PHARMACEUTICALS, AND S.P.I. PHARMACEUTICALS, INC.



1141 Central Parkway
Cincinnati, OH 45202

August 20, 1991

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

**WARNING LETTER
CIN-WL-91-678**

Adam Jerney, President
Elder Pharmaceuticals, and S.P.I. Pharmaceuticals, Inc.
ICM Plaza
3300 Hyland Avenue
Costa Mesa, California 92626

Dear Mr. Jerney:

The Food and Drug Administration has completed the review of the inspectional findings from the inspections of April 4, 8 and May 6, 1991 and on June 28 through July 23, 1991. We have additionally evaluated the August 6, 1991 response to our inspections, provided by Stephen J. Goldner, Acting Vice-President, Regulatory Affairs.

Mr. Goldner stated that the following information will be submitted to the FDA:

1. Data from historical finished product batch demonstrating product integrity (Benoquin Cream), in the absence of
2. A current bill of material specifying the amount of added to account for manufacturing process losses.
3. Documentation for improved manufacturing instructions for providing increased specificity in the stepwise process.
4. A copy of the manufacturing instructions that specify mixer type, the size and number of propellers and the speed range setting.
5. A bill-of-material specifying quantities of components, manufacturing instructions specifying equipment, and validation data to justify the

Exhibit 11

November 17, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Compliance Date for Approved New Drug Applications for Orally Administered
Levothyroxine Sodium Drug Products; Docket No. 97N-0314

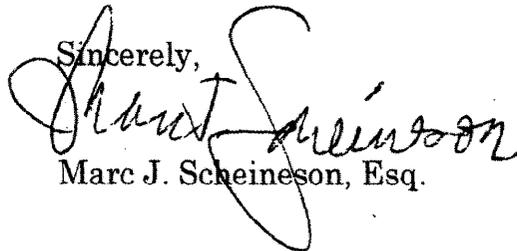
Dear Sir or Madam:

Attached please find a citizen's petition filed on behalf of our client, Jerome Stevens Pharmaceuticals, Inc. (JSP). This petition requests that the Food and Drug Administration (FDA) refuse to extend any further the deadline for manufacturers of orally administered levothyroxine sodium drug products to obtain approved new drug applications (NDAs) as a condition for continuing to market the synthetic thyroid drug. That deadline has already been extended one full year to its current date of August 14, 2001. JSP properly filed an NDA based on the prior deadline of August 14, 2000. That NDA was approved by FDA on August 21, 2000. Therefore, there is already a FDA-approved synthetic thyroid drug on the market. JSP has the manufacturing capacity to satisfy all current demand. It faithfully complied with FDA's request for data. Therefore, others who resisted this requirement should not benefit further, to the prejudice of JSP, through any additional delay in the date an approved NDA must be in place.

We appreciate your accepting this petition for filing, and your properly considering it as part of the administrative record pursuant to 21 C.F.R. § 10.30.

Please contact me at (202) 414-9243 with your response, of if we may be of further assistance.

Sincerely,



Marc J. Scheineson, Esq.

cc: Ms. Christine F. Rogers
Mr. Ronald Steinlauf

1301 K Street, N.W. Delaware
Suite 1100 - East Tower New Jersey
Washington, D.C. 20005 New York
202.414.9200 Pennsylvania
202.414.9299 Virginia
Washington, DC

November 17, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Compliance Date for Approved New Drug Applications for Orally Administered
Levothyroxine Sodium Drug Products; Docket No. 97N-0314

Dear Sir or Madam:

The undersigned respectfully submits this petition on behalf of our client, Jerome Stevens Pharmaceuticals, Inc. (JSP), under the Federal Food, Drug, and Cosmetic Act (FDCA). We request that the Food and Drug Administration (FDA) refuse to extend any further the deadline for manufacturers of orally administered levothyroxine sodium (LS) synthetic thyroid drug products to obtain approved new drug applications (NDAs) as a condition for continuing to market the drug. That deadline has already been extended by one full year to its current date of August 14, 2001.

JSP is a manufacturer of LS. In reliance on the previous FDA regulation requiring NDA submission and approval by August 14, 2000, JSP prepared and submitted a NDA for LS on October 19, 1999 which was approved by FDA on August 21, 2000. JSP has sufficient manufacturing capacity to satisfy demand for the product in the United States if other companies fail to satisfy their regulatory responsibilities.

A. Action Requested

For the reasons stated below, JSP and the undersigned respectfully request that FDA refuse to extend any further the deadline for manufacturers of orally administered LS drug products to obtain approved new drug applications (NDAs) as a condition for continuing to market the drug. That deadline has already been extended by one full year to its current date of August 14, 2001.

B. Statement of Grounds

The current deadline of August 14, 2001 for manufacturers of orally administered LS drug products to obtain approval of their NDAs is itself a significant extension from the initial deadline of August 14, 2000. In light of the concern properly identified by FDA with regard to the potency and stability of orally administered LS drug products, further delay of the deadline would allow potentially unsafe and ineffective products to remain on the market. This situation would create a potential, and unnecessary, risk to public health. With the recent approval of a NDA for JSP's LS product, UNITHROID, there now exists a properly registered and inspected product available to patients in the United States. No medical justification exists to permit unproven products to remain on the

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market. It would also be unfair to JSP, prescribing physicians and consumers to change the rules to which at least one company was required to faithfully comply.

1. Regulatory Background

Orally administered LS is used as a replacement therapy in conditions characterized by diminished or absent thyroid function, such as cretinism, myxedema, nontoxic goiter, or hypothyroidism.

Levothyroxine sodium was first introduced into the market as a prescription drug before 1962, without an approved NDA, in the belief that it was not a "new drug" as defined by the FDCA. The current regulatory requirements for obtaining new drug approval prior to marketing were implemented in 1962. On August 14, 1997, FDA announced in a *Federal Register* Notice that, as part of its program for Drug Efficacy Study Implementation (DESI), LS must comply with the NDA approval requirements. 62 *Fed. Reg.* 43535 (Aug. 14, 1997).

FDA stated in the Notice that it required manufacturers of LS products to file NDAs due to concerns over potential inconsistencies in the potency and bioavailability of the products' active ingredient. Specifically, FDA noted that thyroid replacement therapy is a lifelong endeavor, requiring individualized, patient-specific dosing. Physicians prescribe a low initial dose, and gradually increase it until clinical evaluation and laboratory testing indicate that an optimal dose has been achieved. Once a patient's dose has been established for an existing product, varying potency or bioavailability of that product, or any other, raises substantial risks. If the drug product is of lesser potency or bioavailability, a suboptimal response and hypothyroidism could result. If the drug product is of greater potency or bioavailability, toxic manifestations of hyperthyroidism could result (e.g., cardiac pain, palpitations, or cardiac arrhythmias).

In light of these expressed concerns, FDA stated that, "it is critical that patients have available to them products that are consistent in potency and bioavailability." The Notice described reported incidents of adverse events due to subpotent or superpotent LS products. It also referenced concerns over changes in product formulations that were not reviewed by FDA, that resulted in unexpected increased potency. Moreover, it noted that LS is unstable in the presence of light, temperature, air, and humidity. FDA cited numerous instances of inadequate stability testing which resulted in uneven product potency and unreliable expiration dates.

FDA concluded properly that none of the orally administered LS products then on the market had been shown to demonstrate consistent potency and stability. They could not be considered generally recognized as safe and effective in the Agency's view. LS was, therefore, deemed a new drug under section 201(p) of the FDCA. Manufacturers were required to submit NDAs, or file citizen petitions evaluating the issue of whether their products were subject to the new drug requirements of the FDCA.

~~Despite its concern over the potential safety risks presented by LS products, FDA recognized that they were medically necessary to treat hypothyroidism, and that no alternative therapy was available as an adequate substitute in the event that the drug was removed from the market because no company had a FDA approved NDA. Accordingly, it did not implement the new NDA requirement immediately. It gave manufacturers 3 years -- until August 14, 2000 -- to file and obtain approval of NDAs.~~

On April 26, 2000, FDA published a notice in the *Federal Register* extending the deadline for filing and obtaining approval of NDAs by one additional year to August 14, 2001. 65 *Fed. Reg.* 24488 (April 26, 2000). The basis for the extension was to allow manufacturers additional time to conduct clinical studies and prepare NDA applications. The additional time, in FDA's view, insured that the supply of this medically necessary product would not be disrupted.

2. JSP Has Complied With FDA's Notice and Obtained NDA Approval

In response to FDA's August 14, 1997 *Federal Register* notice, JSP generated and/or gathered the data required to comply with FDA's requirements for the filing of NDAs. On October 19, 1999, JSP submitted an NDA for its product -- NDA 21-210. At the same time, the Company expanded its production capabilities to produce sufficient product to accommodate the total domestic market demand for its product. JSP's NDA was approved on August 22, 2000. FDA approval followed a full pre-approval inspection of JSP's manufacturing facilities to insure compliance with current good manufacturing practices (GMPs).

3. Further Extension of the Deadline is Unnecessary in Light of the Availability of NDA-Approved Product

In light of the availability of orally administered LS with an approved NDA and approved GMP-compliant manufacturing facilities, the basis for extending the deadline again for manufacturers to file and obtain NDA approval no longer applies. There is now available to consumers a LS product proven safe and effective, with consistent potency and bioavailability -- JSP's UNITHROID. Indeed, UNITHROID is the only FDA-approved LS product currently on the American market. The concern that thyroid patients would lose a medically necessary treatment if FDA enforced the NDA requirement no longer applies. FDA's recent extension of the deadline for manufacturers to obtain approved NDAs for orally administered LS, despite providing three year for manufacturers to comply, resulted in an anomaly in the marketplace. A drug product with NDA approval must now compete with products that have not undergone the same required regulatory review. FDA should not expand this inequity and risk to public health by extending a delay in NDA approval now that a compliant product is on the market.

On August 14, 2001, no patient will have to go without an orally administered LS product as the result of other manufacturers' inability to meet the four-year deadline for regulatory approval. Even in the unlikely event that all of the other LS manufacturers were forced to withdraw their products from the market at that time, JSP's UNITHROID would be available to patients with hypothyroidism. As noted above, JSP has increased its production capacity since filing the NDA, and would be able to meet the market demand should the need arise.

In the interest of public health, JSP has undertaken the effort and expense of complying with FDA's notice by the initial deadline. A number of other manufacturers have not yet done so, but may continue to market their products, despite the potential health risks that FDA has identified. To extend the deadline once again when an NDA-approved product is now available, after four years granted by FDA to other manufacturers to come into regulatory compliance, would only perpetuate the risks to public health that FDA has identified and be grossly unfair to compliant manufacturers like JSP. With an NDA-approved product now available, there is no longer any public health rationale for doing so.

Dockets Management Branch
November 17, 2000
Page 4

Finally, FDA is under firm authority to determine that for reasons connected with the potency and variability from lot-to-lot, the LS is not generally recognized as safe (GRAS) within the meaning of §201(p) of the FDCA. The Agency employed proper procedure pursuant to promulgated regulations under 21 CFR §314.200(e) to consider claims that particular manufacturers make LS that is GRAS. These claims require clinical data similar to the data required to compile an NDA in this circumstance. While citizens petitions have reportedly been filed on behalf of at least one manufacturer contending that LS is GRAS, FDA is within its express statutory and regulatory authority to grant or deny such petitions. Certainly FDA's review of the petition(s) and decision can be made quickly so that the petitioner(s) can determine, in the event of a denial, whether to submit an NDA, or withdraw the product from the market. No delay in the August 14, 2001 date should be necessary as a result of the filing of these petitions.

C. Environmental Impact

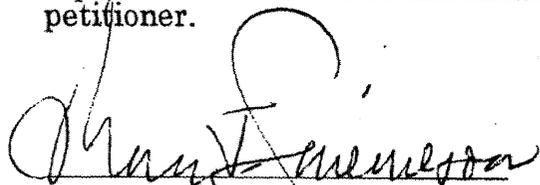
The undersigned claims a categorical exclusion from preparation of an environmental assessment or environmental impact statement under 21 C.F.R. § 25.30.

D. Economic Impact

No information on economic impact has been requested at this time.

E. Certification

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petitioner.



Marc J. Schemeson, Esq.
Regulatory Counsel to Jerome Stevens Pharmaceuticals, Inc.
Reed Smith, LLP
1301 K Street, NW
Washington, DC 20005

cc: Ms. Christine F. Rogers
Mr. Ronald J. Steinlauf

Exhibit 12

January 19, 2000

VIA TELEFAX (301-594-0183)
(Original Sent By Regular Mail)

Ms. Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Room 6027 (HFD-5)
Rockville, MD 20852

Re: Preapproval to Market Levothyroxine Sodium

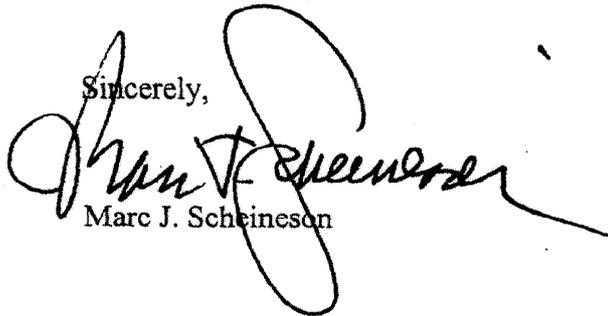
Dear Ms. Axelrad:

We respectfully request a brief meeting with you and my client Jerome Stevens Pharmaceuticals (JSP). The distributor, Watson Pharmaceuticals, would also like to join the meeting. As you know, JSP manufactures levothyroxine sodium under the trade name Unithyroid. This drug is an older product that has been marketed prior to 1962. At FDA's request, JSP prepared and submitted a new drug application (NDA) to continue to market the drug. The NDA was approved on August 21, 2000. The deadline for submitting a NDA for others which failed to comply with FDA's deadline has been extended to August 14, 2001. Reports indicate that FDA may be considering a further extension. JSP seeks the opportunity to review its regulatory history with you and to discuss the need, rationale and fairness for such an additional extension.

Please indicate a time during the next couple of weeks when you and the appropriate policy, legal and review staff might be available to meet and discuss this and related matters. JSP and I appreciate the opportunity to interact with the agency, and your interest and assistance in this regard.

Best regards.

Sincerely,



Marc J. Scheineson

cc: Ronald J. Steinlauf, Esq.

1301 K Street, N.W.
Suite 1100 - East Tower
Washington, D.C. 20005-3373
202.414.9200
Fax 202.414.9299

Delaware
New Jersey
New York
Pennsylvania
Virginia
Washington, DC

Exhibit 13

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 26, 2001

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: *For* C. T. Viswanathan, Ph.D. / S / 3/26/01
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-301, Levoxil®
(levothyroxine sodium), sponsored by Jones
Pharmaceuticals

TO: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug
Products (HFD-510)

As requested by HFD-510, the Division of Scientific Investigations initiated an audit of the analytical portions of the following bioequivalence studies.

Study 338-03: "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine"

Study 338-04: "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Three Strengths of Levothyroxine (Levoxyl)"

The site of the analytical portions of the studies was _____ (now _____). The clinical portion of study #338-03 was conducted at _____ and the clinical portion of study #338-04 was conducted at _____. The inspection was limited to the analytical portion, as requested by HFD-510.

Following the analytical site inspection (2/26-3/2/2001), Form FDA-483 was issued. Our evaluation of the inspectional findings is provided below.

APPEARS THIS WAY
ON ORIGINAL

- 1a. Reserve samples for Jones Pharma levothyroxine study #338-04/20655 were returned to the manufacturer and therefore were not available to FDA for sampling at this clinical site
- 1b. Reserve samples for Jones Pharma levothyroxine study #338-03/20646 were not selected and retained at the clinical site

Although the inspection was intended to cover only the analytical portions of the studies, the discussion of reserve sample retention was noticed during a review of correspondence files. The failure to retain reserve samples at the clinical sites is a violation of 21 CFR 320.38(b)(3). Thus, the identity of the test and reference drug products used in the studies cannot be verified. However, please note that DSI has not examined comparable records of clinical portions of bioequivalence studies for other levothyroxine NDAs.

2. Software Problem Report #15192 was written in response to a user-reported error in regression calculation in study 338-04/20655-2 dated 3/2/2000. To date, there has been no final conclusion, resolution, correction, or evaluation of this error report. The extent and impact on data generated by the affected program, _____ has not been determined.
3. The information systems standard operating procedures for software problem reporting are inadequate in that:
 - a) Software problems are not resolved in a timely manner.
 - b) Software problem report summaries are not reviewed on a periodic basic.

_____ calibration curves were fitted with a computer program _____ written for _____ by a consultant. Calibration data from one run caused the program to abort. The failure could be reproduced on _____ at _____ but not at the consultant's site. Thus, the software failure is unique to the _____ installation. As of this writing, _____ has not determined the cause of the failure. Therefore, the extent of its impact on other data in these studies is unknown.

APPEARS THIS WAY
ON ORIGINAL

Page 3 - David G. Orloff, M.D.

Conclusion:

We recommend that the data from Studies #338-03 and 338-04 be not accepted unless and until it is shown that software failure did not affect other data.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

/S/

Michael F. Skelly, Ph.D.

DSI Final Classification:

VAI - (These studies only.)

APPEARS THIS WAY
ON ORIGINAL

Exhibit B



**American Association of
Clinical Endocrinologists**
The Voice of Clinical Endocrinology

Quick Search
AACEOnline



- Organization
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- The College

Thyroid Awareness Month: 2002

- [TAM Home](#)
- [Neck Check](#)
- [Editorial Background](#)
- [Case Study](#)
- [Gail Devers](#)
- [Facts](#)

FACTS ABOUT THYROID DISEASE

Who Has Thyroid Disease?



United We Stand

- Members
- Contact
- Home

- An estimated 13 million Americans have thyroid disorders, but more than half still remain undiagnosed.¹
- Approximately 1 out of every 8 women will develop a thyroid disorder in her lifetime.²
- Women are 5 to 8 times more likely than men to suffer from a thyroid condition.³
- Although thyroid disease can strike at any time, the elderly are more likely to suffer from hypothyroidism. By age 60, as many as 17 percent of women have an underactive thyroid.⁴

What Are The Genetic Links In Thyroid Disease?

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- Fifty percent of thyroid disease patients' offspring will inherit the thyroid disease gene.⁵
- Fifteen to 20 percent of diabetics and their siblings or parents are at a greater risk of presenting with thyroid disease compared to 4.5 percent of the general population.⁶
- In a large series of American patients with pernicious anemia, nearly half (48.3%) had laboratory test evidence of thyroid disease.⁷
- The overall prevalence of pernicious anemia among children, siblings, parents, and parents' siblings of patients with pernicious anemia is about 2.5 percent, or about 20 times the prevalence in the population at large.⁸
- In a group of 383 patients with documented rheumatoid arthritis, 9.3 percent had thyroid antibodies.⁹
- Painful tendonitis and bursitis of the shoulder was reported in 6.7 percent of thyroid disease patients, but occurs in only about 1.7 percent of the general population.¹⁰

Thyroid Gland: The Body's Regulator

- The thyroid gland is the small, butterfly-shaped gland found just below the Adam's apple. It is central to the proper functioning of the body, regulating its metabolism and organ function. The thyroid produces hormones that influence essentially every organ, tissue and cell in the body. In short, if the thyroid doesn't work properly, neither do you.
- Left untreated, thyroid disease can cause elevated cholesterol levels, osteoporosis, infertility, depression and, in extreme cases, coma or death.
- Six out of every 100 miscarriages can be attributed to thyroid deficiency during pregnancy.¹¹ Untreated hypothyroidism during pregnancy may also negatively impact a child's psychological development, resulting in a lower

I.Q. score and a decrease in motor skills, attention, language and reading abilities.¹²

What Are the Signs & Symptoms of Thyroid Disease?

Hypothyroidism (Underactive)	Hyperthyroidism (Overactive)
Fatigue	Irritability/nervousness
Mood swings	Muscle weakness/tremors
Forgetfulness	Irregular menstrual periods
Weight gain	Weight loss
Dry, coarse skin and hair	Sleep disturbances
Enlarged thyroid (goiter)	Enlarged thyroid (goiter)
Depression	Depression
Hoarse voice	Vision problems or eye irritation
Intolerance to cold	Heat intolerance
Difficulty swallowing	Heavy menstrual periods

For more information, please call Stacey Wacknov or Theresa Liddy at 212-453-2000 Additional information about thyroid disease can be found at the AACE Web site www.aace.com

#

¹ www.aace.com
² Wood M.D., Lawrence C Your Thyroid: A Home Reference Ballantine Books, New York, 1995
³ Wood M.D., Lawrence C Your Thyroid: A Home Reference Ballantine Books, New York, 1995
⁴ Wood M.D., Lawrence C Your Thyroid: A Home Reference Ballantine Books, New York, 1995
⁵ Dayan CM, Daniels GH Chronic Autoimmune Thyroiditis, NEJM 335: 2 99-107, 1996
⁶ Adams A Walston J Silver K Autoimmune Disease Risk in Families with Type 1 Diabetes, www.genetichhealth.com 10/27/01
⁷ Carmel R, Spencer CA. Clinical and subclinical thyroid disorders associated with pernicious anemia. Arch Inter Med 1982; 142: 1465.
⁸ Lee: Wintrobe's Clinical Hematology, 10th ed., Lippincott Williams & Wilkins, 1999
⁹ Wood M.D., Lawrence C Your Thyroid: A Home Reference Ballantine Books, New York, 1995
¹⁰ Wood M.D., Lawrence C Your Thyroid: A Home Reference Ballantine Books, New York, 1995
¹¹ Allan M.D., Walter Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000; 7: 127-130
¹² Haddow JE, Palomaki GE, Allan WC, et.al. Maternal thyroid deficiency during pregnancy and subsequent psychological development in the child. NEJM 1999; 341: 549-55



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Exhibit C



PR NEWSWIRE

New Study Shows Twice as Many Americans May Suffer from Undiagnosed Thyroid Disease

Largest-Ever Prevalence Study Links Mildest Forms of Hypothyroidism to Increases in Cholesterol; Exposes Need for More Widespread Thyroid Testing

DENVER, Feb. 28 /PR Newswire/ -- The largest study to date evaluating the prevalence of thyroid disease indicates there may be more than 13 million Americans who are unaware they have a thyroid condition even though the disease may be impacting their short- and long-term health. This is double the previously suspected number of undiagnosed cases in the United States, according to data published in today's *Archives of Internal Medicine*.

The study also found that even the slightest decrease in thyroid function may increase cholesterol levels, possibly increasing a patient's risk for cardiovascular disease. This link between the early stages of underactive thyroid ("subclinical" hypothyroidism) and cholesterol levels provides evidence that untreated patients may experience serious negative health consequences.

As thyroid function declined, the study found, patients reported more symptoms. But, while there was a positive association between the proportion of symptoms reported and progressive thyroid failure, this distinction was not as clear as would have been expected. In addition, no one symptom was a clear indicator of thyroid failure.

"The link between all stages of hypothyroidism and cardiovascular health, and the vague correlation between symptoms and disease state, points to the need for more widespread thyroid stimulating hormone (TSH) testing and more aggressive treatment, especially for subclinical patients," said E. Chester Ridgway, MD, head of the Division of Endocrinology at the University of Colorado Health Sciences Center.

Study Findings

The study was conducted to determine: the prevalence of abnormal thyroid function; the relationship between thyroid function and lipid levels; and the connection between thyroid failure and the presence of symptoms.

Prevalence

The study found that of the 25,862 participants, 11.7 percent had abnormal serum TSH levels. Evaluating incidence according to over- and underactive thyroid cases, 2,450 patients or 9.5 percent had an underactive thyroid (hypothyroidism) and 570 or 2.2 percent of the population had an overactive thyroid

(hyperthyroidism).

"Surprisingly, the prevalence of hypothyroidism was higher than expected," Dr. Ridgway said. "Based on previous data, we suspected five to ten percent of the population had a failing thyroid gland. But these results here showed that hypothyroid prevalence was on the higher end -- closer to 10 percent."

Among patients not taking thyroid medication, 8.9 percent were hypothyroid and 1.1 percent were hyperthyroid. This indicates 9.9 percent of the population had a thyroid abnormality that had most likely gone unrecognized. When extrapolated to account for national demographics, there may be 13 million Americans with an undiagnosed thyroid condition.

The percentage of patients with hypothyroidism was greater for women for each decade of age after age 34.

Thyroid Disease & Cholesterol

A higher proportion of clinically hypothyroid patients had elevated total cholesterol levels as compared to those with normal thyroid function. While it has been known for decades that overt hypothyroidism contributes to elevated cholesterol levels, this is the largest study to show that the cholesterol levels among patients with mildly decreased thyroid function were significantly higher than the cholesterol levels in euthyroid patients.

Average total cholesterol levels for patients with overt hypothyroidism were 251 mg/dL and the average total cholesterol levels for subclinical hypothyroid patients were 224 mg/dL -- both above 200 mg/dL, the marker used to indicate elevated cholesterol levels that warrant medical attention. Because the connection between hypothyroidism and cholesterol is so clear, the National Cholesterol Education Program and the U.S. Food and Drug Administration recommend thyroid testing in patients with high cholesterol levels.

"This study was novel in that it drew a clearer connection between mild or early stages of thyroid failure and its effect on cholesterol levels," Dr. Ridgway said. "It showed that as the thyroid gland fails and less thyroid hormone is produced, blood cholesterol levels rise. This has serious long-term consequences for the patient's health particularly in the area of cardiovascular disease."

Symptoms Scales as Indicators to Thyroid Disease

Overt hypothyroid patients reported a greater percentage of symptoms than did the subclinically hypothyroid group. Both overt and subclinical patients reported more total symptoms than euthyroid individuals. But no one symptom was a predictor of thyroid failure. While there was an increase in the likelihood of

thyroid disease as the number of reported symptoms increased, these symptoms are often vague and develop slowly so they go un-noticed.

"Thyroid symptoms are so common and are often mistaken for signs of aging, menopause, depression or stress," said Gay Canaris, MD, assistant professor of internal medicine, University of Nebraska Medical Center. "Since we can't rely upon reported symptoms alone to detect disease, we as physicians should be conducting more thyroid testing."

Study Design

This cross-sectional study evaluated the largest-ever patient population. Participants were solicited from the annual statewide health symposium in Colorado which provides testing for hypertension, colon cancer, glaucoma and skin cancer. In 1995, sensitive tests of thyroid function were added to the panel of blood analyses, and a questionnaire for hypothyroid symptoms was included with the survey. Demographics and thyroid function analyses for 25,862 patients, representing 111 sites, were quantified and reported in this study.

The Thyroid Health Survey included a symptoms questionnaire that evaluated traditional thyroid symptoms and asked the patient to further identify each symptom as "current" (present at the time of the survey) or "changed" (symptom that emerged within the past year). A symptom index was calculated in the manner of Billewicz, et al. The survey also included questions on personal history, family history and demographics.

Serum TSH concentrations were measured by third-generation immunochemiluminescent assay. Normal range was a TSH level between 0.3 and 5.1 mIU/L, subclinical hypothyroidism was characterized by an elevated TSH level (greater than 5.1 mIU/L) and a normal T4, and overt hypothyroidism was evaluated as an elevated TSH level (greater than 10.0 mIU/L) and a decreased T4.

The Critical Role of the Thyroid Gland

The thyroid gland plays a vital role in overall body function during all stages of life. Although relatively small, it produces a hormone that influences every cell, tissue and organ in the body. The thyroid regulates the body's metabolism -- the rate at which the body produces energy from nutrients -- and affects heart rate, energy and mood. If a person has normal thyroid function, they are considered to be euthyroid.

When the thyroid gland is not working properly, it can become either underactive (resulting in hypothyroidism) or overactive (resulting in hyperthyroidism). Signs and symptoms of an underactive thyroid include fatigue, depression, forgetfulness,

unexplained weight gain, and menstrual irregularities. An overactive thyroid is marked by irritability/nervousness, sleep disturbances, unexplained weight loss, muscle weakness and vision problems. If left untreated, thyroid disease may lead to an increased risk for heart disease, osteoporosis and infertility.

Thyroid disease can strike anyone at any time, but is more common in women. One woman in eight will develop a thyroid disorder during her lifetime. Incidence also increase with age -- by age 60, more than 20 percent of American women will have a thyroid disorder.

Thyroid disease can be diagnosed through a simple blood test called a TSH (third generation thyroid stimulating hormone). Once diagnosed, hypothyroidism can be treated with a synthetic hormone replacement tablet (levothyroxine sodium tablets, USP), taken once-a-day.

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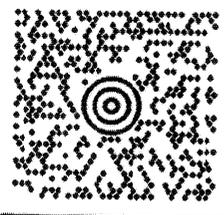
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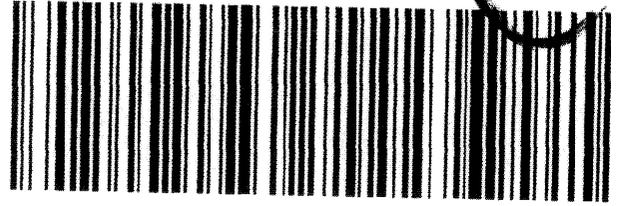


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