UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA	**CRIMINAL NO.**
v.	**VIOLATIONS:** **18 U.S.C. § 1505** **(obstruction of agency proceedings)** **21 U.S.C. §§ 331(d), 333(a)(1), 355(a)** **(distribution of an unapproved new drug)** **21 U.S.C. §§ 331(a), 333(a)(1), 352(f)(1)** **(distribution of a misbranded drug;** **inadequate directions for use)**
FOREST PHARMACEUTICALS, INC.,	
Defendant.	

INFORMATION

The United States Attorney charges that:

GENERAL ALLEGATIONS

At all times material hereto, unless otherwise alleged:

1. **FOREST PHARMACEUTICALS, INC.** (hereafter **"FOREST PHARMACEUTICALS"**) was a wholly owned subsidiary of Forest Laboratories, Inc. (hereafter "Forest Labs") and had its principal place of business in St. Louis, Missouri.

2. **FOREST PHARMACEUTICALS** was engaged in, among other things, the manufacture, promotion, sale and interstate distribution of prescription drugs intended for human use throughout the United States, including the District of Massachusetts. **FOREST PHARMACEUTICALS** employed individuals, including sales representatives, throughout the United States, including the District of Massachusetts. **FOREST PHARMACEUTICALS** had manufacturing and packaging facilities in various locations, including Cincinnati, Ohio.

FOREST PHARMACEUTICALS' distribution center for shipping its various drug products was located in St. Louis, Missouri.

3. Forest Labs was a Delaware corporation with its principal place of business in New York, New York, with publicly traded shares listed on the New York Stock Exchange (ticker symbol: FRX).

THE FDA AND THE FDCA

4. The United States Food and Drug Administration ("FDA") was the federal agency responsible for protecting the health and safety of the public by enforcing the Federal Food, Drug, and Cosmetic Act ("FDCA") and ensuring, among other things, that drugs intended for use in humans were safe and effective for their intended uses and that the labeling of such drugs bore true and accurate information. Pursuant to such responsibility, the FDA published and administered regulations relating to the approval, manufacture, and distribution of drugs.

5. As part of its mission to enforce the FDCA and protect the public health, the FDA had the authority to enter and inspect at reasonable times all establishments where drugs were manufactured, processed, packed, or held for introduction into interstate commerce or after shipment in interstate commerce. 21 U.S.C. § 374(a)(1).

6. The FDCA defined drugs as, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man, and articles intended to affect the structure or any function of the body of man. 21 U.S.C. §§ 321(g)(1)(B) and (C).

7. Prescription drugs under the FDCA were any drugs intended for use in humans which, because of their toxicity or other potentiality for harmful effect, or the method of their

use, or the collateral measures necessary to their use, were not safe for use except under the supervision of a practitioner licensed by law to administer such drugs. 21 U.S.C. § 353(b)(1)(A).

8. A "new drug" was defined, in relevant part, as a drug that was not generally recognized among qualified experts as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. 21 U.S.C. § 321(p).

9. With certain limited exceptions not pertinent here, the FDCA prohibited causing the introduction or delivery for introduction into interstate commerce of, or introducing or delivering for introduction into interstate commerce of, "new drugs" that were not the subject of an FDA-approved new drug application ("NDA") or an investigational new drug application ("IND"). 21 U.S.C. §§ 331(d), 355.

10. The FDCA required that an NDA include proposed labeling for the proposed intended uses of the drug which included, among other things, the conditions for therapeutic use. The NDA was also required to provide, to the satisfaction of the FDA, data generated in adequate and well-controlled clinical investigations that demonstrated that the drug was safe and effective when used in accordance with the proposed labeling.

11. An NDA sponsor was not permitted to promote or market the drug until the FDA had approved its NDA, including the proposed labeling. Once approved, the sponsor was permitted to promote and market the drug only for the conditions of use and dosages specified in the approved labeling. Uses not approved by the FDA, including uses in patient populations beyond those in the drug's approved labeling, were known as "unapproved"or "off-label" uses.

12. The FDCA, and its implementing regulations, required the sponsor to file a new NDA, or a supplement to the existing NDA, in order to label or promote a drug for uses and

dosages different from the conditions for use and dosages specified in the approved labeling. The new or supplemental NDA was required to include a description of the newly proposed indications for use and evidence, from adequate and well-controlled clinical investigations, sufficient to demonstrate that the drug was safe and effective for the newly proposed therapeutic use or uses. Only upon approval of the new NDA, or supplement, could the sponsor promote the drug for the new intended use.

13. The FDCA provided that a drug was misbranded if, among other things, its labeling did not contain adequate directions for use. 21 U.S.C. § 352(f)(1). As the phrase was used in the FDCA and its regulations, adequate directions for use could not be written for medical indications or uses for which the drug had not been proven to be safe and effective through adequate and well-controlled clinical investigations.

14. The FDCA prohibited causing the introduction or delivery for introduction into interstate commerce of, or introducing or delivering for introduction into interstate commerce of, any drug that was misbranded. 21 U.S.C. § 331(a).

LEVOTHROID AND THE FDA APPROVAL PROCESS

15. Levothroid was an orally administered levothyroxine sodium drug product (hereafter "orally administered levothyroxine sodium drug products" are referred to as "levothyroxine drugs"). In the 1950s, drug manufacturers first introduced levothyroxine drugs in the United States to treat patients suffering from hypothyroidism – that is, a medical condition in which an individual has a thyroid hormone deficiency. Manufacturers introduced levothyroxine drugs in the market without first obtaining FDA approval in part because the manufacturers believed that their drugs were not "new drugs" within the meaning of the FDCA. The product

that became Levothroid was introduced in the United States in or around 1965 by a drug manufacturer other than **FOREST PHARMACEUTICALS** without first obtaining FDA approval.

16. In or about 1991, Forest Labs bought the rights to Levothroid. Several years later, **FOREST PHARMACEUTICALS** moved the manufacturing processes for Levothroid to its manufacturing facility in Cincinnati, Ohio. Thereafter, **FOREST PHARMACEUTICALS** manufactured and packaged Levothroid at its Cincinnati manufacturing facility. After manufacture and packaging, **FOREST PHARMACEUTICALS** transferred the Levothroid finished product to its distribution facility in St. Louis, Missouri, from which it sold and distributed Levothroid to customers throughout the United States, including within the District of Massachusetts. At no time through and including August 9, 2003, did **FOREST PHARMACEUTICALS** have an approved NDA to manufacture and distribute Levothroid using the formulation and manufacturing processes then being utilized at its Cincinnati manufacturing facility.

A. <u>The FDA's 1997 Determination That Levothyroxine Drugs Were New Drugs</u>

17. On August 14, 1997, the FDA issued a public notice in the Federal Register (hereafter, "1997 Federal Register notice") announcing its conclusion that all levothyroxine drugs on the market were "new drugs" within the meaning of the FDCA. In this notice, the FDA stated that although levothyroxine drugs had been on the market for years, new information showed that there were significant stability and potency problems with these products. As a result, the FDA concluded that more regulation was needed to ensure that the drugs then being commercially marketed were safe and effective as manufactured.

18. In the 1997 Federal Register notice, the FDA explained that thyroid replacement therapy, the principal therapeutic use of levothyroxine drugs, needed to be established carefully on an individualized basis for each patient, with gradual increases in dosages until an optimal response was achieved as determined by clinical evaluation and laboratory testing. Levothyroxine drugs were "narrow therapeutic index" drugs – that is, a very small difference in potency could make the difference between a therapeutic dosage and a potentially suboptimal or toxic dosage. As a result, overtreatment or undertreatment with levothyroxine drugs could present significant health risks to patients: if a patient received too little medication, the patient could remain hypothyroid; conversely, if a patient received too much medication, the patient could become hyperthyroid and could suffer adverse health consequences including potentially cardiac pain, heart palpitations, or cardiac arrhythmias. Given this risk, the FDA characterized as "critical" the importance that patients receive levothyroxine drugs that were consistent in potency and bioavailability.

19. As described by the FDA in the 1997 Federal Register notice, there had been a history in the 1990s of continuing significant potency and stability problems with levothyroxine drugs that were on the market. These problems included at least ten recalls involving 150 lots and more than 100 million tablets by different manufacturers, including at least one recall by **FOREST PHARMACEUTICALS**, adverse drug experience reports, and reports indicating that, even when a physician consistently prescribed the same brand and labeled dosage strength of a specific levothyroxine drug product, patients received varying dosage strengths of the drug.

20. In the 1997 Federal Register notice, the FDA also expressed concern that, because levothyroxine sodium was unstable in the presence of higher temperatures and humidity levels,

proper manufacturing controls were needed to ensure that the drugs remained fully potent through the labeled expiration date and to ensure that the drugs were of consistent potency from lot to lot. The FDA observed that the "lack of stability and consistent potency has the potential to cause serious health consequences to the public."

21. The FDA further noted that, because levothyroxine drugs were being marketed without approved NDAs, manufacturers of these products were not seeking or obtaining FDA approval each time they reformulated their products. This meant that manufacturers were releasing reformulated products with significant differences in potency before and after reformulation. According to the FDA, these potency differences resulted in serious adverse health consequences for some patients whose conditions had otherwise been safely controlled on the drug prior to reformulation.

22. In light of the particular importance of consistent potency and stability to levothyroxine drugs, and because none of the levothyroxine drugs on the market had been shown to demonstrate consistent potency and stability, the FDA determined that none of these drugs were generally recognized as safe and effective and thus that all of the drugs in this class were "new drugs" within the meaning of the FDCA. As a result, the FDA announced that manufacturers of these products needed to file an NDA and obtain FDA approval to permit continued marketing of their products. The FDA further advised manufacturers that, if they wanted to challenge the determination that their drug product was a "new drug," they needed to file a citizen petition by not later than October 14, 1997.

23. Because the FDA deemed levothyroxine drugs to be medically necessary for millions of patients and given the lack of any available alternative drug that was relied upon by

the medical community as an adequate substitute for the treatment of hypothyroidism, the FDA advised manufacturers that it would allow them three years, until August 14, 2000, to obtain approved NDAs for their products. Until that date, in order to meet patients' medical needs, the FDA stated it would permit manufacturers to continue commercial distribution of their unapproved drugs. The 1997 Federal Register notice provided clear warning to manufacturers about the consequences of distribution thereafter:

> After August 14, 2000, any orally administered drug product containing levothyroxine sodium, marketed on or before the date of this notice, that is introduced or delivered for introduction into interstate commerce without an approved application, unless found by the FDA to be not subject to the new drug requirements of the act under a citizen petition submitted for that product, will be subject to regulatory action.

24. The FDA subsequently concluded that levothyroxine drug manufacturers needed additional time to complete studies and to prepare the NDAs needed to establish that their drugs were safe and effective. In an April 2000 Federal Register notice, the agency extended the previously stated compliance date one year – from August 14, 2000, to August 14, 2001 – during which manufacturers could continue marketing their drugs without approved applications.

B. <u>The FDA's 2001 Guidance for Industry and Phase-Down Plan</u>

25. On July 13, 2001, the FDA issued a Guidance for Industry entitled "Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications" (hereafter "Guidance"). In a concurrent Federal Register announcement, FDA explained that it had approved two NDAs for levothyroxine drugs. The agency noted, however, 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." To provide manufacturers with adequate scale-up time, and to permit patients and physicians time to make a reasonable transition from unapproved to approved products, the FDA announced that, in the exercise of its enforcement discretion, it was establishing a gradual phase-down plan for the unapproved drugs.

26. In the Guidance, the FDA reiterated that marketing levothyroxine drugs without an approved NDA was illegal and could subject a company to various enforcement actions, including "injunction, prosecution, or seizure." The FDA advised, however, that it did not intend to take enforcement action against companies for marketing levothyroxine drugs without an approved NDA, if those companies complied with all aspects of the phase-down plan set forth by FDA in the Guidance. In effect, the Guidance created a voluntary "safe harbor" for companies that wished to continue to distribute levothyroxine drugs without an approved NDA.

27. The phase-down plan announced by FDA in the Guidance was as follows. To qualify for the "safe harbor," manufacturers first had to have an NDA pending, if not already approved, by August 14, 2001. The Guidance explicitly warned manufacturers without an approved or pending NDA that they should cease distribution immediately on August 14, 2001, and it further warned manufacturers who had an NDA pending that they should stop distributing their drug immediately if, after August 14, 2001, they withdrew their pending NDA. Second, the Guidance provided that manufacturers without approved NDAs should gradually reduce commercial distribution of their drugs, over two years, pursuant to a specific phase-down schedule, with all distribution terminating as of August 14, 2003. Third, the Guidance stated that manufacturers without an approved NDA should submit quarterly amendments to their pending

NDAs certifying that they had reduced average monthly distribution in accordance with the phase-down schedule.

28. In a section entitled "Basis for Enforcement Action," the Guidance explicitly discussed the potential legal consequences associated with distributing an unapproved levothyroxine drug without following the phase-down plan:

> Orally administered levothyroxine sodium drug products are new drugs. Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) states: "No person may introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug." A manufacturer who introduces or delivers for introduction into interstate commerce an unapproved drug product is subject to injunction, prosecution, or seizure as authorized by sections 302, 303, and 304 of the Act (21 U.S.C. §§ 332, 333, 334). Violation of an injunction could result in a contempt proceeding or such other penalties as a court may order (e.g., fines). However, FDA does not intend to take action for marketing without an approved application against a manufacturer of levothyroxine sodium drug product who complies with the plan for phased reduction of distribution described in [the Guidance]."

C. FOREST PHARMACEUTICALS' Response to the Federal Register Notices and the Guidance

29. In response to the Federal Register notice, **FOREST PHARMACEUTICALS** did not file a citizen petition challenging the FDA's determination that Levothroid was a new drug within the meaning of the FDCA. Instead, so that **FOREST PHARMACEUTICALS** could continue to manufacture and distribute Levothroid, Forest Labs submitted NDA 21-125 for Levothroid (levothyroxine sodium tablets, USP) on or about September 27, 2000.

30. As part of the NDA process, **FOREST PHARMACEUTICALS** knew and understood that the FDA needed to be provided with stability data that supported the expiration

dates that the company was proposing for Levothroid. Stability testing was a form of laboratory testing that was designed to demonstrate the shelf-life of a drug, that is, the length of time during which the drug had the appropriate identity, strength, quality, purity and potency. **FOREST PHARMACEUTICALS** further knew and understood that the FDA required that this stability data be obtained under specific, controlled temperature and relative humidity conditions – namely, temperature between 25 +/- 2° Celsius and relative humidity between 60% +/- 5% (these conditions will hereafter be referred to as "ICH conditions"). From conversations with FDA representatives, **FOREST PHARMACEUTICALS** knew that, because levothyroxine sodium was highly sensitive to both temperature and humidity, the FDA wanted adequate assurances that the drugs that were going to remain on the market were sufficiently robust to maintain potency even under relatively warm and humid conditions.

31. **FOREST PHARMACEUTICALS** knew that satisfying ICH conditions for stability presented a significant challenge for its Levothroid product. **FOREST PHARMACEUTICALS** discovered during testing of the *commercially distributed* Levothroid (the product being manufactured and sold by **FOREST PHARMACEUTICALS** at the time, as opposed to the *developmental* Levothroid being manufactured and tested as part of the NDA submission) that the drugs lost potency much more rapidly under ICH conditions and thus failed stability testing. As a result, after consulting with FDA, **FOREST PHARMACEUTICALS** had stopped subjecting its commercially distributed Levothroid to ICH conditions during stability testing.

32. **FOREST PHARMACEUTICALS** also knew that obtaining valid stability data for Levothroid under ICH conditions for the NDA was going to present significant difficulties for

a second reason. **FOREST PHARMACEUTICALS** (like some other manufacturers of unapproved product) manufactured its commercially distributed Levothroid with a stability overage – that is, with excessive active ingredient added solely to ensure that the drug would have sufficient potency throughout its entire shelf-life. **FOREST PHARMACEUTICALS** justified this stability overage on the basis that the USP monograph for levothyroxine sodium products indicated that the acceptable range for potency was between 90% and 110%. **FOREST PHARMACEUTICALS** interpreted that requirement to mean that it could release its product with excess active ingredient, as long as the excess was less than 110% of the strength represented on the label.

33. The FDA was aware that **FOREST PHARMACEUTICALS** was distributing levothyroxine drugs with stability overages and, in fact, stability overages were one of the reasons why the FDA imposed the new NDA requirements. While stability overages enabled manufacturers to extend their products' shelf-life artificially, stability overages also meant that manufacturers were distributing product that was super-potent. This presented problems as a patient with the exact same prescription could receive varying amounts of active ingredient over time, depending strictly upon the age of the drug received from the pharmacy. As a result, the FDA repeatedly advised various manufacturers, including **FOREST PHARMACEUTICALS**, that they would need to remove the stability overages from the formulation of their drugs in order to obtain NDA approval for their levothyroxine drugs.

34. Thus, **FOREST PHARMACEUTICALS** knew that it was going to have to overcome two substantial hurdles to obtain NDA approval of Levothroid : first, it needed to remove its stability overages (which in and of itself would cause the product to fail stability

testing even under ambient conditions); and second, it needed to reformulate Levothroid to make it more stable so that it would pass stability testing under the more rigorous ICH conditions.

D. The Levothroid NDA Submission

35. Despite this knowledge, **FOREST PHARMACEUTICALS** never ultimately met the FDA's requirements with respect to the Levothroid NDA. **FOREST PHARMACEUTICALS** repeatedly submitted data to the regulatory personnel at Forest Labs for inclusion in the NDA and in various amendments to the NDA that were based on Levothroid manufactured with stability overages. Moreover, **FOREST PHARMACEUTICALS** repeatedly submitted stability data to Forest Labs for inclusion in the NDA and various amendments to the NDA that purported to have been obtained under ICH conditions when, in fact, it was well-known by plant management personnel and others within **FOREST PHARMACEUTICALS'** Cincinnati plant (where the stability studies were conducted in a room called CRT-5) that serious equipment malfunctions in CRT-5 had resulted in humidity levels significantly below ICH conditions for extended periods of time totaling hundreds of days and thousands of hours. These "humidity excursions" resulted in testing results that misrepresented and overstated Levothroid's potency relative to its expiration date.

36. In an attempt to remedy these significant humidity excursions, on or around January 21, 2003, certain **FOREST PHARMACEUTICALS** management personnel at the Cincinnati plant decided to put a portable home humidifier in CRT-5 as a temporary fix to the humidity problem. **FOREST PHARMACEUTICALS** knew and understood that this temporary fix would not maintain the relative humidity in CRT-5 at ICH levels as the portable

humidifier, which required constant monitoring and refills of water, did not work effectively through the night or through an entire weekend.

COUNT ONE

(Obstruction of an Agency Proceeding
18 U.S.C. § 1505)

37. The allegations in paragraphs 1 through 36 are realleged and incorporated herein as if set forth in full.

38. Between November 17, 2003, and December 3, 2003, the FDA conducted a regulatory inspection of **FOREST PHARMACEUTICALS'** facility in Cincinnati, Ohio pursuant to FDA's statutory inspection authority set forth at 21 U.S.C. § 374.

39. During this inspection, the FDA discovered a portable humidifier in CRT-5, the controlled room **FOREST PHARMACEUTICALS** used for its ICH stability studies in support of the Levothroid NDA. When the FDA investigators asked about this portable humidifier, certain **FOREST PHARMACEUTICALS** management personnel at the Cincinnati plant falsely stated that the portable humidifier was being stored in CRT-5 and falsely denied that the portable humidifier had ever been used for humidity control in CRT-5.

40. The following day, certain **FOREST PHARMACEUTICALS** management personnel at the Cincinnati plant admitted to the FDA investigators that the regular humidifier in CRT-5 was not functioning properly and that the portable humidifier had been used in CRT-5 to increase the humidity level in the room.

41. On or about November 17, 2003, in the Southern District of Ohio and elsewhere, the defendant,

FOREST PHARMACEUTICALS, INC.,

corruptly obstructed, impeded, and endeavored to influence the due and proper administration of the law under which a pending proceeding was being had before an agency of the United States, to wit, an inspection by the FDA of **FOREST PHARMACEUTICALS**, by causing the withholding and concealing of material information that was sought in the course of the FDA's regulatory inspection relating to the data submitted in support of NDA 21-125, Levothroid (levothyroxine sodium, USP) Tablets.

All in violation of 18 U.S.C. § 1505.

COUNT TWO

**(Distribution of an Unapproved New Drug
21 U.S.C. §§ 331(d), 333(a)(1) & 355(a))**

42. The allegations in paragraphs 1 through 29 are realleged and incorporated herein as if set forth in full.

A. FOREST PHARMACEUTICALS' Decision Not to Avail Itself of the Safe Harbor Created in the FDA Guidance

43. Although the FDA's Guidance document created a "safe harbor" through which manufacturers could continue distributing their unapproved levothyroxine drugs while their NDA was pending, **FOREST PHARMACEUTICALS** did not, at any time between in or about August 14, 2001, and in or about August 9, 2003, take any affirmative steps to comply with the Guidance's phase-down plan. Initially, **FOREST PHARMACEUTICALS** hoped that it would, through market forces alone, fall into compliance with the phase-down schedule. **FOREST PHARMACEUTICALS** also hoped that it would obtain NDA approval quickly and that the issue would simply fade away.

44. However, by in or about April 2002, it was clear to **FOREST PHARMACEUTICALS** that the Levothroid NDA was not going to be approved quickly. By in or about April 2002, **FOREST PHARMACEUTICALS** was aware of, among other things, the following facts:

a. In a letter dated January 11, 2002, FDA's Cincinnati District Office had advised Forest Labs that the District Office was recommending to FDA's Center for Drugs Evaluation and Research that it not approve the company's Levothroid NDA 21-125 because of manufacturing deficiencies identified during an inspection of **FOREST PHARMACEUTICALS'** Cincinnati plant that the FDA had conducted in October through December of 2001.

b. During a meeting in January 2002, individuals in the FDA's Cincinnati District Office informed **FOREST PHARMACEUTICALS** that there would be no additional warnings and that FDA might resort to legal action if the company did not remedy manufacturing deficiencies identified in its Cincinnati plant.

c. In a follow-up letter dated March 29, 2002, FDA advised **FOREST PHARMACEUTICALS** that some of its proposed remedies for its Cincinnati plant were inadequate. The problems identified by FDA were numerous and significant, and included the fact that certain Levothroid tablets manufactured by **FOREST PHARMACEUTICALS** had tested sub-potent.

45. Realizing that the FDA had identified only some, but not all, of the known manufacturing deficiencies at the Cincinnati plant, **FOREST PHARMACEUTICALS** did not want to draw further attention to the plant. Several individuals at **FOREST PHARMACEUTICALS** also were concerned that the company's continued failure to comply with the Guidance might bring renewed FDA attention to the Cincinnati plant. Accordingly, after receipt of FDA's January and March 2002 letters, **FOREST PHARMACEUTICALS** began reconsidering whether it should begin complying with FDA's phase-down schedule.

46. On or about April 18, 2002, **FOREST PHARMACEUTICALS** decided internally not to comply with the Guidance's phase-down schedule. In making this decision, **FOREST PHARMACEUTICALS** weighed the legal risk of non-compliance (i.e., enforcement action) against the financial risk of compliance (i.e., lost business), and decided to risk an FDA enforcement action rather than lose sales.

47. After April 2002, **FOREST PHARMACEUTICALS** did not reconsider whether to comply with phase-down. Instead, **FOREST PHARMACEUTICALS** continued distributing its unapproved Levothroid product at rates well over the levels established in the Guidance.

48. During an FDA regulatory inspection of **FOREST PHARMACEUTICALS'** Cincinnati plant beginning in January 2003, FDA investigators asked **FOREST PHARMACEUTICALS** to provide distribution figures for Levothroid. This request was motivated in part by the fact that the FDA had not received any quarterly Levothroid distribution information from the company since **FOREST PHARMACEUTICALS'** April 2002 decision not to comply with the phase-down schedule set forth in the Guidance.

49. On February 5, 2003, FDA investigators learned that **FOREST PHARMACEUTICALS** had deliberately chosen not to comply with, and had, in fact, not complied with, the phase-down schedule set forth in the Guidance.

B. FOREST PHARMACEUTICALS' Decision to Increase Production and Distribution of Levothroid

50. By the spring of 2003, **FOREST PHARMACEUTICALS** employees realized that the FDA was not likely to approve the pending Levothroid NDA before August 14, 2003. As a result, in or about May through in or about July 2003, **FOREST PHARMACEUTICALS** dramatically increased its manufacture of Levothroid and offered its customers special purchase terms in an attempt to induce customers to purchase enough unapproved Levothroid to satisfy demand for the several months between August 14, 2003, when **FOREST PHARMACEUTICALS** knew it would be required to stop commercially distributing Levothroid and a date later that year when it believed its NDA might be approved.

C. FOREST PHARMACEUTICALS' Continued Distribution of Levothroid after Receiving an FDA Warning Letter

51. On August 7, 2003, the FDA issued a Warning Letter to Forest Labs addressing two issues: (1) **FOREST PHARMACEUTICALS'** failure to limit its distribution of its

unapproved new drug Levothroid consistent with the phase-down schedule in the Guidance; and (2) multiple manufacturing problems that the FDA had identified during the January/February 2003 inspection at the Cincinnati plant where **FOREST PHARMACEUTICALS** manufactured Levothroid for commercial distribution.

52. The August 7, 2003 Warning Letter advised Forest Labs that the FDA inspectors had determined during their inspection that **FOREST PHARMACEUTICALS** "made a deliberate decision not to follow the agency's gradual phase-out plan that allows for the continued distribution of unapproved orally administered levothyroxine sodium products under limited circumstances." As a result, the FDA advised Forest Labs that "you are no longer entitled to the enforcement discretion granted by the agency, and are hereby on notice that the distribution of your unapproved product, Levothroid, remains in violation of Section 505 of the Act."

53. **FOREST PHARMACEUTICALS** received the Warning Letter by late morning on Friday, August 8, 2003. Rather than immediately stop Levothroid distribution, **FOREST PHARMACEUTICALS** – which had recently booked many large orders because of the special terms it was offering – instead directed its employees to continue shipping as much Levothroid product as possible. Throughout the day, **FOREST PHARMACEUTICALS** employees at the St. Louis distribution center placed a priority on filling Levothroid orders to the exclusion of filling orders for other drugs that typically would have had priority. Similarly, **FOREST PHARMACEUTICALS** employees overrode the computer system and placed a priority on filling the largest Levothroid orders first. **FOREST PHARMACEUTICALS** also made special arrangements to have its trucking carriers pick up extra trailers full of Levothroid shipments from

the St. Louis distribution center. In addition, **FOREST PHARMACEUTICALS** directed its second shift employees to work overtime that day and into the early hours of the following morning. At approximately 1:00 a.m. on August 9, 2003, **FOREST PHARMACEUTICALS** stopped packaging and shipping Levothroid drug product to its customers. By that time, **FOREST PHARMACEUTICALS** had filled the Levothroid orders for all of its primary larger customers.

54. Beginning as early as August 14, 2001, and continuing thereafter until on or about August 9, 2003, in the District of Massachusetts and elsewhere, the defendant,

FOREST PHARMACEUTICALS, INC.,

did introduce, deliver for introduction, and cause the introduction and delivery for introduction into interstate commerce into Massachusetts and elsewhere, of various quantities of Levothroid, a new drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(p), which was intended to treat hypothyroidism. No approval, pursuant to 21 U.S.C. § 355, was in effect with respect to Levothroid for use in this condition or any other condition.

All in violation of 21 U.S.C. §§ 331(d), 333(a)(1), and 355(a).

COUNT THREE

(Distribution of a Misbranded Drug: Inadequate Directions for Use 21 U.S.C. §§ 331(a), 333(a)(1) & 352(f)(1))

55. The allegations in paragraphs 1 through 14 are realleged and incorporated herein as if set forth in full.

FOREST PHARMACEUTICALS' OFF-LABEL PROMOTION OF CELEXA

56. Celexa was the brand name for the prescription drug citalopram, which was a selective serotonin reuptake inhibitor ("SSRI") drug. A Danish company developed Celexa and licensed Celexa to another subsidiary of Forest Labs for marketing in the United States.

57. In 1998, the FDA approved Celexa for the treatment of adult depression. The FDA never approved Celexa for treatment of any conditions other than adult depression, or for any use in children or adolescents.

58. In 1998, after the FDA approved Celexa for treatment of adult depression, **FOREST PHARMACEUTICALS** began promoting, distributing and selling Celexa throughout the United States, including in the District of Massachusetts.

59. From the outset, **FOREST PHARMACEUTICALS** was well-aware that the FDA had not approved Celexa for treatment of any conditions other than adult depression. Moreover, in or about April 2002, Forest Labs, in an attempt to obtain, *inter alia*, a pediatric indication for Celexa, submitted data to the FDA from two double-blinded, placebo-controlled studies involving the use of Celexa in children. One of these studies (hereafter referred to as the "Forest study"), which had been sponsored by Forest Labs, had been conducted in the United States. The Forest study had positive results, that is, the study indicated that Celexa was more

effective than placebo in treating pediatric patients suffering from depression. The other study (hereafter referred to as the "European study"), had been conducted in Europe and sponsored by the Danish company that developed and owned the rights to Celexa. The European study had negative results, that is, the study did not show Celexa to be any more effective than placebo in treating pediatric depression. On or about September 23, 2002, the FDA denied Forest Labs' request for a pediatric indication for Celexa, stating in part that the European study "is a clearly negative study that provides no support for the efficacy of citalopram in pediatric patients with [major depressive disorder]."

60. **FOREST PHARMACEUTICALS** was equally well-aware that promoting a drug product for indications other than those explicitly approved by the FDA was illegal. For example, in or about August 2000, a Regulatory Affairs employee at Forest Labs circulated a document entitled "Promotion Guidelines for Sales Representatives" and strongly recommended that the document be incorporated into sales training at **FOREST PHARMACEUTICALS**, along with a signature page for each representative to sign confirming that he or she had in fact been trained on permissible and impermissible sales promotion. This draft document made clear that off-label promotion was illegal: "Sales representatives should never initiate, or engage in, discussions about off-label uses or solicit these requests from physicians." The draft document explained that "Indications, dosing, or formulations that are not approved and are not part of the Package Insert have not met the regulatory testing requirements for safety and effectiveness and cannot be promoted as such by Forest." The draft document further affirmatively advised that **FOREST PHARMACEUTICALS** could not hire speakers to provide off-label discussions:

> Forest-organized product-related events are legally promotional in nature even if primarily designed as an educational event for healthcare professionals. If Forest sets the agenda and selects and pays the speaker, the event must abide by the same rules as if a Forest sales representative presented the information and must comply with all FDA promotional regulations. . . . The speaker must be advised prior to the presentation about his/her obligation to only address topics such as uses and doses that are within the approved labeling. Do not select a speaker with the intent that he/she will address off-label uses.

FOREST PHARMACEUTICALS did not adopt this draft document, nor did it for several years thereafter require sales representatives to sign a document that discussed the prohibition against off-label marketing.

61. Beginning in 1998 and continuing thereafter through at least September 2002, **FOREST PHARMACEUTICALS** promoted Celexa for use in treating children and adolescents suffering from depression, even though Celexa was not FDA-approved for pediatric use. **FOREST PHARMACEUTICALS'** off-label promotion consisted of various sales techniques including: (1) directing **FOREST PHARMACEUTICALS** sales representatives who promoted Celexa to make sales calls to physicians who treated children and adolescents; (2) promoting Celexa by various **FOREST PHARMACEUTICALS** sales representatives for use in children and adolescents; (3) hiring outside speakers to talk to pediatricians, child psychiatrists, and other medical practitioners who specialized in treating children and adolescents about the benefits of prescribing Celexa to that patient population; and (4) publicizing and circulating the positive results of the double-blind, placebo-controlled Forest study on the use of Celexa in adolescents while, at the same time, failing to discuss the negative results of the second double-blind, placebo-controlled European study on the use of Celexa in adolescents.

A. FOREST PHARMACEUTICALS Sales Representatives Promoted Celexa for Use in Children and Adolescents

62. **FOREST PHARMACEUTICALS** assigned its sales representatives to specific geographic regions throughout the United States. The sales representatives were supervised by Division Managers, who in turn were supervised by Regional Directors.

63. In order to identify the potential market for Celexa, **FOREST PHARMACEUTICALS** obtained data identifying medical practitioners who prescribed SSRIs. Using this data, **FOREST PHARMACEUTICALS** created "call panels," which were lists of medical practitioners who prescribed SSRIs. **FOREST PHARMACEUTICALS** directed its sales representatives to make sales calls promoting Celexa to the medical practitioners on the "call panels." These Celexa "call panels" included, among others, thousands of child psychiatrists and pediatricians who specialized in treating children and adolescents. **FOREST PHARMACEUTICALS** also directed its Celexa sales representatives to call on physicians who worked in the pediatric wards of hospitals.

64. During sales calls, various **FOREST PHARMACEUTICALS** sales representatives, acting at times with the knowledge and encouragement of their Division Managers and Regional Directors, promoted Celexa for use in treating not only adult patients suffering from depression, but also for use in treating children and adolescents who were suffering from depression. **FOREST PHARMACEUTICALS** sales representatives often documented these details through "call notes," thousands of which reflected off-label promotional activity directed at the use of Celexa in children and adolescents.

65. In certain regions of the country, including New England, various **FOREST PHARMACEUTICALS** Division Managers actively encouraged off-label promotion of Celexa for use in children and adolescents. In 2001, for example, a **FOREST PHARMACEUTICALS** Division Manager in Massachusetts distributed sample "opening statements" to various Celexa sales representatives. One of the "opening statements" recommended Celexa for treatment of "a female adolescent [who] presents with obsessive behavior, an[d] is neurotic about her eating habits, and gets really down on herself when she eats." A **FOREST PHARMACEUTICALS** Regional Director subsequently forwarded these sample opening statements to other **FOREST PHARMACEUTICALS** Division Managers and field sales personnel in the Northeast, with a copy to **FOREST PHARMACEUTICALS** national Vice President of Sales, and included a cover observation that "There are some good opening statements here."

66. Similarly, in February 2002, a different **FOREST PHARMACEUTICALS** Division Manager in Massachusetts required a **FOREST PHARMACEUTICALS** sales representative, as part of that representative's personal development plan, to prepare sample "closing statements" for various patient types, including children. After the sales representative provided these written closing statements to the **FOREST PHARMACEUTICALS** Division Manager (e.g., "I have provided you with some information on treating children with mood and anxiety disorders. . . . Will you prescribe [Celexa] to your pts in this pt population to gain more comfort and experience with it?"), the Division Manager commended the sales representative and forwarded the closing statements to a **FOREST PHARMACEUTICALS** Regional Director.

67. At various times and in New England, certain **FOREST PHARMACEUTICALS** Regional Directors and Division Managers provided their sales representatives with copies of posters and journal articles on studies of Celexa for use in children and adolescents and directed the sales representatives to read the studies, and use them as sales aids in their details to physicians. Various **FOREST PHARMACEUTICALS** Division Managers also directed sales representatives to show off-label studies to physicians, but not leave copies of those studies with the physicians so as to avoid detection that would get the sales representative and **FOREST PHARMACEUTICALS** in trouble.

B. FOREST PHARMACEUTICALS' Use of Outside Speakers to Promote Celexa for Use in Children and Adolescents

68. **FOREST PHARMACEUTICALS** sales representatives and Division Managers identified speakers from lists maintained and approved by **FOREST PHARMACEUTICALS** to organize promotional lunches and dinners as part of which speakers were paid to give a talk about Celexa. Certain of **FOREST PHARMACEUTICALS'** approved speakers were medical practitioners who specialized in treating children and adolescents suffering from depression, and **FOREST PHARMACEUTICALS** paid these practitioners to give promotional talks on the use of Celexa in children and adolescents. Various promotional programs for Celexa organized by **FOREST PHARMACEUTICALS** sales representatives explicitly focused on off-label pediatric and adolescent use: the programs had titles such as "Adolescent Depression," "Adolescent Treatment of Depression," "Assessment and Treatments of Suicidal Adolescents," "Treatment of Child/Adolescent Mood Disorders," "Treatments in Child Depression," "New Treatment Options in Depressive Disorders in Adolescents," "Use of Antidepressants in

Adolescents," "New Topics in the Treatment of Children with Depression," "Benefits of SSRIs in Child Psychology," "Treating Depression and Related Illnesses in Children, Adolescents and Adults," "Celexa in CHP/Ped Practice," "Uses of Celexa in Children," "Treating Difficult Younger Patients,""Treating Pediatric Depression," and "Treating Adolescent Depression."

69. To obtain funding support for these promotional programs, **FOREST PHARMACEUTICALS** sales representatives were required to submit paperwork to their Division Managers describing the proposed program, identifying the medical practitioners who were to be invited to the program, and predicting the expected return on investment from the attendees – that is, the anticipated increase in the number of Celexa prescriptions resulting from the attendees' attendance at the program. **FOREST PHARMACEUTICALS** Division Managers and others within **FOREST PHARMACEUTICALS** consistently approved these requests for funding for promotional programs focusing on the use of Celexa in children and adolescents that were directed to child psychiatrists and other medical practitioners who specialized in treating children and adolescents.

C. FOREST PHARMACEUTICALS Communicated Incomplete and Potentially Misleading Information Concerning the Efficacy of Celexa in Treating Children and Adolescents

70. In or about mid-2001, Forest Labs learned of the positive results from the Forest study and the negative results from the European study, and Forest Labs shared these results with the FDA. Although both studies concerned the use of Celexa to treat children and adolescents suffering from depression, **FOREST PHARMACEUTICALS** treated the studies differently: **FOREST PHARMACEUTICALS** aggressively publicized and promoted the results from the positive Forest study, while at the same time **FOREST PHARMACEUTICALS** did not

publicize or disclose the results of the negative study to persons outside the FDA or the Danish company which sponsored the negative study. As a result, doctors and psychiatrists received incomplete and misleading information concerning all available known data pertaining to the efficacy of using Celexa to treat depression in children and adolescents. **FOREST PHARMACEUTICALS** communicated this incomplete and misleading information in, among others, the following ways: (1) via discussions that **FOREST PHARMACEUTICALS** sales representatives had with medical practitioners about the use of Celexa in treating children; (2) via promotional speeches made by pediatric specialists who were hired by **FOREST PHARMACEUTICALS** to talk about the use of Celexa in treating children and adolescents; and (3) via letters sent by **FOREST PHARMACEUTICALS** Professional Affairs Department to medical practitioners who had requested from **FOREST PHARMACEUTICALS** all available information and data concerning the use of Celexa in treating children and adolescents.

71. Beginning as early as 1998, and continuing thereafter through in or about December 2002, in the District of Massachusetts and elsewhere, the defendant,

FOREST PHARMACEUTICALS, INC.

did introduce, deliver for introduction, and cause the introduction and delivery for introduction into interstate commerce into Massachusetts and elsewhere, of various quantities of Celexa, a drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(g), for unapproved use in pediatric and adolescent patients, which was misbranded within the meaning of 21 U.S.C. § 352(f)(1), in that Celexa's labeling lacked adequate direction for such uses.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1).

FORFEITURE ALLEGATIONS

1. Upon conviction of the violations of Title 21, United States Code, Sections 331(d), 333(a)(1), and 355(a), and Title 21, United States Code, Sections 331(a), 333(a)(1), and 352(f)(1) alleged in this information, defendant,

FOREST PHARMACEUTICALS, INC.,

shall forfeit to the United States pursuant to Title 21, United States Code, Section 334 and Title 28, United States Code, Section 2461(c) the following:

(a) any quantities of Levothroid which were introduced into interstate commerce in violation of Title 21, United States Code, Section 331 and/or 355(a); and

(b) any quantities of Celexa which were misbranded when introduced into interstate commerce or while in interstate commerce, or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which were introduced into interstate commerce in violation of Title 21, United States Code, Section 331.

2. If any of the property subject to forfeiture, as a result of any act or omission of the defendant:

(a) cannot be located upon the exercise of due diligence;

(b) has been transferred or sold to, or deposited with, a third party;

(c) has been placed beyond the jurisdiction of the Court;

(d) has been substantially diminished in value; or

(e) has been commingled with other property which cannot be divided without difficulty;

it is the intent of the United States, pursuant to Title 21, United States Code, Section 853(p), incorporated by reference in Title 28, United States Code, Section 2461(c), to seek forfeiture of any other property of the defendant up to the value of the property subject to forfeiture.

All pursuant to Title 21, United States Code, Sections 334 and 853 and Title 28, United States Code, Section 2461(c), and Rule 32.2 of the Federal Rules of Criminal Procedure.

CARMEN M. ORTIZ
UNITED STATES ATTORNEY

TONY WEST
ASSISTANT ATTORNEY GENERAL
CIVIL DIVISION
U.S. DEPARTMENT OF JUSTICE

By: _____
JAMES E. ARNOLD
ASSISTANT U.S. ATTORNEY

_____ for
JEFFREY I. STEGER
TRIAL ATTORNEY
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