CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

PATENT CERTIFICATION

Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022

OXYCODONE HCl / IBUPROFEN
NDA #21-378

Patent Certification

This application is for a new combination product in which the active ingredients have been previously approved individually. The 505(b)(2) application relies on the Agency's finding of safety and effectiveness for the following listed product

Established Name	Proprietary Name	Dosage Form	Strength	Route	Sponsor	Application #
Oxycodone Hydrochloride	Roxicodone™	Tablet	5 mg	Oral	Roxane	21,011
Ibuprofen	Motrin®	Tablet	400 mg	Oral	McNeil	17,463

Forest Laboratories, Inc. has reviewed the patent and exclusivity information in the Orange Book with respect to the listed products and makes a Paragraph II Certification (all relevant patents have expired).

Patent 4,569,937 covers the product that is the subject of this application. With respect to this patent, Forest Laboratories, Inc. makes a Paragraph IV Certification (non-infringement).

– licensed patent 4,569,937 from DuPont Pharmaceutical Company. Forest Laboratories, Inc. licensed oxycodone/ibuprofen from ~. (see attached statement from –

Signature: Robert W Ashworth

Name: ROBERT ASHWORTH

Title: Senior Director, Regulatory Affairs

Date: 12/04/01

December 3, 2001

VIA FACSIMILE AND FEDERAL EXPRESS

M. Daniel Gordin, Ph.D.
Associate Director, Regulatory Affairs
Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Dr. Gordin:

Pursuant to 314.50(iii)(B)(3). — has a licensing agreement with Forest Laboratories, Inc. for oxycodone/ibuprofen and consents to an immediate effective date.

— licensed U.S. Patent No. 4,569,937 from the DuPont Pharmaceuticals Company with whom it has a license agreement for oxycodone/ibuprofen.

Sincerely

Cc: Ms. Mary Prehn

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In the United States, BTG operates through a wholly owned subsidiary, BTG International Inc.

PATENT INFORMATION

United States Patent [19]

Baker et al.

[11] Patent Number: 4,569,937

[45] Date of Patent: Feb. 11, 1986

[54] ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN

[75] Inventors: Geraldine L. Baker, Minneapolis, Minn.; William K. Schmidt, Wilmington, Del.

[73] Assignee: E. I. Du Pont de Nemours and Company, Wilmington, Del.

[21] Appl. No.: 700,654

[22] Filed: Feb. 11, 1985

[51] Int. Cl.[4] A61K 31/19; A61K 31/44

[52] U.S. Cl. 514/282; 514/557

[58] Field of Search 424/260

[56] References Cited

U.S. PATENT DOCUMENTS

4,322,427 3/1982 Buyniski et al. .

4,489,080 12/1984 Loman 424/260

FOREIGN PATENT DOCUMENTS

0068838 1/1983 European Pat. Off. .

OTHER PUBLICATIONS

S. A. Cooper et al., "Relative Efficacy of an Ibuprofen-Codeine Combination", Clin. Pharmacol. Ther., 27(2), 1980, p. 249.

AMA Drug Evaluations, Fifth Ed., 1983 Chapter 4, pp. 101-102.

Pharmacotherapy, 2, No. 3, May/Jun. 1982, Cooper et al.: Analgesic Efficacy of an Ibuprofen-Codeine Combination, pp. 162-167.

Clinical Pharmacology, K. L. Melmon, M.D., et al., Chap. 11, pp. 498-499, (1972).

The Pharmacological Basis of Therapeutics, L. S. Goodman et al., 5th Ed., Chap. 17, pp. 348-349, (1975).

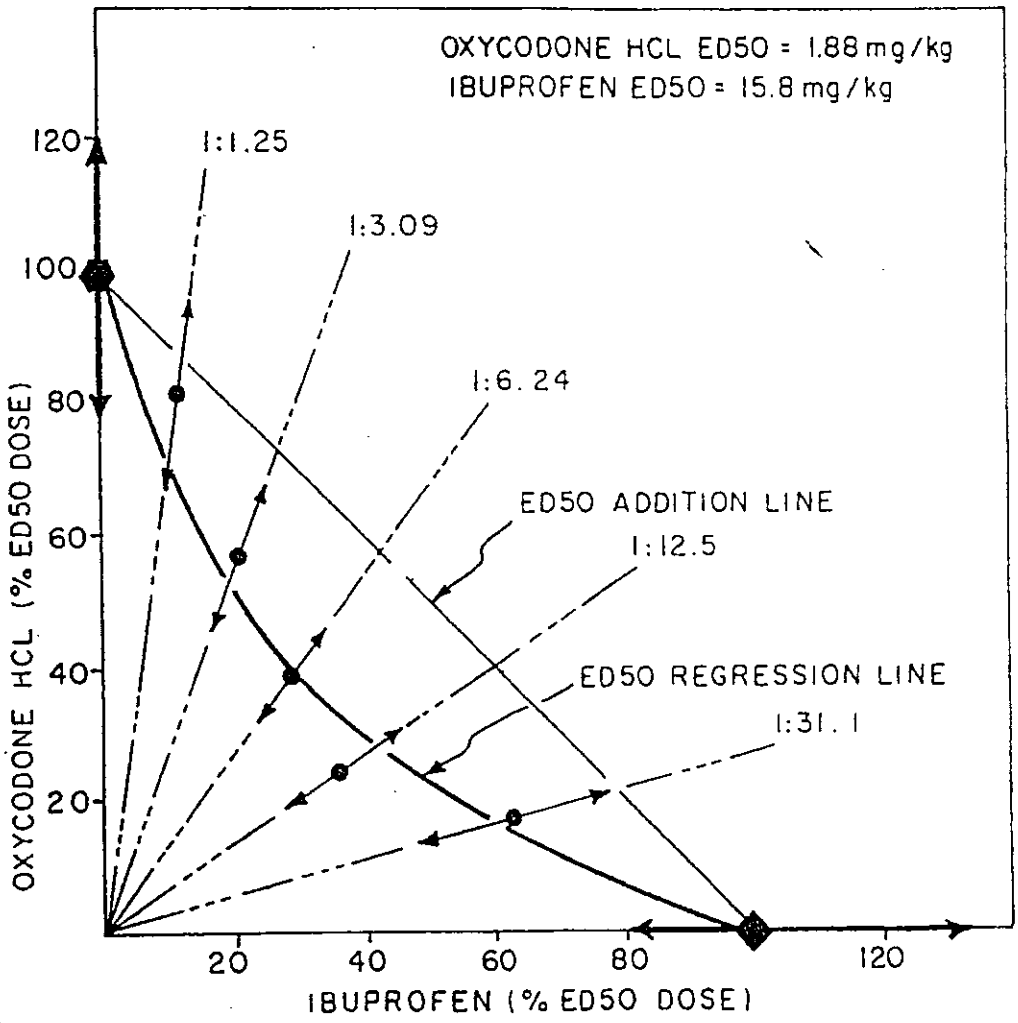
Primary Examiner—Stanley J. Friedman

[57] ABSTRACT

Pharmaceutical compositions of narcotic analgesics and ibuprofen have been found to exhibit unexpectedly enhanced analgesic activity by applying an analysis model which considers data characterizing the analgesic effect of both the pure components as well as the fixed dose ratio combinations. This synergism enables the use of lower doses of either or both drugs with a concomitant reduction in risk of possible side effects.

6 Claims, 1 Drawing Figure

ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN IN THE MOUSE ANTIPHENYLQUINONE WRITHING TEST (5 MIN)



ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN

TECHNICAL FIELD

This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.

BACKGROUND OF THE INVENTION

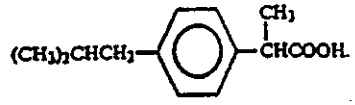
More active analgesic combinations are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages thereby diminishing the expected side effects and toxicity that would result from the otherwise required higher dosages.

U.S. Pat. No. 4,464,376, issued to A. Sunshine et al., on Aug. 7, 1984 describes analgesic and antiinflammatory compositions which comprise caffeine together with a selected non-narcotic/non-steroidal antiinflammatory drug (NSAID) or a selected narcotic analgesic or both. This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone which analgesic effect is further enhanced by the addition of caffeine. Sunshine provides no evidence or suggestion of other than an additive analgesic effect for the combinations.

S. Cooper et al., *Pharmacotherapy*, 2, 162 (1982), describe the analgesic efficacy of an ibuprofen/codeine combination in patients who had undergone dental impaction surgery. Codeine was found to add "a small amount of additional analgesia when used in combination with ibuprofen." This increase in analgesic effects was not statistically significant and there is no suggestion that the combination had a synergistic effect.

U.S. Pat. No. 4,237,140, issued to J. R. Dudzinski on Dec. 2, 1980, describes an analgesic mixture of nalbuphine and acetaminophen. U.S. Pat. No. 4,282,215, issued to J. R. Dudzinski and W. K. Schmidt on Aug. 4, 1981, describes an analgesic mixture of nalbuphine and aspirin. Other nalbuphine analgesic combinations are described in U.S. Pat. No. 4,366,159, issued to M. R. Magruder on Dec. 28, 1982 (with narcotics); U.S. Pat. No. 4,404,210, issued to W. K. Schmidt on Sept. 13, 1983 (with ibuprofen); U.S. Pat. No. 4,407,805, issued to W. K. Schmidt on Oct. 4, 1983 (zomepirac); U.S. Pat. No. 4,402,962, issued to W. K. Schmidt on Sept. 6, 1983 (4,5-bis(4-methoxyphenyl)-2-(trifluoromethylsulfonyl)-1H-imidazole); U.S. Pat. No. 4,407,804, issued to W. K. Schmidt on Oct. 4, 1983 (indomethacin); U.S. Pat. No. 4,404,208, issued to W. K. Schmidt on Sept. 13, 1983 (tiflamizole); U.S. Pat. No. 4,404,209, issued to W. K. Schmidt on Sept. 13, 1983 (sulindac); and U.S. Pat. No. 4,404,211, issued to W. K. Schmidt on Sept. 13, 1983 (flurbiprofen).

U.S. Pat. Nos. 3,228,831 and 3,385,886 issued to Nicholson and Adams disclose the synthesis, formulation, and analgesic properties of α-methyl-4-(2-methylpropyl)benzeneacetic acid, commonly called ibuprofen:



Adams et al., *Arch. Pharmacodyn. Ther.*, 178, 115 (1969), further characterize the use of ibuprofen as an analgesic.

Narcotic analgesics are well known, strong analgesics which can, unfortunately, be addictive and subjected to abuse by parenteral administration. A continuing goal is to be able to reduce the dosage of such narcotic analgesics by combining them with non-addicting ingredients while still maintaining a high level of analgesia.

SUMMARY OF THE INVENTION

According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable sale thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:1 to about 1:800. Preferred ratios of (a):(b) are from about 1:3 to about 1:400, and most preferred ratios are from about 1:30 to about 1:400.

Specifically, a pharmaceutical composition comprising a combination of synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof, has been found to provide enhanced pain relief in mammals.

Another aspect of the invention comprises a method of alleviating pain in a mammal by administering an effective analgesic amount of a composition described above to the mammal.

BRIEF DESCRIPTION OF THE DRAWING

The FIGURE is an isobologram plot characterizing effective pain relieving doses which produce analgesic responses in one half the mice subjected to the phenyl-p-benzoquinone induced writhing test at various dose ratios of oxycodone and ibuprofen.

DETAILED DESCRIPTION OF THE INVENTION

Narcotic analgesics are well known and have been used for many years for the treatment of moderate to severe pain. The term narcotic analgesic when used herein includes but is not limited to oxycodone, oxymorphone, hydrocodone, hydromorphone, morphine, meperidine, and methadone. Oxycodone, oxymorphone, hydrocodone and hydromorphone are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred.

Ibuprofen, which has the chemical name α-methyl-4-(2-methylpropyl)benzeneacetic acid, and its preparation are described in U.S. Pat. Nos. 3,228,831 and 3,385,886, the disclosures of which are hereby incorporated by reference.

When the terms narcotic analgesic or ibuprofen are used herein, it is to be understood that any of the pharmaceutically suitable salts thereof which have analgesic properties in man and other mammals are included by the term. For narcotic analgesics, such salts include the hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates, bitartrates, phosphates, malates, maleates, fumarates, succinates, acetates, terephthalates, and pamoates, while for ibuprofen, pharmaceutically suitable salts would include those of aluminum, calcium, potassium, and sodium.

In a composition of the invention, oxycodone and ibuprofen are combined and have been utilized at dose ratios based on weight of oxycodone to ibuprofen of from 1:1.25 to 1:31.1 in mice subjected to the phenyl-p-benzoquinone induced writhing test to establish anal-

getic effectiveness. The phenyl-p-benzoquinone induced writhing test in mice [H. Blumberg et al., Proc. Soc. Exp. Biol. Med., 118, 763–766 (1965)] is a standard procedure for detecting and comparing the analgesic activity of different classes of analgesic drugs with a good correlation with human analgesic activity. Data for the mouse, as presented in the isobologram, can be translated to other species where the orally effective analgesic dose of the individual compounds is known or can be estimated. The method simply consists of reading the % ED50 DOSE for each dose ratio on the best fit regression analysis curve from the mouse isobologram, multiplying each component by its effective species dose, and then forming the ratio of the amount of oxycodone to ibuprofen. This basic correlation for analgesic properties enables estimation of the range of human effectiveness. [E. W. Pelikan, the Pharmacologist 1, 73 (1959).]

Application of an equieffective dose substitution model and a curvilinear regression analysis utilizing all the data for the individual compounds and various dose ratios for the combinations establishes the existence of unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen, i.e., the resulting activity is greater than the activity expected from the sum of the activities of the individual components.

Compositions of the invention present the opportunity of obtaining relief from pain with reduced dosages of narcotic analgesics, such as oxycodone, thereby diminishing the side effects and toxicity which would result from the otherwise required amounts of the individual drug components.

Dosage Forms

The combination of analgesic agents of the invention can be administered to treat pain by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. The composition of the invention can be administered by any conventional means available for use in conjunction with pharmaceuticals. It can be administered alone, but is generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen. Ordinarily, administration of the composition of the invention in divided doses 2-5 times a day or in a sustained release form is effective to obtain desired results.

Dosage forms (compositions) suitable for internal administration contain a total of from about 5 milligrams to about 600 milligrams of active ingredients per unit. In these pharmaceutical compositions the active ingredients will ordinarily be present in an amount of about 0.5–95% by weight based on the total weight of the composition.

The active ingredients can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions.

Gelatin capsules contain the active ingredients and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the composition of the invention can be illustrated by the following examples:

Eample 1

Oxycodone/Ibuprofen Tablets Formula	(5/60 mg) mg/Tablet
Oxycodone HCl	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	16.0
Stearic Acid	4.0
	225.0

Example 2

Oxycodone/Ibuprofen Tablets Formula	(5/300 mg) mg/Tablet
Oxycodone HCl	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	190.0
Starch, modified	22.0
Stearic Acid	8.0
	525.0

Example 3

Oxycodone/Ibuprofen Tablets Formula	(2.5/300 mg) mg/Tablet
Oxycodone HCl	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	212.5
Starch, modified	22.0
Stearic Acid	8.0
	545.0

Example 4

Oxycodone/Ibuprofen Capsules Formula	(5/60 mg) mg/Capsule
Oxycodone HCl	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	112.0
Starch	8.0

-continued

Oxycodone/Ibuprofen Capsules Formula	(5/60 mg) mg/Capsule
	325.0

Example 5

Oxycodone/Ibuprofen Capsules Formula	(5/300 mg) mg/Capsule
Oxycodone HCl	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	90.0
Starch, modified	7.0
Starch	8.0
	410.0

Example 6

Oxycodone/Ibuprofen Capsules Formula	(2.5/300 mg) mg/Capsule
Oxycodone HCl	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	110.0
Starch, modified	9.5
Starch	8.0
	430.0

Example 7

Oxymorphone/Ibuprofen Tablets Formula	(5/60 mg) mg/Tablet
Oxymorphone HCl	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	16.0
Stearic Acid	4.0
	225.0

Example 8

Oxymorphone/Ibuprofen Formula	(5/300 mg) mg/Tablet
Oxymorphone HCl	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	190.0
Starch, modified	22.0
Stearic Acid	8.0
	525.0

Example 9

Oxymorphone/Ibuprofen Formula	(2.5/300 mg) mg/Tablet
Oxymorphone HCl	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	212.5
Starch, modified	22.0
Stearic Acid	8.0
	545.0

Example 10

Oxymorphone/Ibuprofen Capsules Formula	(5/60 mg) mg/Capsule
Oxymorphone HCl	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	112.0
Starch	8.0
	325.0

Example 11

Oxymorphone/Ibuprofen Capsules Formula	(5/300 mg) mg/Capsule
Oxymorphone HCl	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	90.0
Starch, modified	7.0
Starch	8.0
	410.0

Example 12

Oxymorphone/Ibuprofen Capsules Formula	(2.5/300 mg) mg/Capsule
Oxymorphone HCl	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	110.0
Starch, modified	9.5
Starch	8.0
	430.0

Example 13

Hydrocodone/Ibuprofen Tablets Formula	(5/60 mg) mg/Tablet
Hydrocodone Bitartrate	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	16.0
Starch	4.0
	225.0

Example 14

Hydrocodone/Ibuprofen Tablets Formula	(5/300 mg) mg/Tablet
Hydrocodone Bitartrate	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	190.0
Starch, modified	22.0
Starch	8.0
	525.0

Example 15

Hydrocodone/Ibuprofen Tablets Formula	(2.5/300 mg) mg/Tablet
Hydrocodone Bitartrate	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	212.5
Starch, modified	22.0

-continued

Hydrocodone/Ibuprofen Tablets Formula	(2.5/300 mg) mg/Tablet
Starch	8.0
	545.0

Example 16

Hydrocodone/Ibuprofen Capsules Formula	(5/60 mg) mg/Capsule
Hydrocodone Bitartrate	5.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	112.0
Starch	8.0
	325.0

Example 17

Hydrocodone/Ibuprofen Capsules Formula	(5/300 mg) mg/Capsule
Hydrocodone Bitartrate	5.0
Ibuprofen	300.0
Microcrystalline Cellulose	90.0
Starch, modified	7.0
Starch	8.0
	410.0

Example 18

Hydrocodone/Ibuprofen Capsules Formula	(2.5/300 mg) mg/Capsule
Hydrocodone Bitartrate	2.5
Ibuprofen	300.0
Microcrystalline Cellulose	110.0
Starch, modified	9.5
Starch	8.0
	430.0

Example 19

Hydromorphone/Ibuprofen Tablets Formula	(3/60 mg) mg/Tablet
Hydromorphone HCl	3.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	18.0
Stearic Acid	4.0
	225.0

Example 20

Hydromorphone/Ibuprofen Tablets Formula	(3/300 mg) mg/Tablet
Hydromorphone HCl	3.0
Ibuprofen	300.0
Microcrystalline Cellulose	190.0
Starch, modified	24.0
Stearic Acid	8.0
	525.0

Example 21

Hydromorphone/Ibuprofen Tablets Formula	(1.5/300 mg) mg/Tablet
Hydromorphone HCl	1.5
Ibuprofen	300.0
Microcrystalline Cellulose	213.5
Starch, modified	22.0
Stearic Acid	8.0
	545.0

Example 22

Hydromorphone/Ibuprofen Capsules Formula	(3/60 mg) mg/Capsule
Hydromorphone HCl	3.0
Ibuprofen	60.0
Microcrystalline Cellulose	140.0
Starch, modified	114.0
Starch	8.0
	325.0

Example 23

Hydromorphone/Ibuprofen Capsules Formula	(3/300 mg) mg/Capsule
Hydromorphone HCl	3.0
Ibuprofen	300.0
Microcrystalline Cellulose	90.0
Starch, modified	9.0
Starch	8.0
	410.0

Example 24

Hydromorphone/Ibuprofen Capsules Formula	(1.5/300 mg) mg/Capsule
Hydromorphone HCl	1.5
Ibuprofen	300.0
Microcrystalline Cellulose	110.0
Starch, modified	10.5
Starch	8.0
	430.0

Test Methods

The unexpectedly enhanced analgesic activity obtained in the method of the invention is evidenced by tests conducted on mice. Male CF_1 mice obtained from Charles River Breeding Laboratories, fasted for 16–22 hours and weighing 18–22 g at the time of testing are used throughout. All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or of oxycodone hydrochloride solutions. A dosing volume of 10 ml/kg is used for each sequential solution or suspension. All doses are coded and the test is performed under a code not known to the observer.

A stock suspension of ibuprofen is prepared by mixing 251.4 mg ibuprofen with 70 ml of an aqueous vehicle containing 2% by volume of Tween 80 ®, a pharmacological dispersant manufactured by Fisher Scientific Company and containing 100% polysorbate 80, and 0.25% by weight of Methocel ® A15C powder, a suspending agent manufactured by DOW Chemical Com-

pany and containing 100% methylcellulose, in distilled water. The mixture is sonicated at 150 watts for 1-2 minutes with an ultrasound system, then shaken for two hours at 280 oscillations/minute with 15-20 gm of glass beads. The resultant suspension contains 3.59 mg/ml of ibuprofen; all dosing suspensions are prepared by dilution of the stock suspension with the Methocel ®/-Tween 80 ® vehicle; the vehicle control is Methocel ®/Tween 80 ®. All suspensions are prepared fresh daily.

Stock solutions of oxycodone HCl are prepared by dissolving dry oxycodone hydrochloride powder with the Methocel ®/Tween 80 ® vehicle. All dosing solutions are prepared by dilution of the stock solution with the Methocel ®/Tween 80 ® vehicle; the vehicle control is Methocel ®/Tween 80 ®.

As indicated above, the standard procedure based upon the prevention of phenyl-p-benzoquinone induced writhing in mice is utilizeed to detect and quantify the analgesic activity of compositions containing oxycodone and ibuprofen.

Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen, or vehicle, are injected intraperitoneally with a challenge dose of phenyl-p-benzoquinone 5 minutes prior to the designated observation period. The phenyl-p-benzoquinone is prepared as an 0.1 mg/ml solution in 5% by volume of ethanol in water; the writhing dose is 1.25 mg/kg injected in a volume of 0.25 ml/20g. For scoring purposes a "writhe" is indicated by whole body stretching or contraction of the abdomen; mice are observed 10 minutes for the presence or absence of writhing beginning 5 minutes after receiving the phenyl-p-benzoquinone dose. Each mouse is used only once, then discarded. The alleviation of pain is quantified by determining the dosage at which 50% of the mice in a test group exhibit an analgesic response for the compsition being tested. This dosage as described herein is referred to as the ED50. All ED50 values and their 95% confidence limits are determined numerically by the computer-assisted methods of Finney. [D. J. Finney, "Probit Analysis", Third Edition, Cambridge University Press, Cambridge, England, 1971].

In order to study the interaction between oxycone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected. Four or five coded doses of each selected combination are studied for analgesic effectiveness at 5 minutes using an experimental design which permits coding and complete randomization of the separate dosage forms tested. Altogether 35 separate dosage forms are used and each form is represented in each experimental session. The experiments are continued by running experimental sessions with an equal number of mice per group being tested until the total number, N, of mice tested per group is 21. Later, an additional 22 mice/dose are tested at all dose ratios and the results are pooled with the original data to yield N=43 mice/dose.

The nature of the analgesic interaction (addition, synergism, or antagonism) is determined by graphing the results in a Loewe isobologram [S. Loewe, *Pharm. Rev.* 9:237-242 (1957)]. The isobologram is a quantitive method for measuring interactions between drugs where dose-effect relationships are depicted in a multidimensional array with lines connecting dose pairs that are equieffective in relationship to a common pharmacological endpoint. In this instance, the antiphenylquinone writhing test is used to estimate a common level of analgesic activity (ED50dose) for the two component drugs separately and for each fixed dose-ratio combination. In the isobolographic figure, areas of dose addition, synergism, and/or antagonism are clearly defined by reference to the theoretical "ED50 Addition Line." According to Loewe's isobolographic theory, ED50's falling under the curve (between the ED50 Addition Line and the origin) would represent unexpectedly enhanced analgetic activity and combination ED50's located above the line would represent unexpectedly diminished analgetic activity.

Most importantly, the isobolographic technique permits a full range of doses and dose combinations to be examined where the proportion of the first drug to the second actually varies from 0 to infinity, and to determine, by virtue of the graphical display, whether any one or more of the paired drug combinations displays unique pharmacological properties in comparison to the entire body of data generated. The isobologram is also valuable for organizing the data in a form which is easily amenable to statistical assessment of observed differences.

The synergistic interaction of oxycodone hydrochloride and ibuprofen on phenyl-p-benzoquinone induced writhing in mice is demonstrated by the data in Table I and in the FIGURE, the Loewe isobologram. In the isobolographic figure, the analgesic effect of oxycodone alone is presented in the ordinate, and that of ibuprofen alone is on the abscissa. The dotted lines radiating from the origin represent the exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1. ED50 values are marked on the ordinate and abscissa, representing oxycodone and ibuprofen alone, and on the dotted radial lines, representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios. The arrows extending above and below each ED50 point represent the 95% confidence limits of the ED50's.

As drawn in the FIGURE, the solid diagonal line joining the ED50 values of the two drugs given separately represents the "ED50 Addition Line," the theoretical line for simple additivity of drug effects which would be observed in the absence of a synergistic response. The drawing clearly shows that in the method of the invention, all of the tested fixed ratio compositions give unexpectedly enhanced analgetic activity since the ED50 values for each of these ratios fall below the line of simple additivity.

By utilizing an equieffective dose substitution model and a statistical regression analysis of all of the data, one can obtain a more reliable assessment of the existence of a synergistic property, in this case unexpectedly enhanced analgesic activity. The effects of two compounds are additive if the response to a dose of the two in combination does not change when a portion of one is removed from the mixture and replaced by an equipotent portion of the other. If such substitution increases the response, the mixing together of the compounds is said to potentiate their effect and synergism exists.

Consider ED50 doses of mixtures of X units of compound B with Y units of compound A, whose ED50 doses are β and α, respectively. Given the hypothesis of additivity, all doses of mixtures satisfying the straight line relation,

$$Y = \alpha - \frac{\alpha}{\beta} X.$$

will be ED50 doses. To test the hypothesis of additivity, ED50 doses of mixtures are estimated through probit analysis of data from experiments run at various ratios of A to B. Linear and curvilinear regression models are fitted to the data to estimate the amounts of A in respective ED50 doses, given the amount of B, (or, conversely, the amount of B, given A). If a curvilinear regression fit the data significantly better than a straight line regression, the hypothesis of additivity is refuted and synergism exists for the two compounds for the property of interest.

Values of Y calculated from the straight line of Equation 1, and values of Y calculated from the curvilinear regression are plotted against X on an ED50 isobologram to describe the synergism.

It is convenient to standardize the units of dose such that 100 units of either compound alone is its respective estimated ED50 dose. The additivity hypothesis, then, will be represented by a straight line from 100 on the Y-axis to 100 on the X-axis on the isobologram, and Equation (1) becomes:

$$Y = 100 - X$$

The isobologram in the FIGURE shows the straight line additivity hypothesis for oxycodone HCl and ibuprofen five minutes post oral dosing in the mouse antiphenylquinone writhing test. Data are standardized to the ED50 doses of oxycodone HCl (1.88 mg/kg) and ibuprofen (15.8 mg/kg). Synergism is demonstrated by the regression fitted to ED50 dose levels estimated by probit analysis. Its curvilinearity is statistically significant.

The regression is fitted to the data by the method of least squares. Residual squared deviations about the line of best fit are minimized in directions along lines from the origin through respective data points on the isobologram, these lines making angles with X-axis, $\tan^{-1}(Y/X)$. This is accomplished by a transformation prior to the regression analysis. Its inverse is applied to transform the coordinates of the regression curve back to the X,Y coordinates of the isobologram.

Let D_r be an ED50 dose of a mixture of A and B, where r is the fraction of compound B in the mixture; i.e.

$$r = \frac{X}{X + Y}.$$

It follows from Equation 1 that

$$D_r = \frac{\alpha\beta}{\alpha r + \beta(1 - r)}.$$

From the additivity hypothesis, the logarithms of the ED50 doses at various mixture ratios are a straight line function of ($\text{Log } D_r$). To test the hypothesis, polynomial regressions, as follows, are fitted to ED50 estimates from experimental data obtained at various mixture ratios:

$$F_r = \log D_r = b_0 + \sum_{i=1}^{K} b_i \left(\log \left[\frac{\alpha\beta}{\alpha r + \beta(1 - r)} \right] \right)^i \quad (2)$$

The additivity hypothesis is refuted if a polynomial of degree higher than one fit the data significantly better than a straight line.

$$F_r = b_0 + b_1 \left[\log \left(\frac{\alpha\beta}{\alpha r + \beta(1 - r)} \right) \right]$$

Since X and Y are uniquely determined by F_r and r, the coordinates of the regression are transformed readily to the coordinates of the isobologram.

If data are scaled to ED50 dose levels of 100 standard dose units, Equation (2) becomes

$$F_s = \log 100 = 2. \quad (2.1)$$

The additivity hypothesis implies that F_s is independent of r_i, and may be tested by analysis of the regression model

$$F_s = b_0 + \sum_{i=1}^{K} b_i r_i^i. \quad (2.2)$$

the subscripts, s, indicating that the data are scaled. A statistically significant regression will refute the hypothesis.

The method of least squares utilizes jointly the information contained in all of the separate data points. Statistical significance of the curvilinearity of the regression model establishes the existence of synergism (or antagonism) of the compounds in the biological system studied. The parameters in the model describe its intensity over the range of mixture ratios, from 0 to 1, the nature of which is seen readily when the regression is plotted on the isobologram. This method was used to determine the best-fitting ED50 regression line through the seven (7) ED50 data points representing equivalent levels of analgetic activity for each of the five (5) dose-ratios and for oxycodone and ibuprofen alone given in Table I. As shown in the isobologram plot of the FIGURE, the calculated quadratic polynomial "ED50 Regression Line" fits the data significantly better than the straight "ED50 Addition Line" using stringent, 95% confidence limits ($P < 0.016$). Thus, consistent with Loewe's isobolographic model, the hypothesis of analgesic additivity is refuted and analgesic synergism is established for all combinations of oxycodone and ibuprofen.

By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone from test results in other warm blooded mammals, it is possible to use the isobologram in conjunction with the correlation method discussed above to predict the equivalent range of maximum potentiating dosages for man. Thus, utilizing the data of the present invention and the equivalent ratios in man, it is predicted that oxycodone and ibuprofen would demonstate analgetic potentiation over a range of doses exceeding 1:1 to 1:800. Within this range, doses of 1:3 to 1:400 are preferred while doses of 1:6 to 1:400 are most preferred. Based on the above results with oxycodone showing synergism over a broad compositional range, one skilled in the art would project

synergism with other narcotic analgesics, particularly oxymorphone, hydrocodone, and hydromorphone which are all potent orally in man in the range of about 1 mg ot 10 mg per dose.

As described above, all tests of statistical significance establishing the best fit regression equation for the experimental data and its difference from the ED50 Addition Line were carried out using stringent 95% confidence limits. The use of less stringent limits merely reinforces the conclusions.

TABLE 1

ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS IN THE MOUSE ANTIPHENYLQUINONE WRITHING TEST
5 Min. (N = 43 Mice/Dose)

DRUG COMBINATIONS Oxycodone: Ibuprofen	DRUG DOSE (mg/kg) Oxycodone	Ibuprofen	% MICE BLOCKED	ED50 AT 5 MIN (95% Confidence Limits) Oxycodone	Ibuprofen
Control (0:0)	0	0	4.7	—	—
Oxycodone	0.36	0	11.6		
Only (1:0)	0.72	0	4.7		
	1.44	0	39.5	1.88	0.0
	2.88	0	81.4	(1.52–2.23)	
	5.76	0	95.3		
1:1.25	0.3	0.37	14.0		
	0.6	0.75	16.3		
	1.2	1.50	32.6	1.54	1.92
	2.4	2.99	88.4	(1.25–1.81)	(1.55–2.26)
	4.8	5.99	97.7		
1:3.12	0.24	0.75	11.6		
	0.48	1.50	20.9		
	0.96	2.99	41.9	1.08	3.33
	1.92	5.99	86.0	(0.861–1.29)	(2.66–3.96)
	3.84	11.97	100.0		
1:6.24	0.18	1.12	4.7		
	0.36	2.25	20.9		
	0.72	4.49	41.9	0.733	4.57
	1.44	8.98	93.0	(0.598–0.868)	(3.73–5.42)
	2.88	17.96	97.7		
1:12.5	0.12	1.50	11.6		
	0.24	2.99	30.2		
	0.48	5.99	44.2	0.460	5.75
	0.96	11.97	86.0	(0.356–0.565)	(4.45–7.07)
	1.92	23.95	97.7		
1:31.1	0.06	1.87	7.0		
	0.12	3.74	16.3		
	0.24	7.48	39.5	0.321	9.98
	0.48	15.0	72.1	(0.249–0.399)	(7.76–12.4)
	0.96	29.9	88.4		
Ibuprofen	0	2.25	7.0		
Only (0:1)	0	4.49	11.6	0.0	15.8
	0	8.98	20.1		(12.8–21.0)
	0	17.96	62.8		

What is claimed is:

1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

2. The pharmaceutical composition of claim 1 in oral dosage form.

3. The pharmaceutical composition of claim 1 which contains in addition a suitable pharmaceutical carrier.

4. A method of alleviating pain in a mammal which comprises administering to said mammal affected with pain an effective analgesic amount of the composition of claim 3.

5. A method of alleviating pain in a mammal which comprises administering to said mammal affected with pain an effective analgesic amount of the composition of claim 1.

6. A method of alleviating pain in a mammal which comprises administering to said mammal affected with pain an effective analgesic amount of the composition of claim 2.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,569,937

DATED : February 11, 1986

INVENTOR(S) : Geraldine Lee Baker et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

The title page showing the illustrative figure should appear as shown on the attached sheet.

Column 9, line 19, "utilizecd" should read -- utilized --.

Column 9, line 45, "oxycone" should resd -- oxycodone --.

Column 13, line 4, "1mg ot 10mg" should read -- 1mg to 10mg --.

Signed and Sealed this

Thirteenth Day of *May 1986*

[SEAL]

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

United States Patent [19]

Baker et al.

[11] Patent Number: 4,569,937

[45] Date of Patent: Feb. 11, 1986

[54] ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN

[75] Inventors: Geraldine L. Baker, Minneapolis, Minn.; William K. Schmidt, Wilmington, Del.

[73] Assignee: E. I. Du Pont de Nemours and Company, Wilmington, Del.

[21] Appl. No.: 700,654

[22] Filed: Feb. 11, 1985

[51] Int. Cl.[4] A61K 31/19; A61K 31/44

[52] U.S. Cl. 514/282; 514/557

[58] Field of Search 424/260

[56] References Cited

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4,489,080 12/1984 Loman 424/260

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0068838 1/1983 European Pat. Off. .

OTHER PUBLICATIONS

S. A. Cooper et al., "Relative Efficacy of an Ibuprofen-Codeine Combination", Clin. Pharmacol. Ther., 27(2), 1980, p. 249.

AMA Drug Evaluations, Fifth Ed., 1983 Chapter 4, pp 101-102.

Pharmacotherapy, 2, No. 3, May/Jun. 1982, Cooper et al.: Analgesic Efficacy of an Ibuprofen-Codeine Combination, pp. 162-167.

Clinical Pharmacology, K. L. Melmon, M.D., et al., Chap. 11, pp. 498-499, (1972).

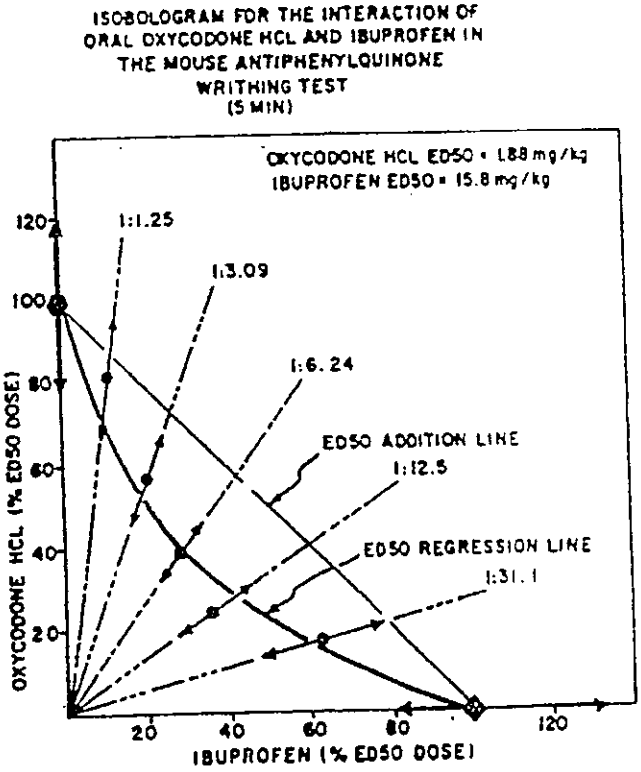
The Pharmacological Basis of Therapeutics, L. S. Goodman et al., 5th Ed., Chap. 17, pp. 348-349, (1975).

Primary Examiner—Stanley J. Friedman

[57] ABSTRACT

Pharmaceutical compositions of narcotic analgesics and ibuprofen have been found to exhibit unexpectedly enhanced analgesic activity by applying an analysis model which considers data characterizing the analgesic effect of both the pure components as well as the fixed dose ratio combinations. This synergism enables the use of lower doses of either or both drugs with a concomitant reduction in risk of possible side effects.

6 Claims, 1 Drawing Figure



Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-378

NAME OF APPLICANT / NDA HOLDER
Forest Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Combunox

ACTIVE INGREDIENT(S)	STRENGTH(S)
Oxycodone Ibuprofen	5 mg 400 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

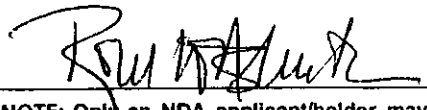
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☑ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	07/20/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Robert Ashworth, PhD	
Address Plaza III, Suite 602 Harborside Financial Center	City/State Jersey City, NJ
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EXCLUSIVITY SUMMARY FOR NDA # 21-378 SUPPL # N/A

Trade Name Combunox Generic Name oxycodone HCl and ibuprofen, USP (5/400 mg)

Applicant Name Forest Laboratories, Inc. HFD # 170

Approval Date If Known November 26, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____three_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

"No" for this oxycodone/ibuprofen product
Note: On 7-1-98, ibuprofen received pediatric exclusivity down to 6 M of age

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _21-011__ __Roxicodone (Oxycodone HCl)__

NDA# _17-463__ __Motrin (ibuprofen)_____

For additional products see attached list.

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

OXY-MD-05, OXY-MD-06, OXY-MD-08, OXY-MD-10

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study OXY-MD-05, titled, "A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg alone, and Oxycodone 5 mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery"

Study OXY-MD-06, titled, "A Double-Blind, Placebo - Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone, Oxycodone HCl 5 mg Alone, and Oxycodone HCl 10 mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery"

Study OXY-MD-08, titled, "A Randomized, Double-Blind, Multiple-Dose Evaluation of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg in Patients with Moderate to Severe Pain

Following Dental or Orthopedic Surgery"

Study OXY-MD-10, titled, "A Double-Blind, Placebo and Comparator Controlled , Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/ Ibuprofen 400 mg in Female Patients with Moderate to Severe Post-Abdominal or Pelvic Surgical Pain"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

All Investigations

IND # 52,310 YES /X/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not

be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

Appl No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021587	Yes	CHLORPHENIRAMINE MALEATE; IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	SUSPENSION; ORAL	1MG/5ML;100MG /5ML;15MG/5ML	CHILDREN'S ADVIL ALLERGY SINUS	WYETH CONS
021441	Yes	CHLORPHENIRAMINE MALEATE; IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET; ORAL	2MG;200MG;30 MG	ADVIL ALLERGY SINUS	WYETH CONS
021472	No	IBUPROFEN	CAPSULE; ORAL	200MG	IBUPROFEN	BANNER PHARMACAP S
074782	Yes	IBUPROFEN	CAPSULE; ORAL	200MG	IBUPROFEN	PHARM FORM
020603	Yes	IBUPROFEN	SUSPENSION/DR OPS; ORAL	40MG/ML	CHILDREN'S MOTRIN	MCNEIL
075217	No	IBUPROFEN	SUSPENSION/DR OPS; ORAL	40MG/ML	IBUPROFEN	PERRIGO
020812	Yes	IBUPROFEN	SUSPENSION/DR OPS; ORAL	100MG/2.5ML	PEDIATRIC ADVIL	WYETH CONS
074916	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	IBUPROFEN	ALPHARMA US PHARMS
020516	Yes	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S MOTRIN	MCNEIL
074937	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S IBUPROFEN	PERRIGO
021604	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ELIXSURE	TARO
020589	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ADVIL-FLAVORED	WYETH CONS
020589	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ADVIL	WYETH CONS

020601	Yes	IBUPROFEN	TABLET, CHEWABLE; ORAL	100MG	JUNIOR STRENGTH MOTRIN	MCNEIL
020601	No	IBUPROFEN	TABLET, CHEWABLE; ORAL	50MG	CHILDREN'S MOTRIN	MCNEIL
076359	No	IBUPROFEN	TABLET, CHEWABLE; ORAL	100MG	IBUPROFEN	PERRIGO
076359	No	IBUPROFEN	TABLET, CHEWABLE; ORAL	50MG	IBUPROFEN	PERRIGO
020944	No	IBUPROFEN	TABLET, CHEWABLE; ORAL	100MG	JUNIOR STRENGTH ADVIL	WYETH CONS
020944	No	IBUPROFEN	TABLET, CHEWABLE; ORAL	50MG	CHILDREN'S ADVIL	WYETH CONS
071057	No	IBUPROFEN	TABLET; ORAL	200MG	IBU-TAB 200	ALRA
075661	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	BASF
076117	No	IBUPROFEN	TABLET; ORAL	100MG	IBUPROFEN	DR REDDYS LABS INC
071333	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	INTERPHARM
072199	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	INTERPHARM
071144	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	IVAX PHARMS
072903	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	IVAX PHARMS
072901	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	IVAX PHARMS
074931	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	LEINER
076741	No	IBUPROFEN	TABLET; ORAL	100MG	IBUPROFEN	LNK

075139	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	LNK
075010	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	LNK
020602	No	IBUPROFEN	TABLET; ORAL	100MG	JUNIOR STRENGTH MOTRIN	MCNEIL
070475	No	IBUPROFEN	TABLET; ORAL	200MG	MEDIPREN	MCNEIL
073019	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	MCNEIL
019012	Yes	IBUPROFEN	TABLET; ORAL	200MG	MOTRIN MIGRAINE PAIN	MCNEIL
019012	Yes	IBUPROFEN	TABLET; ORAL	200MG	MOTRIN IB	MCNEIL
071215	No	IBUPROFEN	TABLET; ORAL	200MG	MEDIPREN	MCNEIL
072249	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	MUTUAL PHARM
071229	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	MUTUAL PHARM
071870	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	MYLAN
076460	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	NEIL
071163	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	OHM
071214	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROHM	OHM LABS
071575	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PAR PHARM
070481	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PAR PHARM
070985	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PAR PHARM
075367	No	IBUPROFEN	TABLET; ORAL	100MG	JUNIOR STRENGTH	PERRIGO

					IBUPROFEN	
072095	No	IBUPROFEN	TABLET; ORAL	200MG	TAB-PROFEN	PERRIGO
072096	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PERRIGO
072098	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PERRIGO
072097	No	IBUPROFEN	TABLET; ORAL	200MG	CAP-PROFEN	PERRIGO
075995	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PERRIGO
073691	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PVT FORM
072299	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PVT FORM
071265	No	IBUPROFEN	TABLET; ORAL	200MG	PROFEN	PVT FORM
071735	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PVT FORM
071732	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	PVT FORM
071807	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	SANDOZ
070733	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	SANDOZ
074533	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	SANDOZ
074525	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	SANDOZ
071639	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	VINTAGE PHARMS
070435	No	IBUPROFEN	TABLET; ORAL	200MG	IBUPROFEN	WATSON LABS
020267	No	IBUPROFEN	TABLET; ORAL	100MG	JUNIOR STRENGTH ADVIL	WYETH CONS
018989	No	IBUPROFEN	TABLET; ORAL	200MG	ADVIL	WYETH CONS

020402	Yes	IBUPROFEN POTASSIUM	CAPSULE; ORAL	200MG	ADVIL LIQUI-GELS	WYETH CONS
020402	Yes	IBUPROFEN POTASSIUM	CAPSULE; ORAL	200MG	ADVIL MIGRAINE LIQUI-GELS	WYETH CONS
021374	Yes	IBUPROFEN POTASSIUM; PSEUDOEPHEDRINE HYDROCHLORIDE	CAPSULE; ORAL	200MG;30MG	ADVIL COLD AND SINUS	WYETH CONS
021128	Yes	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	SUSPENSION; ORAL	100MG/5ML;15MG/5ML	CHILDREN'S MOTRIN COLD	MCNEIL CONS SPECLT
076478	No	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	SUSPENSION; ORAL	100MG/5ML;15MG/5ML	IBUPROFEN AND PSEUDOEPHEDRINE HCL	PERRIGO
021373	No	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	SUSPENSION; ORAL	100MG/5ML;15MG/5ML	CHILDREN'S ADVIL COLD	WYETH CONS
019899	No	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET; ORAL	200MG;30MG	SINE-AID IB	MCNEIL CONS SPECLT
074567	No	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET; ORAL	200MG;30MG	IBUPROHM COLD AND SINUS	OHM LABS
075588	No	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET; ORAL	200MG;30MG	IBUPROFEN AND PSEUDOEPHEDRINE HCL	PHARM FORM
019771	Yes	IBUPROFEN; PSEUDOEPHEDRINE HYDROCHLORIDE	TABLET; ORAL	200MG;30MG	ADVIL COLD AND SINUS	WYETH CONS

Active Ingredient Search Results from "OB_Rx" table for query on "ibuprofen."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020716	AB	Yes	HYDROCODONE BITARTRATE;	TABLET; ORAL	7.5MG;200MG	VICOPROFEN	ABBOTT

			IBUPROFEN				
076604	AB	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7 5MG;200MG	HYDROCODONE BITARTRATE AND IBUPROFEN	ANDRX PHARMS
076642		Yes	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	5MG;200MG	HYDROCODONE BITARTRATE AND IBUPROFEN	INTERPHARM
076642	AB	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7.5MG;200MG	HYDROCODONE BITARTRATE AND IBUPROFEN	INTERPHARM
076023	AB	No	HYDROCODONE BITARTRATE; IBUPROFEN	TABLET; ORAL	7.5MG;200MG	HYDROCODONE BITARTRATE AND IBUPROFEN	TEVA
074978	AB	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	IBUPROFEN	ALPHARMA US PHARMS
019842	AB	Yes	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	MOTRIN	MCNEIL CONS SPECLT
076925	AB	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	IBUPROFEN	PERRIGO R AND D
019833	BX	No	IBUPROFEN	SUSPENSION; ORAL	100MG/5ML	CHILDREN'S ADVIL	WYETH CONS
071058	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBU-TAB	ALRA
071059	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBU-TAB	ALRA
018197	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBU	BASF
070083	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBU	BASF
075682	AB	No	IBUPROFEN	TABLET;	400MG	IBUPROFEN	BASF

			ORAL			
070088	No	IBUPROFEN	TABLET; ORAL	600MG	IBU	BASF
075682 **AB**	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	BASF
070099 **AB**	No	IBUPROFEN	TABLET; ORAL	600MG	IBU	BASF
075682 **AB**	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	BASF
070745 **AB**	No	IBUPROFEN	TABLET; ORAL	800MG	IBU	BASF
076112 **AB**	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	DR REDDYS LABS INC
076112 **AB**	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	DR REDDYS LABS INC
076112 **AB**	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	DR REDDYS LABS INC
071334 **AB**	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	INTERPHARM
071335 **AB**	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	INTERPHARM
071935 **AB**	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	INTERPHARM
071145 **AB**	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	IVAX PHARMS
071146 **AB**	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	IVAX PHARMS
071769 **AB**	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	IVAX PHARMS
017463 **AB**	No	IBUPROFEN	TABLET; ORAL	300MG	MOTRIN	MCNEIL CONS SPECLT

017463	AB	No	IBUPROFEN	TABLET; ORAL	400MG	MOTRIN	MCNEIL CONS SPECLT
017463	AB	No	IBUPROFEN	TABLET; ORAL	600MG	MOTRIN	MCNEIL CONS SPECLT
017463	AB	Yes	IBUPROFEN	TABLET; ORAL	800MG	MOTRIN	MCNEIL CONS SPECLT
071230	AB	No	IBUPROFEN	TABLET; ORAL	300MG	IBUPROFEN	MUTUAL PHARM
071231	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	MUTUAL PHARM
071232	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	MUTUAL PHARM
072004	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	MUTUAL PHARM
070045	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	MYLAN
070057	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	MYLAN
071999	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	MYLAN
070818	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	OHM LABS
070469	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROHM	OHM LABS
070329	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	PAR PHARM
070330	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	PAR PHARM
070986	AB	No	IBUPROFEN	TABLET;	800MG	IBUPROFEN	PAR PHARM

				ORAL			
071666	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	PLIVA
071667	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	PLIVA
071668	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	PLIVA
071266	AB	No	IBUPROFEN	TABLET; ORAL	300MG	IBUPROFEN	PVT FORM
071267	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	PVT FORM
071268	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	PVT FORM
072300	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	PVT FORM
070734	AB	No	IBUPROFEN	TABLET; ORAL	300MG	IBUPROFEN	SANDOZ
070735	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	SANDOZ
070736	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	SANDOZ
072169	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	SANDOZ
071644	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	VINTAGE PHARMS
070436	AB	No	IBUPROFEN	TABLET; ORAL	400MG	IBUPROFEN	WATSON LABS
070437	AB	No	IBUPROFEN	TABLET; ORAL	600MG	IBUPROFEN	WATSON LABS
071547	AB	No	IBUPROFEN	TABLET; ORAL	800MG	IBUPROFEN	WATSON LABS

Active Ingredient Search Results from "OB_Rx" table for query on "oxycodone."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
040199	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	AMIDE PHARM
040304	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	BARR
040289	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	DURAMED PHARMS BARR
040303	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	ENDO PHARMS
040257	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	MALLINCKRODT
040219	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	MUTUAL PHARM
088790	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	TYLOX	ORTHO MCNEIL PHARM
040061	AA	No	ACETAMINOPHEN; OXYCODONE	CAPSULE; ORAL	500MG;5MG	ROXILOX	ROXANE

			HYDROCHLORIDE				
040106	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	VINTAGE PHARMS
040234	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	CAPSULE; ORAL	500MG;5MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS
089351		No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	SOLUTION; ORAL	325MG/5ML;5MG/5ML	ROXICET	ROXANE
040203	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCODONE AND ACETAMINOPHEN	AMIDE PHARM
087406	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCODONE AND ACETAMINOPHEN	BARR
040272	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCODONE AND ACETAMINOPHEN	DURAMED PHARMS BARR
040434	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;10MG	PERCOCET	ENDO PHARMS
040330		Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;2.5MG	PERCOCET	ENDO PHARMS

040330	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	PERCOCET	ENDO PHARMS
085106	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	PERCOCET	ENDO PHARMS
040434	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;7.5MG	PERCOCET	ENDO PHARMS
040341	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	500MG;7.5MG	PERCOCET	ENDO PHARMS
040341	AA	Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	650MG;10MG	PERCOCET	ENDO PHARMS
040545	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;10MG	OXYCODONE AND ACETAMINOPHEN	MALLINCKRODT
087463	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCET	MALLINCKRODT
040545	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;7.5MG	OXYCODONE AND ACETAMINOPHEN	MALLINCKRODT
040550	AA	No	ACETAMINOPHEN; OXYCODONE	TABLET; ORAL	500MG;7.5MG	OXYCODONE AND ACETAMINOPH	MALLINCKRODT

			HYDROCHLORIDE			EN	
040550	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	650MG;10MG	OXYCODONE AND ACETAMINOPHEN	MALLINCKRODT
087003	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	ROXICET	ROXANE
089775		Yes	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	500MG;5MG	ROXICET 5/500	ROXANE
040105	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCODONE AND ACETAMINOPHEN	VINTAGE PHARMS
040535	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;10MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS
040171	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;5MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS
040535	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	325MG;7.5MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS
040371	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	500MG;7.5MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS

040371	AA	No	ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE	TABLET; ORAL	650MG;10MG	OXYCODONE AND ACETAMINOPHEN	WATSON LABS
007337	AA	Yes	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET; ORAL	325MG;2.25MG;0.19 MG	PERCODAN-DEMI	ENDO PHARMS
007337	AA	Yes	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET; ORAL	325MG;4.5MG;0.38 MG	PERCODAN	ENDO PHARMS
040260	AA	No	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET; ORAL	325MG;4.5MG;0.38 MG	OXYCODONE AND ASPIRIN	MUTUAL PHARM
087794	AA	No	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET; ORAL	325MG;4.5MG;0.38 MG	OXYCODONE AND ASPIRIN	MUTUAL PHARM
040255	AA	No	ASPIRIN; OXYCODONE HYDROCHLORIDE; OXYCODONE TEREPHTHALATE	TABLET; ORAL	325MG;4.5MG;0.38 MG	OXYCODONE AND ASPIRIN	WATSON LABS
075923	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	10MG	OXYCODONE HCL	ENDO PHARMS

075923	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	20MG	OXYCODONE HCL	ENDO PHARMS
075923	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	40MG	OXYCODONE HCL	ENDO PHARMS
075923	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	80MG	OXYCODONE HCL	ENDO PHARMS
076318	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	80MG	OXYCODONE HCL	IMPAX LABS
020553	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	10MG	OXYCONTIN	PURDUE PHARMA LP
020553	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	20MG	OXYCONTIN	PURDUE PHARMA LP
020553	AB	Yes	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	40MG	OXYCONTIN	PURDUE PHARMA LP
020553	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED RELEASE; ORAL	80MG	OXYCONTIN	PURDUE PHARMA LP
076168	AB	No	OXYCODONE HYDROCHLORIDE	TABLET, EXTENDED	80MG	OXYCODONE HCL	TEVA

				RELEASE ; ORAL				
021011	AB	Yes	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	15MG		ROXICODONE	AAIPHARMA
021011	AB	No	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	30MG		ROXICODONE	AAIPHARMA
076636	AB	No	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	15MG		OXYCODONE HCL	AMIDE PHARM
076636	AB	No	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	30MG		OXYCODONE HCL	AMIDE PHARM
076758	AB	No	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	15MG		OXYCODONE HCL	MALLINCKRODT
076758	AB	No	OXYCODONE HYDROCHLORIDE	TABLET; ORAL	30MG		OXYCODONE HCL	MALLINCKRODT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
11/26/04 02:33:07 PM

Bob Rappaport
11/26/04 03:10:52 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-378 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: December 19, 2001 Action Date: November 26, 2004

HFD 170 Trade and generic names/dosage form: Combunox (Oxycodone HCl and Ibuprofen)

Applicant: Forest Laboratories, Inc. Therapeutic Class: 4S

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: short term (no more than 7 days) management of acute, moderate to severe pain

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ■ No: Please check all that apply: X Partial Waiver X Deferred ____ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr. 0	Tanner Stage____
Max____	kg____	mo.____	yr. 2	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ■ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 2 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 17 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ■ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-378
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
11/24/04 04:35:34 PM

Debarment Certification

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Item 16
NDA 21-378
Oxycodone/Ibuprofen Tablets – New Drug Application

DEBARMENT CERTIFICATION

Forest Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food , Drug, and Cosmetic Act in connection with this application.

Lawrence S. Olanoff, M.D., Ph.D.
Executive Vice-President
Forest Laboratories, Inc.

9/3/02
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Lawrence S. Olanoff MD Ph.D.	Executive VP- Forest Laboratories
FIRM/ORGANIZATION	
Forest Laboratories, Inc.	
SIGNATURE	DATE
[signature]	May 11, 2004

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

Attachment 1 to FORM FDA 3454

No clinical investigator in the OXY-MD-10 trial had any financial arrangements to disclose.

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
1	**Shireen Ahmad, MD** Northwestern University Department of Anesthesia 251 E. Huron, Suite F5-704 Chicago, IL 60611	Shireen Ahmad, MD	Y Y Y Y	
2	**Scott R. Barton, MD** JBA Research 1045 E. 3900 South Suite 100 Salt Lake City, UT 84121	Scott R. Barton, MD	Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
2	**Scott R. Barton, MD (cont.)**		Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y	
3	**Jeffrey Wall, MD** Truman Medical Center University of Missouri, Kansas City OB/GYN Administration 2301 Holmes Street Kansas City, MO 64108	Jeffrey W. Wall, MD	Y Y Y Y	
4	**Christine Brody, MD** Damluji Research Center 591 Camino De La Reina #1219 San Diego, CA 92108	Christine Brody, MD	Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
6	**Robert Berkowitz, MD** Crozer-Keystone Health System One Medical Center Blvd. Chec House Upland, PA 19013	Robert Berkowitz, MD	Y Y Y Y Y	
7	**Michael J. Drass, MD** Allegheny Pain Management, PC 620 Howard Avenue Altoona, PA 16601	Michael J. Drass, MD	Y Y Y Y Y	
8	**Behnam Khaleghi, MD** Department of Anesthesiology Cooper Hospital/Univ. Med Center One Cooper Plaza - Room 202 Camden, NJ 08103	Benham Khaleghi, MD	Y Y Y Y Y Y Y	
10	**Linda Haddox, MD** Coastal Medical Research 2701 S. Ridgewood Ave. Suite C7 South Daytona, FL 32119	Linda Haddox, MD	Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
12	**James L. Head, MD** Southern Drug Research 1222 14th Ave., South Suite 301 Birmingham, AL 35205	James L. Head, MD	Y Y Y Y Y Y Y Y Y Y	
13	**Hugh C. Hemmings, Jr., MD** Weill Medical College New York Presbyterian Hospital Box 50, 525 E. 68th Street New York, NY 10021	Hugh Hemmings, Jr., MD	Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
14	**Timothy S. Houden, MD** JBA Research 1045 E. 3900 South Suite 100 Salt Lake City, UT 84121	Timothy S. Houden, MD	Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
14	**Timothy S. Houden, MD (cont.)**	Scott D. Swift, MD	Y Y Y Y Y N N	Both listed on 1572 dated 4/5/02. Note to File (dated 4/25/02) stated no longer employed by site; documents unobtainable. SIV 5/23/02
15	**Gary R. Jones, MD** Four Seasons Clinic for Women 1500 W. 38th Street #25 Austin, TX 78731	Gary R. Jones, MD	Y Y Y Y Y Y N	Listed on 1572 dated 5/6/02. Deleted from updated 1572 (signed 6/4/02). Site was not initiated until 6/21/02.
17	**Mark Thomas Matsunaga, MD** St. Agnes Healthcare Clinical Research Center 900 Caton Avenue Box 212 Baltimore, MD 21229	Mark T. Matsunaga, MD	Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
18	**Tillman Wayne McDonald, MD** Progressive Research, LLC 5-E Cleveland Ct. Greenville, SC 29607	Tillman W. McDonald, MD	Y Y Y Y Y Y Y Y Y Y Y Y	
19	**Martin Moliver, MD** Millenium Research Institute, Inc. 6771 SW 106 Street Miami, FL 33156	Martin Moliver, MD	Y Y Y Y Y Y Y Y Y Y Y Y	
20	**John Morgan, MD** Southern Drug Research 1222 14th Ave., South Suite 301 Birmingham, AL 35205	John Morgan, MD	Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
21	**Jeffrey D. Quinn, MD**	Jeffrey D. Quinn, MD	Y	
	JBA Research		Y	
	1045 E. 3900 South		Y	
	Suite 100		Y	
	Salt Lake City, UT 84121		Y	
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Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
21	**Jeffrey D. Quinn, MD (cont.)**		Y Y N	Listed on 1572 dated 4/5/02. Note to File (dated 4/25/02) stated no longer employed by site; documents unobtainable. SIV 5/24/02
22	**Jebadural Ratnaraj, MD** Washington University School of Medicine Department of Anesthesiology Campus Box 8054 660 S. Euclid Avenue St. Louis, MO 63110	Jebadural Ratnaraj, MD	Y Y Y Y Y Y Y Y Y	
23	**Lowell W. Reynolds, MD** Loma Linda University Center for Pain Management and Research 11406 Loma Linda Drive Suite #514 Loma Linda, CA 92354	Lowell W. Reynolds, MD	Y Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
24	**Steve M. Rhondeau, MD** JBA Research 1045 E. 3900 South Suite 100 Salt Lake City, UT 84121	Steven M. Rhondeau, MD	Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
24	**Steve M. Rhondeau, MD (cont.)**	Karen A. Zempolich, MD	Y Y Y Y Y N	Listed on 1572 dated 4/5/02. Note to File (dated 4/25/02) stated no longer employed by site; documents unobtainable. SIV 5/22/02
26	**James E. Lyle III, MD** Alabama Clinical Therapeutics 1100 East Park Drive Suite 406 Birmingham, AL 35235	James E. Lyle, III, MD	Y Y Y Y Y Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
27	**Neil Singla, MD** Huntington Memorial Hospital 100 W. California Blvd. Pasadena, CA 91109	Neil K. Singla, MD	Y Y Y Y Y Y Y Y Y	
28	**Ronald P. Spencer, MD** RenStar Medical Research 104 S. East First Ave. Suite B Ocala, FL 34471	Ronald P. Spencer, MD	Y Y Y Y Y Y Y Y Y Y	
29	**Thomas G. Stavoy, MD** Coastal Medical Research 2701 S. Ridgewood Ave. Suite C7 South Daytona, FL 32119	Thomas Stavoy, MD	Y Y Y Y Y Y Y Y Y Y Y	

Site #	Principal Investigator Name & Address	Investigator Names	Financial Disclosure Form 3454 Signed and no financial information to disclose	Reason Financial Information Not Obtained
30	**Stephanie Van Zandt, MD** Morton Plant Mease Healthcare 207 Jeffords Street Mailstop 110 Clearwater, FL 33756	Stephanie Van Zandt, MD	Y Y Y Y Y Y Y	
31	**John G. Wideman, MD** Cullman Clinical Research, Inc. 1890 Alabama Highway 157 Suite 220 Cullman, AL 35058-0609	John G. Wideman, MD	Y Y	
32	**Bret A. Wittmer, MD** Commonwealth Biomedical Research, LLC 1470-A Chelsea Drive Madisonville, KY 42431	Bret A. Wittmer, MD	Y Y Y Y Y	

FINANCIAL DISCLOSURE STATEMENT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Lawrence S. Olanoff	Executive Vice-President
FIRM/ORGANIZATION	
Forest Laboratories, Inc.	
SIGNATURE	DATE
LSOlanoff	10/25/01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FINANCIAL DISCLOSURE
PRINCIPAL INVESTIGATORS AND SUB-INVESTIGATORS

Pursuant to 21 CFR 312.54 (c)(4), financial disclosure was obtained from the following investigators and sub-investigators who participated in Studies OXY-MD-05, OXY-MD-06, and OXY-MD-08 that are submitted in NDA 21-378 to support the approval of oxycodone/ibuprofen combination product:

Protocol No. OXY-MD-05

Title: A Double Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone and Oxycodone HCl 5 mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery

Site Number	Investigator/Sub-Investigators
1	Dr. Thomas Van Dyke Boston University School of Dental Medicine Boston, MA
2	Dr. Leonard Litkowski University of Maryland Dental School Baltimore, MD
3	Dr. Theodore Kiersch Cranial Pain Research Tucson, AZ

Protocol No. OXY-MD-06

Title: A Double Blind, Placebo-Controlled, Single Dose Parallel Study of the Analgesic Efficacy, and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg alone, Oxycodone HCl 10 mg Alone and Oxycodone HCl 5 mg in Patients with Moderate to Severe Pain Following Dental Surgery

Site Number	Investigator/Sub-Investigators
1	Dr. Dennis Adamson Provo Recovery Center Provo, Utah
2	Dr. Steven Christensen SLC Recovery Center Salt Lake City, Utah

Protocol No. OXY-MD-08

Study Title: A Randomized, Double Blind, Multiple-dose Evaluation of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg in Patients with Moderate to Severe Pain Following Dental or Orthopedic Surgery

Site Number	Investigator/Sub-Investigators
1	Dr. Thomas Van Dyke Boston University School of Dental Medicine Boston, MA
2	Dr. Dennis Adamson Provo Recovery Center Provo, Utah
3	Dr. Steven Christensen SLC Recovery Center Salt Lake City, Utah

Site Number	Investigator/Sub-Investigators
4	Dr. Robert Sorrell Alabama Orthopaedic Center, PC Birmingham, AL
5	Dr. Brice Brackin Shelby Medical Center Alabaster, AL
8	Dr. Joseph Gimbel Arizona Research Center, LLC Phoenix, AZ
9	Dr. Martin Hale Park Place Orthopedics & Rehabilitation Plantation, FL

Site Number	Investigator/Sub-Investigators
10	Dr. Hubert Riegler Latttimore Orthopedics, P.C. Rochester, NY
11	Dr. Leonard Litkowski University of Maryland Dental School Baltimore, MD
12	Dr. Theodore Kiersch Cranial Pain Research Tucson, AZ
13	Dr. Jay Katz Tucson Orthopaedic Institute Tucson, AZ

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

MEMORANDUM

Date:	November 24, 2004
To:	File, NDA 21-378
From:	R. Daniel Mellon, Ph.D. Supervisory Pharmacologist, DACCADP
Subject:	Secondary Pharmacology Toxicology Review for Combunox™ (Oxycodone/Ibuprofen)
Date of Submission:	May 27, 2004

Background: Forest Laboratories submitted NDA 21-378 for a second cycle review on May 27, 2004. The original submission was reviewed and determined to be approvable, as relayed by a letter to the sponsor signed by Dr. McCormick on October 18, 2002. In that letter, the following pharmacology/toxicology related deficiencies were listed (numbers are consistent with the actual letter):

5. Conduct Segment I (Fertility) and Segment III (peri- and post-natal development) studies as a requirement for this NDA. Depending on the timing of the resubmission, you may provide justification of these as a Phase 4 commitment.

6. Provide assessment in two species of the carcinogenic potential of this drug product unless you can demonstrate post-marketing data from similar combination drug products containing oxycodone that the drug product will not be used chronically.

7. Provide appropriate patent certification to support reference to labeled nonclinical information regarding other marketed products.

8. The following deficiencies pertain to the acceptance specifications for oxycodone HCl. Submit revised specifications as recommended below.

a. Limit the acceptance criteria of individual drug substance impurities other than — to NMT — or provide nonclinical toxicologic qualification (3-month toxicity study using adequate levels of the impurities in an appropriate species). We recommend that you consult with the agency in the design of these studies.

b. Submit adequate qualification of the potentially genotoxic — impurity — e either via demonstration that it is a human metabolite or via two in vitro genotoxicity testing studies (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). If no qualification is submitted, or if it is determined to be genotoxic, limit it (e.g., via in-process controls or drug substance acceptance criteria) to '

c. If — is determined to be genotoxic, or if no genotoxicity testing is submitted for it, submit adequate qualification of the — — impurities either via demonstration that they are significant human metabolites or via genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay); or, if no qualification is submitted, or the impurity is determined to be genotoxic, limit the impurity (e.g., via in-process controls or drug substance acceptance criteria) to "< —

This memo will summarize each of the above requirements and discuss both the recommended labeling and phase 4 commitments pertaining to pharmacology and toxicology issues.

Response and Comments: Dr. Mamata De reviewed two genetic toxicology for the impurity — that were submitted by the sponsor.

Approvable Item 5: The sponsor has stated their intention to initiate Segment I and III studies as a phase 4 commitment post approval. Although a significant amount of time has elapsed since the approvable letter in October of 2002, this will be acceptable.

Approvable Item 6: This requirement was overturned by Dr. John Jenkins, Director of the Office of New Drugs, Center for Drug Evaluation and Research following evaluation of the second dispute resolution request submitted by Forest Laboratories. As a result, carcinogenicity studies are not required for this NDA.

Approvable Item 7: Forest Laboratories provided patent certification for AAI Pharma's Roxicodone (NDA 21-011) and McNeil's Ibuprofen (NDA 17-463). The Roxicodone label does not currently contain data regarding potential mutagenicity of oxycodone. If the NDA is approved, the lack of mutagenicity data for Combunox™ will be addressed in labeling. The sponsor should commit to providing adequate mutagenicity data for the label as a phase 4 commitment.

Approvable Item 8: Please see the Chemistry, Manufacturing and Control Review for specific details. Forest Laboratories submitted two genetic toxicology studies for — — Dr. Mamata De reviewed these studies and found them to be

adequate. During a meeting with the sponsor on April 2, 2004, the Forest asked the following question: *Does the FDA agree that the genotoxic potential of — has been adequately assessed and that the weight of evidence indicates lack of genotoxic effect?* The Division responded as follows:

- The Division must evaluate all of the available data regarding the identified and tested — impurities.
- Although — has tested negative in the *in vitro* bacterial reverse mutation assay and the *in vivo* mouse micronucleus assay, this compound tested positive in the *in vitro* chromosome aberration assay.
- Currently the weight of evidence does not suggest the lack of a genotoxic effect for —
- As such, — has not been adequately qualified and should either be reduced to NMT — or adequately qualified.
- The Agency does not concur with Forest's belief that genetic toxicology studies are "organized in a tiered manner" or that they should be viewed in perspective of their "hierarchical nature."
- ICH S2B: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (July 1997) clearly states:

  "Registration of pharmaceuticals requires a comprehensive assessment of their genotoxic potential. t is clear that no single test is capable of detecting all relevant genotoxic agents. herefore, the usual approach should be to carry out a battery of *in vitro* and *in vivo* tests for genotoxicity. uch tests are complementary rather than representing different levels of hierarchy."

- The Division cannot accept the simple explanation of cytoxicity without further characterization of the finding.

  Muller and Kasper, 2000 wrote:

  "A rationale for non-relevancy of in vitro positive results is needed. Usually, it will not suffice to simply quote cytotoxicity as the reason without providing additional information....conclusive evidence for absence of effects in in vivo tests for genotoxicity and carcinogenicity may overrule positive in vitro genotoxicity tests..."

- The Division encourages Forest to provide data that supports your proposal that — nduced chromosome aberrations *in vitro* are not biologically relevant.

  Muller and Kasper, 2000 wrote:

  "the demonstration of a coincidence of genotoxicity and high levels of cytotoxicity, which seems to be a major factor for biologically non-relevant *in vitro* positive new pharmaceuticals, usually requires quite extensive testing. Hence, for new pharmaceuticals it is practice to provide, in addition to *in vitro* results that may be thresholded, a wealth of information from *in vivo* studies on genotoxicity, carcinogenicity, metabolism, pharmacokinetics, etc. the results of which help in assessing the biological relevance of *in vitro* positives."

In conclusion, the sponsor was informed the following:

- Submit aggressive interim specifications and a clear plan to reduce the levels of genotoxic impurities and/or provide data to support the position that the existing in vitro data is not biologically relevant.

At this time, the sponsor has submitted the interim specification of NMT — , as agreed upon by the Division with — . This interim specification will be acceptable and should not delay approval of the NDA if the sponsor commits to continuing to work with the — r and the Division to aggressively identify, characterize and, if need be, qualify any —

Labeling

Following further discussion, the following recommendations on labeling are made as of November 22, 2004 (Note labeling may change during final negotiations):

Carcinogenicity, Mutagenicity and Impairment of Fertility

Studies to evaluate the potential effects of the combination of oxycodone and ibuprofen on carcinogenicity, mutagenicity or impairment of fertility have not been conducted.

Pregnancy
Teratogenic Effects
Pregnancy Category C

Animal studies to assess the potential effects of the combination of oxycodone and ibuprofen on embryo-fetal development were conducted in the rat and rabbit model.

Pregnant rats were treated by oral gavage with combination doses of oxycodone:ibuprofen mg/kg/day (0.25:20, 0.5:40, 1.0:80, or 2.0:160) on days 7-16 of gestation. There was no evidence for developmental toxicity or teratogenicity at any dose, although maternal toxicity was noted at doses of 0.5:40 and above. The highest dose tested in the rat (2.00:160 mg/kg/day) is equivalent to the maximum recommended human daily dose (20:1600 mg/day) on a body surface area (mg/m^2) basis. This dose was associated with maternal toxicity (death, clinical signs, decreased BW).

Pregnant rabbits were treated by oral gavage with combination doses of oxycodone/ibuprofen (0.38:30, 0.75:60, 1.50:120 or 3.00:240 mg/kg/day) on gestation days 7-19. Oxycodone/ibuprofen treatment was not teratogenic under the conditions of the assay. Maternal toxicity was noted at doses of 1.5:120 (reduced body weight and food consumption) and 3:240 mg/kg/day (mortality). The NOAEL for maternal toxicity, 0.75:60 mg/kg/day, is 0.75 fold the proposed maximum daily human dose based upon the body surface area. Developmental toxicity, as evidenced by delayed ossification and reduced fetal body weights, was noted at the highest dose, which is approximately 3 times the MRHD on a mg/m^2 basis, and is likely due to maternal toxicity. The fetal no adverse effect level (NOAEL) of 1.50:120 mg/kg/day is approximately 1.5 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Combunox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the ibuprofen component, Combunox should not be used during the

third trimester of pregnancy because it could cause problems in the unborn child (premature closure of the ductus arteriosus and pulmonary hypertension in the fetus/neonate).

Labor and Delivery

Combunox™ should not be used during the third trimester of pregnancy due to the potential for ibuprofen to inhibit prostaglandin synthetase which may prolong pregnancy and inhibit labor. Oxycodone is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn[1].

Nursing Mothers[2]

Ibuprofen is not transferred to breast milk in significant quantities. The American Academy of Pediatrics classified ibuprofen as compatible with breastfeeding. In studies using a 1 mcg/mL assay, ibuprofen was not detected in the milk of lactating mothers. Oxycodone is excreted in human milk. Withdrawal symptoms and/or respiratory depression have been observed in neonates whose mothers were taking narcotic analgesics during pregnancy. Although adverse effects in the nursing infant have not been documented, withdrawal can occur in breast-feeding infants when maternal administration of an opioid analgesic is discontinued.

Because of the potential for serious adverse reactions in nursing infants from the oxycodone present in COMBUNOX™, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Phase 4 Commitments

Description of Commitment: Conduct a Fertility and Early Embryonic Development (Segment I) study in a single species. Please refer to ICH S5A Guideline "Detection of Toxicity to Reproduction for Medicinal Products."

Protocol Submission: by March 2005
Study Start: by June 2005
Final Report Submission: by February 2006

Description of Commitment: Conduct a Peri- and Postnatal Development (Segment III) study in a single species. Please refer to ICH Guidance S5B(M) Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products"

Protocol Submission: by March 2005

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[1] Coustan, D.R. and Mochizuki, T.K. 1998. Handbook for Prescribing Medications During Pregnancy, Third Edition. Lippincott-Ravan, Philadelphia, Page 307.

[2] Marx, C.M., Pucino, F., Carlson, J.D., Driscoll, J.W. and Ruddock, V. 1986. Oxycodone excretion in human milk in the puerperium (abstract). Drug Intell Clin Pharm 20:474; and Dickson, P.H., Lind,A., Studts, P., Nipper, H.C., Makoid, M. and Therkildsen, D. 1994. The routine analysis of breast milk for drugs of abuse in a clinical toxicology laboratory. J. Forensic Sci 39:207-214; and Briggs, G.G., Freeman, R.K. and Yaffe, S.J. 1998. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Williams & Wilkins, Baltimore, MD, Pages 814-815.

Study Start: by June 2005
Final Report Submission: by May 2006

Description of Commitment: Complete a standard battery of genotoxicity studies of oxycodone hydrochloride or provide data from another source.

Certification or Protocol Submission: by March 2005
Study Start: by June 2005
Final Report Submission: by May 2006

We remind you of your commitment to continue to work with —
— and the Agency to aggressively identify, characterize, and provide adequate specifications for any/all potentially genotoxic — impurities and/or degradation products that may be present in the oxycodone drug substance.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

R. Daniel Mellon
11/24/04 05:01:08 PM
PHARMACOLOGIST

MEMORANDUM

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

Date: November 22, 2004

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170

From: Silvia N. Calderon, Ph.D.
Team Leader, Controlled Substance Staff, HFD-009

Through: Michael Klein, Ph.D.
Acting Director, Controlled Substance Staff, HFD-009

Subject: NDA 21-378, Oxycodone 5mg -Ibuprofen 400mg tablets
Sponsor: Forest Laboratories, Inc.

This memorandum responds to a consult from the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170, with respect to the label of Forest Laboratories oxycodone 5mg- ibuprophen 400mg combination product.

The following label changes are recommended based on similar labeling changes recently applied to other Schedule II opioid products.

SUMMARY AND RECOMMENDATIONS

1. In the "WARNINGS" section it is recommended that the current '
' subsection be replaced by a "*Misuse, Abuse and Diversion of Opioids*" subsection. A similar subsection has been recently incorporated into the labels of other Schedule II products.
Recommended wording for this section:

   WARNINGS:

   "*Misuse Abuse and Diversion of Opioids*"

   BRANDNAME contains oxycodone, which is an opioid agonist, and a Schedule II controlled substance. Opioid agonists have the potential for being abused and are sought by abusers, people with addiction disorders and are subject to diversion.

   BRANDNAME can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing BRANDNAME in

situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion (see DRUG ABUSE AND DEPENDENCE).

2. In the "WARNINGS" section, it is suggested to add a warning regarding the interactions of oxycodone with other depressants such as alcohol and other opioids. The incorporation of the following subsection is suggested:

   Interactions with Alcohol and Drugs of Abuse: Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central system depression.

3. Under the "PRECAUTIONS" section, "General" subsection it suggested to modify the paragraph proposed by the Sponsor that states tha
   — Please note that CSS's proposed language is indicated in bold and deletions are indicated by strikethrough text.

4. It is suggested that the proposed "DRUG ABUSE AND DEPENDENCE" section be replaced to incorporate similar wording used in other Schedule II opioids to describe substance abuse, dependence and tolerance. Please note that CSS's proposed language is indicated in bold and deletions are indicated by strikethrough text.

   DRUG ABUSE AND DEPENDENCE
   BRANDNAME contains oxycodone, which is a mu-opioid agonist with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. BRANDNAME, and other opioids used in analgesia, can be abused and are subject to criminal diversion.

   Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease utilizing a multidisciplinary approach, but relapse is common.

   "Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physical dependence usually assumes clinically significant dimensions after several days to weeks of continuous opioid use.

Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shorter duration of analgesic effect, and subsequently by a decreases in the intensity of analgesia. The rate of development of tolerance varies among patients

Physicians should be aware that abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. BRANDNAME, like other opioids, may be diverted for non-medical use. Record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

5. Under the "DOSAGE AND ADMINISTRATION" section, it is suggested to delete the

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Silvia Calderon
11/23/04 05:55:19 PM
CHEMIST

Michael Klein
11/24/04 08:31:38 AM
CHEMIST

Office of Drug Safety

MEMO

To: Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

From: Linda M. Wisniewski, RN
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise P. Toyer, PharmD
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

Carol A. Holquist, RPh
Director, Division of Medication Errors and Technical Support, HFD-420

CC: Lisa Basham-Cruz
Project Manager, Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Date: September 30, 2004

Re: ODS Consult 04-0220-1 Combunox (Oxycodone HCl and Ibuprofen Tablets, USP)) 5 mg/400 mg; NDA# 21-378

This memorandum is in response to a September 27, 2004 request from your Division for a review of the labels and carton labeling for Combunox. The proposed proprietary name was found acceptable by DMETS on September 20, 2004 (See ODS Consult 04-0220).

DMETS reviewed the labels and labeling submitted September 21, 2004, from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

We recommend expressing the established name to read as follows: Oxycodone HCl and Ibuprofen Tablets, USP.

B. CONTAINER LABEL (30 count, 100 count, 500 count, and 4 X 25 Blister Carton)

1. See GENERAL COMMENT.

2. Ensure that the established name is at least ½ the size of the proprietary name. See 21 CFR 201.10(g)(2). DMETS also recommends increasing the prominence of the strength, commensurate with the established name.

3. In the current presentation, the CII graphic color is dark and makes reading the strength difficult. DMETS recommends lightening the font color so that the graphic appears in the background and does not interfere with the readability of the strength.

4. Relocate the net quantity (e.g. to lower third of the label) so that it is not in close proximity to the strength.

C. CONTAINER LABEL (Blister foil back)

1. See GENERAL COMMENT and comments B2 and B3.

2. DMETS questions whether th[redacted] on the label is the proposed form of the tablet, or, if it is a graphic that is part of the label. As it currently appears, it is distracting and decreases the readability of the proprietary name, established name, and strength. Please clarify.

D. INSERT LABELING

No insert labeling was provided at this time.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Direct Line: (201) 386-2142
Fax: (201) 524-9711

November 23, 2004

Bob Rappaport, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 9B45
5600 Fishers Lane
Rockville, MD 20857

NDA: **21-378 Combunox™ (Oxycodone HCl and Ibuprofen) Tablets**
Re: **Phase IV Commitments**

Dear Dr. Rappaport:

Reference is made to NDA 21-378 and the May 25, 2004 response to Approvable letter dated October 18, 2002 and a teleconference between Forest and the Division on November 22, 2004.

Forest agrees to the following Phase IV commitments:

PEDIATRICS:

1. The conduct of a deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 12 to 17. (Final Report Submission: November 31, 2007)

2. The conduct of a deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 2 to 12. (Final Report Submission: November 31, 2009.)

PHARMACOLOGY/TOXICOLOGY:

1. Conduct a Fertility and Early Embryonic Development (Segment I) study in a single species. Please refer to ICH S5A Guideline "Detection of Toxicity to Reproduction for Medicinal Products."

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by February 2006

2. Conduct a Peri- and Postnatal Development (Segment III) study in a single species. Please refer to ICH Guidance S5B(M) Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products"

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

3. Complete a standard battery of genotoxicity studies of oxycodone hydrochloride or provide data from another source.
   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

   We will continue to work with our — and the Agency to aggressively identify, characterize, and provide adequate specifications for any/all potentially genotoxic — impurities and/or degradation products that may be present in the oxycodone drug substance.

CHEMISTRY:

1. The limits for bulk density, tap density and particle size distribution have not been established for Sodium Starch Glycolate, NF. Based on the analysis of at least five additional batches, we will establish the limits for bulk density, tap density and particle size distribution and report in the NDA Annual Report.

2. We will change the established name from (Oxycodone HCl/Ibuprofen) to (Oxycodone HCl and Ibuprofen) and increase the prominence of the established name and strength on the carton and container labels.

If there are any questions related to this submission, please contact me at (201) 386-2142 or in my absence Doreen V. Morgan, PharmD at (201) 386-2131.

Sincerely,

Michael K. Olchaskey, PharmD
Associate Director, Regulatory Affairs
Michael.Olchaskey@frx.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601).

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Forest Laboratories, Inc.	11/23/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
201-386-2142	201-524-9711
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Harborside Financial Center Plaza III, Suite 602 Jersey City, NJ 07311	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Oxycodone HCl and Ibuprofen	Combunox	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	5 mg/400 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
acute pain

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Phase IV commitments

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Phase IV commitments

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 680, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Michael K. Olchaskey, PharmD	11/23/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Harborside Financial Center, Plaza III, Suite 602, Jersey City, NJ 07311	(201) 386-2142

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Phase 4 TCon
11/22/04

MEMORANDUM OF TELECON

DATE: November 22, 2004

APPLICATION NUMBER:
NDA 21-378; Combunox (Oxycodone HCL/ibuprofen) 5/400 mg

BETWEEN:

Name: Kenneth Newman, MD; Clinical Development
Robert Ashworth, PhD; Regulatory Affairs
Charles Lindamood, PhD; Pharmacology and Toxicology
Kimberly Voigt-Blum, PhD; Toxicology
Robert Jackson; Project Management
Michael Olchaskey, PharmD, RAC; Associate Director, Regulatory Affairs

Representing: Forest Laboratories, Inc.

AND

Name: Bob Rappaport, MD; Division Director
Rigoberto Roca, MD; Deputy Division Director
Dan Mellon, PhD; Supervisory Pharmacologist
Kim Colangelo: Associate Director for Regulatory Affairs, OND
Lisa Basham-Cruz, MS; Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: Discussion of Agency Proposed Phase 4 Commitments emailed to the sponsor on November 19, 2004.

BACKGROUND: Forest Laboratories, Inc. submitted their complete response to the Agency's October 18, 2002, approvable letter for NDA 21-378, on May 25, 2004. The PDUFA goal date for this action is November 27, 2004.

The Division emailed the sponsor a list of Phase 4 Commitments/agreements on November 19, 2004 (Appendix A). The sponsor responded with a subsequent email on November 22, 2004 (Appendix B). The purpose of this teleconference was to discuss the sponsor's concerns about the proposed Phase 4 Commitments regarding the requirement for pediatric studies in the 2-12 age group, and the requirement for genotoxicity studies.

Teleconference Minutes:

Dr. Rappaport began the discussion by noting that the Division has waived the pediatric study requirement for the lowest age group (0-2 years). He added that there may be a valid argument that this fixed-dose, combination product is not appropriate for pediatric patients between the ages of 2 and 12. A comprehensive rationale, with support from literature, etc., should be submitted to the Agency for review to justify a waiver for that age group. The action letter for this application will state that a study is required; however the potential exists for a future waiver based upon a satisfactory evaluation of the justification by the Agency.

Dr. Rappaport discussed the sponsor's proposal to include genotoxicity data from — . He explained that the sponsor has not completed the requirements to reference the — product in a 505(b)(2) application, i.e., the sponsor has not provided certification to — patents, nor have they conducted bioavailability studies comparing their product to — Dr. Rappaport said that the Division will provide general language for the genotoxicity section of the package insert for the sponsor's consideration. The package insert may then be updated in the future using an appropriate regulatory pathway.

The sponsor inquired whether they may conduct pediatric studies under a Written Request from the Agency. Dr. Rappaport answered affirmatively.

Minutes Recorder:
Lisa Basham-Cruz, MS

Basham-Cruz, Lisa

From: Basham-Cruz, Lisa
Sent: Friday, November 19, 2004 5:08 PM
To: 'Olchaskey, Michael'
Subject: Phase 4 Coms/Agreements

Michael,

Attached please find our proposals for Phase 4 commitments and agreements. If necessary, we will discuss on Monday. Upon commitment/agreement, we will need a formal submission stating as such prior to the action.

Have a great weekend!

Lisa

-----Original Message-----
From: Olchaskey, Michael [mailto:Michael.Olchaskey@frx.com]
Sent: Tuesday, November 16, 2004 1:52 PM
To: BashamL@cder.fda.gov
Subject: Test of secure e-mail

Hi Lisa,

Test of secure e-mail.

Regards,

Michael

NDA 21-378
11-19-04

Proposed Phase 4 Commitments and agreements:

Pediatrics:

1. Deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 12 to 17.

   Final Report Submission: November 31, 2007

2. Deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 2 to 12.

   Final Report Submission: November 31, 2009.

Pharm/Tox:

1. Conduct a Fertility and Early Embryonic Development (Segment I) study in a single species. Please refer to ICH S5A Guideline "Detection of Toxicity to Reproduction for Medicinal Products."

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by February 2006

2. Conduct a Peri- and Postnatal Development (Segment III) study in a single species. Please refer to ICH Guidance S5B(M) Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products"

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

3. Complete a standard battery of genotoxicity studies of oxycodone hydrochloride or provide data from another source.
   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

We remind you of your commitment to continue to work with — and the Agency to aggressively identify, characterize, and provide adequate specifications for any/all potentially genotoxic alpha — impurities and/or degradation products that may be present in the oxycodone drug substance.

Chemistry:

We would like you to agree to the following:

1. The limits for bulk density, tap density and particle size distribution have not been established for Sodium Starch Glycolate, NF. Based on the analysis of at least five additional batches, establish the limits for bulk density, tap density and particle size distribution and report in the NDA Annual Report.

2. Change the established name from (Oxycodone HCl/Ibuprofen) to (Oxycodone HCl and Ibuprofen) and increase the prominence of the established name and strength on the carton and container labels.

APPENDIX A

November 19, 2004 EMAIL from the Agency:
NDA 21-378
11-19-04

Proposed Phase 4 Commitments and agreements:

Pediatrics:

1. Deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 12 to 17.

   Final Report Submission: November 31, 2007

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Pharm/Tox:

1. Conduct a Fertility and Early Embryonic Development (Segment I) study in a single species. Please refer to ICH S5A Guideline "Detection of Toxicity to Reproduction for Medicinal Products."

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   Study Start: by June 2005
   Final Report Submission: by February 2006

2. Conduct a Peri- and Postnatal Development (Segment III) study in a single species. Please refer to ICH Guidance S5B(M) Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products"

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

3. Complete a standard battery of genotoxicity studies of oxycodone hydrochloride or provide data from another source.
   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

We remind you of your commitment to continue to work with [redacted] and the Agency to aggressively identify, characterize, and provide adequate specifications for any/all potentially genotoxic [redacted] impurities and/or degradation products that may be present in the oxycodone drug substance.

Chemistry:

We would like you to agree to the following:

1. The limits for bulk density, tap density and particle size distribution have not been established for Sodium Starch Glycolate, NF. Based on the analysis of at least five additional batches, establish the limits for bulk density, tap density and particle size distribution and report in the NDA Annual Report.

2. Change the established name from (Oxycodone HCl/Ibuprofen) to (Oxycodone HCl and Ibuprofen) and increase the prominence of the established name and strength on the carton and container labels.

APPENDIX B
November 22, 2004 Response from Sponsor:

Hi Lisa,

With regard to the Division's proposed Phase IV commitments, we will accept each of them as written with the following exceptions:

PEDIATRICS

We request that the Agency reconsider the need for additional studies in pediatric patients.

A total of 300 patients aged 12-17 were randomized in the single dose studies, of which 109 patients were randomized to treatment with Combunox. In a multiple dose study, 58 patients aged 12-17 were enrolled and treated with Combunox for up to 7 days. These studies demonstrated that the pediatric patients had similar efficacy and safety to the patients aged 18-64. This information should be incorporated in the labeling irrespective of the Agency's determination of the need for additional studies in this group.

Forest and the Division have previously discussed the issue of conducting a pediatric study in the treatment of acute moderate to severe pain in pediatric patients ages 2-12. Forest believes that a fixed-dose combination containing 5 mg of oxycodone and 400 mg of ibuprofen would not be appropriate for this age group, nor would such a product represent a meaningful therapeutic benefit over existing pain therapies used in this population. Therefore, Forest believes that the Agency should grant a waiver for this specific age group. There is no approved oxycodone dose for this population. Therefore, the appropriate oxycodone dose is unknown, and should be determined by dose ranging studies rather than a fixed combination. Furthermore, the approved dose of ibuprofen in children is 10 mg/kg. The 400 mg dose of ibuprofen in Combunox is significantly above the approved pediatric dose and may entail significant safety issues.

GENOTOXICITY

Forest proposes to incorporate in the Combunox labeling the same language used in the approved product labeling for the oxycodone products by
— . For your convenience this is as follows:

Regards

Michael

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
11/24/04 04:45:59 PM
CSO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
11/22/04 04:25:24 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA **21-378**	Efficacy Supplement Type SE-	Supplement Number
Drug: **Combunox (Oxycodone HCl and Ibuprofen, USP) 5/400 mg**		Applicant: **Forest Laboratories, Inc.**
RPM: **Lisa Basham-Cruz**	HFD-170	Phone # **301-827-7420**

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (x) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 21-011: Roxicodone (Oxycodone IR) Tablets NDA 17-463: Motrin (ibuprofen)

❖ Application Classifications: • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC)	(X) Standard ( ) Priority
❖ User Fee Goal Dates	November 26, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) (X) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (X) Verified : Licensed Patent No. 4,569,937 from BTG. Complies with 21 CFR314.50(i)(3) *Licensing Agreements*
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	• Included • No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE October 18, 2002
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X (Agreed Upon PI)
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	CSS, DMETS
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Motrin & Roxicodone
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Minor editorial Changes in AP letter
• Applicant proposed	X
• Reviews	DMETS
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	Minutes, Nov. 22, 2004 Agreement: Submission dated November 23, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Type C: 6/16/99 EOP2: 3/16/99
• Pre-NDA meeting (indicate date)	7/26/01
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other: Post Action Meetings	12/17/02, 4/2/04
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	1st Cycle: October 17, 2002 2nd Cycle: November 26, 2004
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	1st Cycle: 9/23/02 2nd Cycle: 11/24/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	2nd Cycle Review; Section 1.4.2
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	November 26, 2004
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	11/16/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1st Cycle: 9/13/02 2nd Cycle: N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	1st Cycle: 10/17/02 2nd Cycle: 11/19/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	11/19/04
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 11/15/04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/12/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review

Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

   Roxicodone (oxycodone HCl 15 & 30 mg Tablets); NDA 21-011

   Motrin (Ibuprofen 400 mg Tablet); NDA 17-463

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES NO

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

***NOTE:** If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a new combination of oxycodone and ibuprofen (5/400 mg).

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

__X__ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Roxicodone; August 31, 2000

Motrin; November 16, 1994

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

__X__ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent 4,569,937 licensed from DuPont by — Forest Laboratories licenced oxycodone/ibuprofen from —

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

__X__ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES NO

The applicant did not explicitly identify which parts relied on which applications.
The Agency relied on information about safety and efficacy from previous findings of S&E for the Motrin and Roxicodone NDAs.

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 52,310 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
11/24/04 04:43:03 PM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Wisniewski
10/6/04 07:38:40 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/6/04 02:28:40 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS

Carton + Container DMETS Discipline Review Letter 10/25/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

DISCIPLINE REVIEW LETTER

Forest Laboratories
Harborside Financial Center, Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD, RAC
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your December 19, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone HCl and Ibuprofen Tablets, USP.

We also refer to your submission dated September 21, 2004.

The Division of Medication Errors and Technical Support (DMETS) has reviewed your proposed Carton and Container Labels and has identified the following deficiencies. We request a prompt written response in order to continue our evaluation of your NDA.

1. CONTAINER LABEL (30 count, 100 count, 500 count, and 4 X 25 Blister Package)

   a. The established name should read, "(Oxycodone HCl and Ibuprofen) Tablets, 5 mg/400 mg."

   b. The established name should be at least ½ the size of the proprietary name. Refer to 21 CFR 201.10(g)(2).

   c. The prominence of the strength should be increased, commensurate with the established name.

   d. In the current presentation, the CII graphic color is dark and makes reading the strength difficult. Lighten the color font so that the graphic appears in the background and does not interfere with the readability of the strength.

   e. Relocate the net quantity (e.g., to lower third of the label) so that it is not in close proximity to the strength.

2. CONTAINER LABEL (Blister Foil back)

   a. The established name should read, "(Oxycodone HCl and Ibuprofen) Tablets, 5 mg/400 mg."

   b. The established name should be at least ½ the size of the proprietary name. Refer to 21 CFR 201.10(g)(2).

   c. The prominence of the strength should be increased, commensurate with the established name.

   d. In the current presentation, the CII graphic color is dark and makes reading the strength difficult. Lighten the color font so that the graphic appears in the background and does not interfere with the readability of the strength.

   e. Clarify whether the — on the label is the proposed form of the tablet, or if it is a graphic that is part of the label. As it currently appears, it is distracting and decreases the readability of the proprietary name, established name, and strength.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Center for Drug Evaluation and Research

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/s/

Sara Stradley
10/25/04 02:44:54 PM
for Parinda Jani

INTEROFFICE MEMO

TO: NDA 21-378, Oxycodone/Ibuprofen
FROM: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist
DATE: October 15, 2002

I concur with the pharmacologist's recommendation that the drug combination is approvable from a non-clinical perspective.

Pharmacology: Oxycodone produces typical mu-opioid receptor mediated effects such as analgesia, sedation, respiratory depressio, muscle rigidity, miosis and neuroendocrine parameters. Ibuprofen, a non-competitive reversible cyclooxygenase inhibitor, produces analgesia via decreased production of prostaglandins.

Safety pharmacology: Oxycodone produces CNS (analgesia, drowsiness, mood change, euphoria), cardiovascular (hypotension, bradycardia, peripheral vasodilation, reduced peripheral vascular resistance, inhibition of baroreceptor reflex), respiratory (respiratory depression) and gastrointestinal effects (reduced motility). Ibuprofen has no significant safety pharmacology effects.

General toxicology: Studies up to 1-month duration with the drug combination were performed in rats and dogs. The observed toxicities were consistent with the known effects of opioids and NSAIDs. Of note, high doses of the combination of oxycodone and ibuprofen at 1:80 or 1:40 ratios in dogs produced a greater incidence of unformed and/or liquid feces and fecal occult blood than ibuprofen alone. There were, however, no associated gross or microscopic findings. Although the studies in dogs did not achieve the maximum tolerated doses and may not fully characterize the potential for gastrointestinal toxicity of the combination, the known toxicological profile of the drugs and follow-up clinical assessment of the gastrointestinal effects preclude the need for further preclinical assessment. However, wording in the product label that describes the increased potential for gastrointestinal toxicity of the drug combination should be considered.

Genetic toxicology: No studies were performed by the sponsor. The sponsor referred to Oxycontin (NDA 20-553) for information related to oxycodone and submitted published information concerning the genotoxic potential of ibuprofen. The sponsor should provide patent certification for reference to Oxycontin.

Carcinogencity: The carcinogenic potential of this drug combination has not been adequately evaluated. This potential should be assessed in 2 species unless the sponsor can demonstrate that the product will not be used chronically.

Reproductive toxicology: Embryo-fetal development studies with the drug combination were performed with in rats and rabbits. The drug combination was not teratogenic but did have developmental effects in rabbits that included an increased incidence of resorptions and fetal toxicity (growth retardation and weight change). Thus, the Pregnancy category for this drug product should be "C". As per previous agreement,

fertility and pre- and post-natal development studies in rats may be completed as a post-marketing commitment although the sponsor will be encouraged to complete these studies prior to approval of the marketing application.

Based upon the above-mentioned results, this marketing application is approvable from a non-clinical perspective. The sponsor should provide patent certification for their reference to the Oxycontin label for genetic toxicology information for oxycodone. In addition, the sponsor should perform fertility and pre- and post-natal developmental studies. Carcinogenicity studies in two species should be performed unless the sponsor can demonstrate that the product will not be used chronically. A review of the product label was not performed at this time.

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/s/

Timothy McGovern
10/15/02 04:17:08 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Controlled Substance Staff
Attn: Corinne Moody
HFD-009

FROM: Bob Rappaport, M.D.
Division Director, Division of Anesthetic, Critical Care and Addiction Drug Products

DATE	IND NO.	NDA NO	TYPE OF DOCUMENT:	DATE OF DOCUMENT
Octeber 4, 2004		21-378	PACKAGE INSERT	July 13, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Combunox (Oxycodone/Ibuprofen)	standard	Opiate analgesic	**November 10, 2004** (Action date: November 19)

NAME OF FIRM: Forest Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER:

CSS specialty review for Pkg Insert

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Review of package insert.
Please evaluate the package insert text from an abuse liability perspective. The electronic (WORD) label is available through the EDR (NDA 21-378, July 13, 2004 BL submission). The PDUFA date is November 27th (day after Thanksgiving) so we are taking the action on November 19th. The "Desired Completion Date" above is somewhat arbitrary, as labeling negotiations may occur up to the action date. Please contact Lisa E. Basham-Cruz, Regulatory Project Manager, with any questions at 301-827-7420. Please cc any formal response to Lisa Basham-Cruz (basham).
Please display our consult tracking number prominently on the cover of your response: 2004.170.A.00087
Thank you!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Lisa E. Basham-Cruz	☐ MAIL ☐ HAND ■ DFS

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/s/

Lisa Basham-Cruz
10/4/04 04:59:00 PM

Tradename Acceptable Letter 9/21/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

DISCIPLINE REVIEW LETTER

Forest Laboratories
Harborside Financial Center, Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD, RAC
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your December 19, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone/Ibuprofen 5/400 mg Tablets.

We also refer to your submission dated June 7, 2004.

We have completed our review of the suggested tradename Combunox and we find it acceptable at this time. However, if the approval of this application is delayed beyond 90 days from the date of this letter, the name must be reevaluated to rule out any objections based upon approval of other proprietary or established names from this date forward.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
9/21/04 10:26:44 AM

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 2, 2004

NDA NUMBER: 21-378

NAME OF DRUG: Combunox
(Oxycodone HCl and Ibuprofen Tablets, USP)
5 mg/400 mg

NDA HOLDER: Forest Laboratories, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), to review the proprietary name, Combunox, regarding potential name confusion with other proprietary and established drug names. Insert labeling was provided for review and comment. Container labels and carton labeling were not submitted for review and comment at this time.

PRODUCT INFORMATION

Combunox is indicated for the short term management of acute, moderate, to severe pain. Combunox is a combination product consisting of 5 mg oxycodone and 400 mg ibuprofen. Combunox is proposed as oral tablets and will be supplied in bottles of 30, 100, and 500 as well as a unit dose package of 100 tablets. The recommended dose of Combunox is one tablet not to exceed four tablets in a 24-hour period. The proposed drug may be used for up to 7 days. Combunox is a Schedule II controlled substance.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Combunox to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.
[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com
[5] WWW location http://www.uspto.gov/tmdb/index.html.

review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Combunox. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns about the name Combunox with regard to promotional claims.

2. The Expert Panel Discussion (EPD) and independent investigation identified several proprietary names that were thought to have the potential for confusion with Combunox. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other
Combunox	Oxycodone HCl and Ibuprofen Tablets, USP 5 mg/400 mg	1 tablet by mouth, not to exceed 4 tablets in 24 hours; may be used for up to 7 days	
Condylox	Podofilox 0.5%, Solution and Gel	Gel: Apply twice daily to warts with applicator tip or finger Solution: Apply twice daily in the morning and evening (every 12 hours) to the warts with a cotton-tipped applicator supplied with the drug Apply twice daily for 3 consecutive days then withhold use for 4 consecutive days. This 1-week cycle of treatment may be repeated up to 4 times until there is no visible wart tissue.	Look-alike, Sound-alike
Combipres	Chlorthalidone/Clonidine HCl Tablets, 15 mg/0.1 mg, 15 mg/0.2 mg, 15 mg/0.3 mg	1 tablet one or two times a day	Look-alike
Combivent	Ipratropium Bromide/Albuterol Sulfate, Inhalation Aerosol (Each actuation delivers 18 mcg ipratropium and 103 mcg albuterol)	2 inhalations four times a day (do not exceed 12 in 24 hours)	Look-alike
Combivir	150 mg Lamivudine/300 mg Zidovudine	1 tablet by mouth twice daily without regard to food	Look-alike

*Frequently used, not all-inclusive.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Combunox were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Combunox with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Combumox (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient RX: Combunox 1 po q 6 hr x 7 days #28	Combunox Take one by mouth every six hours for seven days. Dispense number twenty-eight.
Inpatient RX: Combunox 1 po q6h #28	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. drug product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name Combunox, the primary concerns raised were related to look-or sound-alike confusion with Condylox, Combipres, Combivent, and Combivir.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not always predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to sample size. The majority of misinterpretations were misspelled variations of the proposed name, Combunox.

a. Condylox was identified to have look- and sound-alike potential with the proposed proprietary name, Combunox. Condylox is used in the treatment anogenital and external warts. Condylox contains the active ingredient podofilox and is available in a 0.5% topical gel and 0.5% topical solution. The usual dose of Condylox is to apply twice daily to the warts with an applicator or finger. The product is applied twice daily for three consecutive days then withheld for four consecutive days. This one-week cycle of treatment may be repeated up to four times until there is no visible wart tissue. Condylox and Combunox have slight look-alike similarities in that the first three letters ('Con' vs. 'Com') and the last two letters ('ox') are alike when scripted (see below). However, the middle part of each name looks different ('dyl' vs. 'bun'). Condylox contains a downstroke 'y' and an upstroke 'l' which helps distinguish it from Combunox. The sound-alike similarities stem from the beginning sounds of each name ('Cond' vs. 'Comb') and the rhyming endings ('lox' vs. 'nox'). However, when spoken, the middle letters ('dyl' vs. 'bun') help to distinguish one name from the other. In addition, there are differences which help distinguish Condylox from Combunox. The two drugs have different dosage forms (tablet vs. gel/solution), routes of administration (oral vs. topical), directions for use (1 tablet by mouth, not to exceed 4 tablets in 24 hours vs. apply twice daily in the morning and evening to the warts with a cotton-tipped applicator or finger), and indications for use. In addition, Condylox is applied for three days and then withheld for four consecutive days. Combunox, on the other hand, is given daily for up to seven days. Furthermore, Combunox is a Schedule II controlled substance and will most likely be stored in a locked cabinet separate from other prescription medications such as Condylox. Due to the above mentioned differences, as well as differences in the middle of each name when pronounced and written, DMETS believes there is decreased risk for error between Combunox and Condylox.

Condylox Combunox

b. Combipres was identified to have look-alike potential with the proposed proprietary name, Combunox. Combipres is indicated for the treatment of hypertension. Combipres is a combination product which contains the active ingredients chlorthalidone and clonidine. Combipres is available as an oral tablet in the following strengths: 15 mg/0.1 mg, 15 mg/0.2 mg, and 15 mg/0.3 mg. The usual dose of Combipres is one tablet once or twice daily.

Combipres and Combunox have slight look-alike similarities in that they share the same first four letters ('Comb'); however, the ending of each name looks different (see below) and helps distinguish one proprietary name from the other. The two drugs share overlapping dosage forms (tablet), routes of administration (oral), and dosing regimens (both may be taken once or twice daily). However, Combipres is available in three different strengths (0.1 mg, 0.2 mg, and 0.3 mg) and therefore a differentiating strength must be identified prior to prescription filling. Combunox, on the other hand, is available in a single strength and may be prescribed without regard to product strength. Furthermore, Combunox is a Schedule II controlled substance and will most likely be stored in a locked cabinet separate from other prescription medications such as Combipres. Due to strength differences, as well as a lack of convincing look-alike characteristics, DMETS believes that there is decreased risk for confusion and error between the two products.

Combipres Combunox

c. Combivent was identified to have look-alike potential with the proposed proprietary name, Combunox. Combivent is an inhalation aerosol for the treatment of bronchospasm in patient with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and require a second bronchodilator. Combivent contains the active ingredients, ipratropium bromide and albuterol sulfate, and is available in a 14.7 gram metered dose inhaler. Each actuation delivers 18 mcg ipratropium and 103 mcg albuterol. The usual dose of Combivent is two inhalations four times a day. Combivent and Combunox have look-alike similarities in that the beginning ('Comb') letters of each name are identical. However, the ending ('ivent' vs. 'unox') letters of each name look different when scripted (see below) and help differentiate one name from the other. Both drugs have overlapping dosing regimens (both may be administered four times a day) and do not need a differentiating strength when prescribed. The two products have different dosage forms (inhalation aerosol vs. tablet), routes of administration (oral vs. inhalation), and indications for use. Furthermore, Combunox is a Schedule II controlled substance and will most likely be stored in a locked cabinet separate from other prescription medications such as Combivent. Due to product differences, as well as a lack of convincing look-alike similarities, DMETS believes that there is decreased risk for confusion and error between Combivent and Combunox.

Combivent Combunox

d. Combivir was identified to have look-alike potential with the proposed proprietary name, Combunox. Combivir is an antiretroviral agent used in the treatment of HIV infection in combination with other antiretrovirals. Combivir is a combination oral tablet which contains the following active ingredients 150 mg lamivudine and 300 mg zidovudine. The usual dose of Combivir is one tablet twice daily. Combivir and Combunox have look-alike similarities in that they share the same four beginning letters ('Comb'). However, the ending letters ('ivir' vs. 'unox') look different when scripted and help differentiate one name from the other (see below). The two products have different indications for use (HIV vs. pain). In addition, Combunox is a Schedule II controlled substance and will most likely be stored in a locked cabinet separate from other prescription medications such as Combivir. The

two drugs do have overlapping dosage forms (tablet), routes of administration (oral), and dosing regimens (both may be dosed twice daily). Even though the two drugs have overlapping product characteristics, the lack of look-alike similarities when scripted lead DMETS to believe that there is decreased risk for confusion and error between the two products.

Combunox Combunox

III. LABELING REVIEW:

DMETS reviewed the insert labeling for Combunox and has identified the following area of possible improvement.

We recommend expressing the established name to read as follows throughout the text of the insert:: (Oxycodone HCl and Ibuprofen Tablets, USP).

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Combunox. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days form the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. Please provide container labels and carton labeling for review and comment.

C. DDMAC finds the proprietary name, Combunox, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

_____

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

_____

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

APPENDIX A

Verbal	Inpatient	Outpatient
Carbunox	Cimbemox	Combuvax
Combunox	Combimox	Combunox
Combunox	Cimbumox	Combunex
Combunox	Combumox	Combunox
Combunox	Combimox	Combunox
Communox	Combremox	Combivox
Pulminox	Combumox	Combunox
Comunox	Combumox	Combunox
Coviviox	Combumox	Combunix
Combunox	Cymbernox	Combunox
Comunox	Combumox	Combunox
Combunox	Combemox	Combunox
Ovunox	Combemox	Combunox
Combunox	Combimox	Combumox
Combinox	Combumox	Combumex
	Combimox	Combunex
	Combumox	Combumix
		Combimox

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/s/

Nora L. Roselle
9/16/04 08:29:52 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/20/04 01:55:52 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/20/04 02:00:51 PM
DRUG SAFETY OFFICE REVIEWER

ORIGINAL

FOREST LABORATORIES, INC.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Direct Line: (201) 386-2142
Fax: (201) 524-9711

August 4, 2004

N000(C)
NEW CORRESP

Bob Rappaport, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Attn: Document Control Room 9B45
5600 Fishers Lane, PKLN
Rockville, MD 20857

NDA: **21-378 Oxycodone/Ibuprofen Tablets**
RE: **Response to Telephone Request for Information - Re: July 20, 2004**

Dear Dr. Rappaport:

Reference is made to NDA 21-378 Oxycodone/Ibuprofen 5/400 mg Tablets and the Complete Response to the Approvable Letter dated May 26, 2004. Reference is also made to a telephone call from Ms. Lisa Basham-Cruz on July 20, 2004.

In response to the telephone call, enclosed please find:

1. a completed FORM FDA 3542a regarding Patent Information
2. An updated list of Drug Product Manufacturing, Packaging and Analytical Testing Sites.

If there are any questions related to this submission, please contact me at 201-386-2142 or in my absence Doreen V. Morgan, PharmD at 201-386-2131.

Sincerely,

Michael K. Olchaskey, PharmD, RAC
Associate Director, Regulatory Affairs
Michael.Olchaskey@frx.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Forest Laboratories, Inc.	8/4/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
201-386-2142	201-524-9711
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Harborside Financial Center Plaza III, Suite 602 Jersey City, NJ 07311	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Oxycodone HCl/Ibuprofen 5/400mg Tablets	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	5 mg/400 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

acute pain

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Other - Response to Telephone Request for Information Re: July 20 ,2004

PROPOSED MARKETING STATUS (check one) ☒ *PRESCRIPTION PRODUCT (Rx)* ☐ *OVER THE COUNTER PRODUCT (OTC)*

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

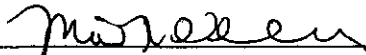
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Michael K. Olchaskey, PharmD, RAC	8/4/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Harborside Financial Center, Plaza III, Suite 602, Jersey City, NJ 07311	(201) 386-2142

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

04-Oct-2004
4:52:15PM

ACTION ITEM

Priority: Medium

Due Date:10-Nov-2004

Tracking Number:	2004.170.A.00087	Request Type:	Review - Labeling
Attention:	calderons 009	Return By:	10-Nov-2004
Document Date:	13-Jul-2004	Receipt Date:	14-Jul-2004
Requested Due Date:	10-Nov-2004		
Consulted By:	HFD-170 (bashaml)		
Contact:	bashaml		
Phone:	301-827-7420	FAX:	301-4463-7068
E-Mail Address:	bashaml@cder.fda.gov		
Subject:	NDA 21-378/July 13, 2004 PI		
Action Requested:	CSS review of PI		
Comment:			

Use the space below to indicate the action taken

DMETS Tradename Review
2nd CYCLE

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 8, 2004 **DATE OF DOCUMENT:** June 7, 2004	**DESIRED COMPLETION DATE:** September 1, 2004 **PDUFA DATE:** November 27, 2004	**ODS CONSULT #:** 04-0220

TO:

Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

THROUGH:

Lisa Basham-Cruz
Project Manager
HFD-170

PRODUCT NAME:	**NDA SPONSOR:** Forest Laboratories, Inc.
Combunox (Oxycodone HCl and Ibuprofen Tablets, USP) 5 mg/400 mg **NDA#:** 21-378	

SAFETY EVALUATOR: Nora Roselle, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Combunox. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days form the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the insert labeling recommendations outlined in section III of this review. Please provide container labels and carton labeling for review and comment.
3. DDMAC finds the proprietary names, Combunox, acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

4/2/04 Post Action Minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Attention: Michael K. Olchaskey, PharmD, RAC
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to the meeting between representatives of your firm and FDA on April 2, 2004. The purpose of the meeting was to discuss the preparation of your NDA resubmission for Oxycodone HCl/Ibuprofen Tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: April 4, 2004 @ 2:30pm

Location: Potomac Conference Room

Sponsor: Forest Laboratories, Inc.

Drug Name: Oxycodone HCl/Ibuprofen Tablets

Type of Meeting: Post-Action/Pre-resubmission Meeting

Meeting Chair: Rigoberto Roca, M.D.
Division of Anesthetic, Critical Care and Addiction Drug Products

Minutes Recorder: Lisa E. Basham-Cruz, Regulatory Project Manager

Forest Laboratories, Inc.	**Title**
Dr. Ken Newman	Executive VP, Scientific Affairs
Dr. Charles Lindamood III	Executive Director, Pharmacology & Toxicology
Dr. Kimberly Viogt-Blum	Senior Research Scientist, Toxicology
[redacted]	Consultant
Dr. Sebastian Assenza	VP, Pharmaceutical R&D
Dr. Robert Ashworth	Executive Director, Regulatory Affairs
Dr. Michael Olchaskey	Associate Director, Regulatory Affairs
Dr. David Lust	Acting Director, Regulatory Affairs
FDA	**Title**
Bob Meyer, MD	Director, ODE II
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Eric Duffy, PhD	Director, ONDC II
David Jacobson-Kram, PhD	Associate Director Pharm/Tox; OND
Kenneth Hastings, PhD	Associate Director of Pharm/Tox; ODE II/III
Ravi Harapanhalli, PhD	Acting Team Leader, Chemistry
Dan Mellon, PhD	Supervisory Pharmacologist
Thomas J. Permutt, PhD	Team Leader, Statistics
D. Elizabeth McNeil, MD	Medical Reviewer
David Lee, PhD	Biopharmaceutics Reviewer
Dionne Price, PhD	Mathematical Statistician
Lisa Basham-Cruz, MS	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss the preparation of the resubmission for NDA 21-378, in response to the Agency's, October 18, 2002, approvable letter.

Minutes:

Following introductions, the discussion moved to discipline-specific issues and to the questions submitted by the Sponsor in their March 4, 2004, meeting package.

Note: The Sponsor's questions are presented below in bolded text. Agency responses, prepared prior to the meeting and presented on slides, are shown in italics. Where noted, the sponsor's presentation is presented in italics, as well. Discussion is presented in normal text.

Question re: response to item 9a of 10/18/02 approvable letter: Does the Agency agree with the position that Forest will not include specification limits on at this time?

- *The description of , is not consistent between the NDA and the DMF. It consists of*
- *The variation in the .t of the excipients is likely to affect the stability of*
-
- *is inadequate. It does not include the specifications for and other degradation products that are likely formed in*
- *The COA does not identify the retest/expiration dating period for this*
- *Forest's acceptance specifications for this should therefore include specifications for and other degradation products.*
- *Forest should also identify appropriate retest interval/shelf life for this material.*

The sponsor said that claims that the other ingredients in are proprietary, so the sponsor is not aware of their identities. The sponsor assays for ibuprofen as a control measure. Dr. Duffy suggested that the sponsor discuss with and encourage them to provide the names of the excipients to the DMF. The excipients must be identified as they may affect the Forest stated that they will establish specifications for the acceptance testing of

Question 3: Does the FDA agree with our proposal to reduce the current specification for

- *The Division and Mallinckrodt are discussing the interim specification of NMT for : and are pursuing an aggressive plan to reduce the impurity further to NMT*
- *The same interim specification should be established to accept the drug substance from*
- *Alternately, : should be assessed for carcinogenic potential in a single species.*

The sponsor agreed to commit to the specification and timeframe for reducing the specification that has agreed to with the Agency.

Question 2: Does the FDA agree that the genotoxic potential of has been adequately assessed and that the weight of evidence indicates lack of genotoxic effect?

- *The Division must evaluate all of the available data regarding the identified and tested impurities.*
- *Although : has tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay, this compound tested positive in the in vitro chromosome aberration assay.*
- *Currently the weight of evidence does not suggest the lack of a genotoxic effect for*
- *As such, has not been adequately qualified and should either be reduced to NMT or adequately qualified.*
- *The Agency does not concur with Forest's belief that genetic toxicology studies are "organized in a tiered manner" or that they should be viewed in perspective of their "hierarchical nature."*
- *ICH S2B: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (July 1997) clearly states:*

  "Registration of pharmaceuticals requires a comprehensive assessment of their genotoxic potential. It is clear that no single test is capable of detecting all relevant genotoxic agents. Therefore, the usual approach should be to carry out a battery of in vitro and in vivo tests for genotoxicity. Such tests are complementary rather than representing different levels of hierarchy."

- *The Division cannot accept the simple explanation of cytoxicity without further characterization of the finding.*

- *Muller and Kasper, 2000 wrote:*

  "A rationale for non-relevancy of in vitro positive results is needed. Usually, it will not suffice to simply quote cytotoxicity as the reason without providing additional information....conclusive evidence for absence of effects in in vivo tests for genotoxicity and carcinogenicity may overrule positive in vitro genotoxicity tests..."

- *The Division encourages Forest to provide data that supports your proposal that — — -induced chromosome aberrations in vitro are not biologically relevant.*

- *Muller and Kasper, 2000 wrote:*

  "the demonstration of a coincidence of genotoxicity and high levels of cytotoxicity, which seems to be a major factor for biologically non-relevant in vitro positive new pharmaceuticals, usually requires quite extensive testing. Hence, for new pharmaceuticals it is practice to provide, in addition to in vitro results that may be thresholded, a wealth of information from in vivo studies on genotoxicity, carcinogenicity, metabolism, pharmacokinetics, etc. the results of which help in assessing the biological relevance of in vitro positives."

Question 1: Is our approach to responding to the selected issues acceptable such that a submission would be deemed complete?

- *The approach for submission of clinical data could constitute a complete submission.*

- *The decision on whether an approval would be granted will depend on the final review of the submitted data.*

- *Pharmacology Toxicology and CMC Response:*

  - *The Reproductive Toxicology studies described in the approval letter are still required for the NDA.*

  - *Submit aggressive interim specifications and a clear plan to reduce the levels of genotoxic impurities and/or provide data to support the position that the existing* in vitro *data is not biologically relevant.*

Dr. Mellon clarified that the reproductive toxicity studies should be started at the time of NDA submission.

— , representing Forest, gave a presentation on the sponsor's interpretation of the results of an *in vitro* chromosome aberration assay for — Dr. — slides are reproduced below:

Summary and Interpretation of Genotoxicity Data for —

Consultant to Forest Laboratories
U.S. FDA – April 2, 2004

Tiered Approach to Genetic Toxicology Testing

- *Evaluate activity initially in sensitive bacterial and cell culture assays*
- *Determine whether positive responses translate into activity in the whole animal*
- *Decisions are based on the weight of the evidence*
- *The Salmonella mutagenicity test plus the mouse micronucleus assay is the current most effective primary screen for potential human carcinogens determined by NIEHS validation studies*

Testing Scheme for Genotoxic Activity for —

- *Salmonella-Escherichia coli mammalian-microsome reverse mutation assay*
  –Sensitive indicator of mutagenic activity
- *In vivo mouse micronucleus assay*
  –Measures induced chromosomal effects in the whole animal
- *Accordingly, this testing scheme was proposed by Forest Laboratories and accepted by the FDA*
- — *tested negative in both assays*

CHO Cell Culture Chromosomal Aberration Assay

- *A — sponsored study reported that — was positive in a CHO chromosomal aberration assay*

Tier Approach

Weight of Evidence Indicates Lack of Genotoxic Activity for —

- *Negative in the Salmonella-Escherichia coli mammalian-microsome reverse mutation assay*

- *Positive in the CHO chromosomal aberration assay*

- *Negative in the in vivo mouse micronucleus assay*

- *CHO chromosomal effects do not translate to activity in the whole animal*

High False Positive Rate with in vitro Cytogenetic Assays

- *Galloway, S. M. (2000) Cytotoxicity and chromosome aberrations in vitro: experience in industry and the case for an upper limit on toxicity in the aberration assay. Environ. Molec. Mutagen 35, 191-201*

- *Muller, L., and Kasper, P. (2000). Human biological relevance and the use of threshold-arguments in regulatory genotoxicity assessment: experience with pharmaceuticals, Mutat. Res. 464, 19-34*

- *Muller, L., and Sofuni, T. (2000). Appropriate levels of cytotoxicity for genotoxicity tests using mammalian cells in vitro, Environ. Molec. Mutagen 35. 202-205*

False Positive Responses in Cell Culture Cytogenetic Assays

- *Experience indicates that current guidelines require testing to toxicity limits that are excessive, leading to a high proportion of false positive responses and lack of biological relevance*

— *. CHO Assay Results are Suggestive of the High Toxicity Artifact*

- *Without metabolic activation. Positive response seen only at the highest dose, with toxicity near 50%.*

- *With metabolic activation. Positive response at top two doses. But, toxicity was excessive (only 32% and 17% relative mitotic index). Dose-response curves were unusual.*

- *Positive responses were likely the result of the high toxicity artifact commonly seen in this assay.*

Positive Response in the CHO Assay was Likely the Result of the Common High-Toxicity Artifact

Concentration (µg/mL)	4 hr -S9 RMI (%ABS)	20 hr -S9 RMI (%ABS)	4 hr +S9 RMI (%ABS)	4 hr +S9 RMI (%ABS)
0	100 (1.5)	100 (0.0)	100 (4.0)	100 (1.5)
0.05		80		115
0.1	92	54	100	144
0.5	89	53 (2.0)	130	120
1.0	101 (1.0)	**60 (5.0*)**	78 (4.0)	93 (2.5)
5.0	63 (5.5)	0	**111 (10.0*)**	**137 (10.0*)**
7.5	**47 (15.0*)**	0		
10.0			**32 (13.0*)**	**17 (12.7*)**

RMI = relative mitotic index %ABS = % of cells with aberrations
***Bold** = statistically significant increase in %ABS*

Summary

- *Weight of evidence indicates that — is not genotoxic and is unlikely to present an increased risk of mutations or cancer, particularly at the low exposure levels found in the drug product*

Dr. Jacobson-Kram said that the Agency must follow ICH guidelines, and according to the guidelines this is a positive result. He also stated that benzene is negative in *in vitro* assays, which shows the nonconcordance of the assays with clastogenicity.

Dr. Mellon explained how the Division developed the required specifications for these structural alert compounds. Briefly, he described how the evaluation was based on the limits required for benzene, a known carcinogen, by EPA as a drinking water standard (2-20 ppm) and by FDA as a standard when benzene is necessary to manufacture drugs (2 ppm). The Division is requiring 10 ppm for the structural alert compounds, and in Forest's case, due to the combination with an NSAID, — . The sponsor said that they understand the Division's logic in developing these limits. The sponsor described how — — and the latter is not carcinogenic in rodents according to NTP studies. Dr. Jacobson-Kram said that this, in his opinion, adds to the weight of evidence. The sponsor asked for confirmation that they could get approval with a — interim specification pending resolution of this issue. Dr. Mellon answered affirmatively, assuming the proposed timeline for reaching the — level is reasonable. Dr. Mellon and Dr. Jacobson-Kram indicated their intention to solicit input from the Genetic Toxicology Subcommittee members concerning a potential plan for the characterization of ' — The Division

agreed to inform Forest of the results of this discussion as soon as a proposal was developed. Dr. Hastings suggested that the sponsor encourage — to partner with their competitors to resolve this issue so that efforts are not duplicated.

Action Items:

The Division will contact Forest Laboratories with a possible path forward following solicitation of comments from the Genetic Toxicology Subcommittee.

- Lisa E. Basham-Cruz
  Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
4/30/04 04:43:04 PM

7 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

CDER Dispute Resolution Response 12/12/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories, Inc.
ATTENTION: Robert W. Ashworth, Ph.D.
Senior Director, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Dr. Ashworth:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone/Ibuprofen (5 mg/400 mg) Tablets.

Your September 18, 2003, request for formal dispute resolution, received on September 22, 2003, concerned the Agency's request for a multiple-dose study of 1 to 2 weeks duration confirming the efficacy of the oxycodone/ibuprofen combination versus ibuprofen alone. In separate requests for formal dispute resolution (FDR) dated February 14, 2003, and March 25, 2003, you appealed the requests for additional safety (preclinical and clinical) and efficacy data conveyed to you by the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) in their October 18, 2002, approvable letter. CDER responded to these FDR requests in letters dated March 17, 2003 (Dr. Bob Meyer, Director, Office of Drug Evaluation II) and May 29, 2003 (Dr. John Jenkins, Director, Office of New Drugs). Both letters upheld the Division's requests for additional data; this is the third iteration of your original appeal.

We have reviewed your appeal and the outcome of the November 12, 2003, meeting with you and conclude that the following paths forward are available to you to support approval of this application (as detailed in the attached minutes of this meeting):

1. Conduct a multiple-dose study of the oxycodone/ibuprofen (5 mg/400 mg) combination versus ibuprofen alone to satisfy the combination drug policy standard. Resubmit your NDA with the results of this study as well as full responses to the other deficiencies noted in the Division's October 18, 2002 approvable letter.

OR

2. Resubmit your NDA to include adequate multiple-dose safety data for the oxycodone/ibuprofen (5 mg/400 mg) combination along with the data from the new gynecologic pain study, as well as full responses to the other deficiencies noted in the Division's October 18, 2002 approvable letter. DACCADP will consider this resubmission for possible approval of the combination drug product with a limited indication and labeling that describes the lack of efficacy data at multiple doses.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Mark McClellan, Commissioner, Food and Drug Administration. The appeal should be sent through the Agency's Chief Mediator and Ombudsman. Any questions concerning this appeal should be addressed via Ms. Kim Colangelo, Dispute Resolution Project Manager, at (301) 594-3937.

Sincerely,

[illegible]

Steven Galson, M.D.
Acting Director
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, November 12, 2003

TIME: 11:00 a.m. - 12:30 p.m.

LOCATION: Rockwall 7204

APPLICATION: NDA 21-378, Oxycodone/Ibuprofen (5 mg/400 mg) Tablets

TYPE OF MEETING: Formal Dispute Resolution

MEETING CHAIR: Steven Galson, M.D.

MEETING RECORDER: Beth Duvall-Miller

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Office/Division Name
1. Ms. Beth Duvall-Miller	Project Management Officer	Office of New Drugs
2. Dr. Steve Galson	Acting Director	Center for Drug Evaluation and Research (CDER)
3. Dr. Mark Goldberger	Acting Deputy Director	Center for Drug Evaluation and Research
4. Dr. John Jenkins	Director	Office of New Drugs
5. Dr. Sandy Kweder	Deputy Director	Office of New Drugs
6. Dr. Bob Meyer	Director	Office of Drug Evaluation II
7. Dr. Bob Rappaport	Director	Division of Anesthetic, Critical Care, and Addiction Drug Products
8. Ms. Leah Ripper	Associate Director for Regulatory Affairs	Office of Drug Evaluation II

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Dr. Robert Ashworth	Senior Director, Regulatory Affairs	Forest Laboratories, Inc.
2. Dr. Kenneth Newman	Senior Director, Medical	Forest Laboratories, Inc.
3. Dr. Lawrence Olanoff	Executive Vice President, Scientific Affairs	Forest Laboratories, Inc.
4. Dr. Michael Olchaskey	Associate Director, Regulatory Affairs	Forest Laboratories, Inc.
5	Consultant	

BACKGROUND:

Forest Laboratories, Inc. submitted new drug application (NDA) 21-378 for Oxycodone/Ibuprofen (5 mg/400 mg) Tablets under 505(b)(2) of the FD&C Act on December 19, 2001. The combination product is intended for the short term (up to seven days) management of acute pain. Forest received an approvable letter for NDA 21-378 from the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) on October 18, 2002 that detailed the need for additional safety (preclinical and clinical) and efficacy data amongst other deficiencies. Forest then met with DACCADP on December 17, 2002 to further discuss the deficiencies.

After this meeting, Forest sought resolution of the division's requests for additional data through CDER's Formal Dispute Resolution (FDR) process. CDER responded to Forest's FDR requests in letters dated March 17, 2003 (Dr. Bob Meyer, Director, Office of Drug Evaluation II) and May 29, 2003 (Dr. John Jenkins, Director, Office of New Drugs). Both letters upheld the Division's requests for additional data; specifically, the letters requested that Forest conduct a multiple-dose study of 1-2 weeks duration confirming the efficacy of the oxycodone/ibuprofen combination versus placebo and ibuprofen alone. Forest believes that this request for a multiple-dose study to demonstrate superiority of the combination product over ibuprofen alone is contrary to Agency precedent, is inconsistent with prior agreements with the Division, and is methodologically unfeasible.

In a submission dated September 18, 2003, Forest sustained the FDR process by requesting a meeting at the level of the Center Director to request that CDER readjudicate their request for additional efficacy data.

MEETING OBJECTIVE:

Adjudication of CDER's request for additional safety and efficacy data for approval of NDA 21-378.

DISCUSSION POINTS:

1. *CDER Precedent*: Forest cited two recent approvals of analgesic drug products (Ultracet and Vicoprofen) that CDER approved based on single-dose studies alone. Forest questioned whether CDER would reevaluate such past approvals of analgesics in light of the new standard for multiple-dose studies that is now being requested of Forest. Dr. Rappaport responded that, while he is not familiar with the details of the Ultracet approval (both products having been reviewed in another division), he is familiar with the Vicoprofen approval, and, as the Division has informed Forest at prior meetings, it is not considered to be a good example of Agency policy in this area. Dr. Rappaport noted that DACCADP has recommended, for at least the past two years, that sponsors conduct repeat dose studies in support of approval of new drug products for an acute pain indication. Dr. Galson noted that ultimately the standards for approval must evolve along with the current science and knowledge in medicine in order to best serve the public's health. He noted that when the standards change we do not routinely revisit the approval of old drugs, but rather we apply the new standards to the review and approval of new drug products.

2. *Previous Agreements with DACCADP*: Forest said that DACCADP's recommendations and standards for analgesic drug development changed near the end of the review cycle for NDA 21-378. Furthermore, Forest said that CDER's withdrawal of the 1992 Guidance for the Clinical Evaluation of Analgesic Drugs without posting a replacement guidance caused confusion and uncertainty for sponsors developing drugs in this area (e.g., lack of clarity on an appropriate pain model, study duration, study endpoints). Forest also noted that the request for a study to demonstrate the superiority of the combination over ibuprofen in order to satisfy the combination drug policy after multiple dosing was first requested in the April 29, 2003 meeting with Dr. Jenkins. It was clarified that the division had requested a multiple-dose study in the original approvable letter, but that the division had not requested that the combination rule be addressed in this study (e.g., the study was not envisioned to have the ability to distinguish the efficacy of the combination versus ibuprofen alone on multiple dosing). Dr. Jenkins clarified that he did not find this study design to be useful to address the combination policy issue and reiterated why a multiple-dose study of appropriate design was needed to demonstrate that both ingredients of the combination product contributed to its claimed effects with multiple dosing. Dr. Galson stated that he agreed that it would be necessary for Forest to submit data on multiple dosing to show that the product meets the combination drug regulations (21 CFR 300.50). He noted that FDA needed to make such decisions based on data and could not base them on clinical anecdotes.

3. *Methodology*: Forest explained that a multiple-dose study lacks the sensitivity (i.e., cannot show a statistically significant difference) to demonstrate superiority of a combination product over its single components in an acute pain model. Forest explained that acute pain decreases and varies significantly over time and the maximum signal/noise ratio is seen at the first dose. Forest stated that they were not aware of any studies that have demonstrated an ability to distinguish a combination from single ingredients on multiple dosing. Furthermore, Forest noted that approximately ½ of patients being treated for acute pain receive rescue medication within the first six hours of dosing, which further confounds the ability to analyze and interpret results seen at repeated doses. Dr. Rappaport commented that, recently, Dr. Dejardins had reported on studies that did, indeed, demonstrate the efficacy of repeat doses in post-operative bunionectomy patients. Forest acknowledged that data but noted that those studies were not of a combination drug product. Dr. Jenkins acknowledged the difficulties outlined by Forest, but encouraged Forest to consider alternative study designs that may optimize the sensitivity of a repeat dose study. Dr. Jenkins questioned whether the reason Forest was not aware of any studies that showed adequate sensitivity of a multiple-dose acute pain model is because investigators have not focused on innovative study designs that may in fact provide the needed levels of sensitivity.

4. *Introduction of Controlled Substance into Market*: CDER noted that this product must be carefully assessed for safety and efficacy since it includes a controlled

appropriate only where there is a "significant patient population requiring such concomitant therapy." To date, the data provided in the application have, at best, supported a modest early effect of combination use in the acute dental pain setting. Efficacy in other settings and in multiple doses has not been demonstrated, nor has the proper dosing interval been determined. A multiple-dose study in an another appropriate patient population is needed to provide both increased support of the proposed dosing interval, as well as additional evidence of efficacy in a patient population "requiring such concurrent therapy" as required under 21 CFR 300.50. I would parenthetically note that with an extension period out to one month, such a study would also generate additional useful safety data. With these new data, the total safety data could likely satisfy what would be needed for approval, barring any unforeseen safety signals.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John K. Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo. Any questions concerning your appeal should be addressed via Kim Colangelo at (301) 594-5479.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
3/17/03 11:22:55 AM

Basham-Cruz, Lisa

From: Comfort, Shaun
Sent: Wednesday, September 11, 2002 12:10 PM
To: Calderon, Silvia N
Cc: Basham-Cruz, Lisa
Subject: RE: NDA 21-378 Oxycodone/Ibuprofen

Thanks Silvia

Shaun

-----Original Message-----
From: Calderon, Silvia N
Sent: Wednesday, September 11, 2002 10:44 AM
To: Comfort, Shaun
Cc: Leiderman, Deborah; Rappaport, Bob A
Subject: RE: NDA 21-378 Oxycodone/Ibuprofen

Shaun,

As I stated in the last group meeting the role of CSS in the review of this drug product combination was comment on the label It was also decided in the same meeting that we were not going to send final comments on the label since the product was not going to be approved.

In other words we will contribute to the label when final label is submitted. There are no scheduling issues pending for this product and the Sponsor concurred that the product was going to be subject to CII regulations. This is a low concentration oxycodone combination product (Ibuprofen/Oxycodone 400/5 mg) and will not require a risk management plan or PPI.

Thank you,
Silvia

-----Original Message-----
From: Comfort, Shaun
Sent: Wednesday, September 11, 2002 9:30 AM
To: Calderon, Silvia N
Cc: Basham-Cruz, Lisa; Rappaport, Bob A; McCormick, Cynthia G
Subject: NDA 21-378 Oxycodone/Ibuprofen

Good Morning Silvia,

I spoke to you last month about doing a CSS consult on this product. I'm finishing up my NDA review to give to Dr. McCormick later this week. I know you are busy but I wanted to know if you had reached any conclusions regarding this combination product? If so, I would like to know what you have found so that I can include your opinions in a CSS section of the NDA review. Thanks.

Shaun

Shaun Comfort, M.D.
Medical Officer
Division of Anesthetic, Critical Care, and Addiction Drug Products
comforts@cder.fda.gov
(301) 827-7404

12/17/02 Post Action Mtg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Attention: Robert Ashworth, PhD
Senior Director, Regulatory Affairs

Dear Dr. Ashworth:

Please refer to the meeting between representatives of your firm and FDA on December 17, 2002. The purpose of the meeting was to discuss the FDA's Approvable action on your NDA for Oxycodone/Ibuprofen Tablets, and your responses to select deficiencies included in our October 18, 2002, action letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

NDA 21-378

12-17-02 meeting minutes

SPONSOR MEETING ATTENDEES

Meeting Date: December 17, 2002

Location: Parklawn Building, Chesapeake Conference Room (3:00-4:30pm)

IND/ Name: NDA 21-278 (Oxycodone/Ibuprofen Tablets)

Sponsor: Forest Laboratories

Type of Meeting: Post Action Meeting

Meeting Chair: Bob Rappaport, M.D.
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170

Forest	Title
Robert Ashworth, PhD	Senior Director, Regulatory Affairs
Andrew Friedman, RPh	Manager, Regulatory Affairs
Ivan Gergel, MD, MBA	Vice President, Clinical Research
Robert Jackson	Senior Director, Project Management
Charles Lindamood, PhD	Senior Director, Pharmacology/Toxicology
Kenneth Newman, MD	Senior Director, Medical
Lawrence S. Olanoff, MD, PhD	Executive Vice President, Scientific Affairs
Theresa Fico, PhD	Director of Toxicology
Neil Shusterman, MD	Vice President, Forest Research Inst., Med. Dept.
FDA HFD-170	**Title**
Bob Meyer, M.D.	Director, ODE II
Bob Rappaport, MD	Acting Division Director
Tim McGovern, PhD	Supervisory Pharmacologist
Tom Permutt, PhD	Mathematical Statistician, Team Leader
Sharon Hertz, MD	Team Leader, Analgesics and Neuropathy
Dale Koble, PhD	Chemistry Team Leader
Shaun Comfort, MD	Medical Reviewer
David Lee, PhD	Biopharmaceutics Reviewer
Dan Mellon, PhD	Pharmacology Reviewer
Dionne Price, PhD	Mathematical Statistician
Ravi Harapanhalli, PhD	Chemistry Reviewer
Lisa Malandro	Regulatory Project Manager
Lisa Basham-Cruz, MS	Regulatory Project Manager

Meeting Minutes:

Dr. Rappaport began the meeting by stating that the object of the meeting was to discuss what is needed to get the product approved. He recognized that the product came to the Division at a time when the Agency was establishing requirements for analgesic development, and that the Agency has raised the bar in terms of requirements for approval. The requirements that the Division has placed on the Sponsor are no greater than those required of other Sponsors, but rather new Sponsors are faced with much more stringent requirements. In that sense, the Division has been quite flexible with the Sponsor. The Agency is requiring all Sponsors to study immediate-release formulations in 3-month efficacy studies and 1-year safety studies. Post marketing data has verified that immediate-release products labeled for treatment of acute pain are being utilized for treatment of chronic pain. Therefore, our requirements on this issue are not arbitrary. The Agency also recognizes, however, the importance of being flexible with companies that are far along in their development plan. Specific inadequacies for this product that must be addressed include dosing and evaluation beyond a single dose. Dr. Rappaport expressed his hope that the meeting time would be utilized to reach agreement on the requirements for approval of Forest's oxycodone/ibuprofen tablets.

The discussion moved to the issues/deficiencies identified by the Sponsor in the briefing package. The issues were addressed by discipline rather than numerically. The original deficiencies identified in the October 18, 2002, action letter are printed in bolded type. The Sponsor's responses, as presented in the meeting package and summarized by the reviewer, are presented in italics. Agency responses prepared prior to the meeting, and presented on slides are bulleted. Discussion is presented in normal text.

Dr. Mellon addressed the Pharmacology/Toxicology items 5, 6, and 8b.

FDA Item #5:
Conduct Segment I (fertility) and Segment III (peri- and post-natal development) studies as a requirement for this NDA. Depending on the timing of the resubmission, you may provide justification of these as a Phase 4 commitment.

Forest Response:
Historically, combinations of FDA approved substances have required only Segment II studies. Forest's proposed labeling is consistent with other approved opioids and opioid-containing products.

Agency Response:

- Segment I and II studies are required according to ICH M3 guidance.
- As discussed in the teleconference on July 26, 2001, Segment I and III studies will be required. Although originally a Phase 4 commitment, the Sponsor is encouraged to submit these studies prior to approval of the marketing application.

FDA Item #6:
Provide assessment in two species of the carcinogenic potential of this drug product unless you can demonstrate post-marketing data from similar combination drug products containing oxycodone that the drug will not be used chronically.

Agency response:

- The Division feels that the drug product is likely to be used chronically, regardless of the labeled indication.
- Requests for adequate carcinogenicity assessment for all opioid and opioid-containing products is the current standard in the Agency.
- As discussed in the teleconference on July 26, 2001, if post-marketing surveillance shows that the product is used chronically, carcinogenicity assessment will be required.
- Depending on the timing of the resubmission, you may provide these as a Phase 4 commitment. Alternately, you may refer to publicly available data, if it is available, at the time of resubmission.

Post Meeting Note: The Sponsor may submit justification as to why carcinogenicity studies may not be required based on post-marketing data of similar products demonstrating that they are not used chronically. The Sponsor is encouraged to resolve these issues as soon as possible.

The Sponsor inquired whether the Agency was requiring Sponsors of currently marketed products to "go back" and conduct these studies. Drs. Rappaport and Mellon said that the Agency is not requiring Sponsor's to "fill in the blanks", but is addressing this absence of data as applications come in. Dr. Rappaport added that there is no way of determining the carcinogenicity of the drug substance from clinical experience. This policy is not one of the Division, but is accepted throughout the Agency. The Sponsor noted the apparent dichotomy between the requirements for previously approved drugs and those currently under review. Dr. Rappaport clarified that the standards have changed over time. Now Sponsors are required to produce data that were neglected previously. The Agency no longer bases study requirements solely on the proposed use of a product, but on the expected use, as well. The Sponsor inquired whether these studies could potentially be performed as Phase 4 commitments. Dr. Mellon responded that the data is preferred at the time of resubmission, but depending on the timing, a deferral to Phase 4 may be requested. At a minimum, the studies should be underway at the time of resubmission. Dr. Rappaport clarified that the studies will be accepted as Phase 4 commitments, but must be underway upon resubmission.

FDA Item #8b: Submit adequate qualification of the potentially genotoxic — impurity — either via demonstration that it is a human metabolite or via two in vitro genotoxicity test studies.... If no qualification is submitted, or if it is determined to be genotoxic, limit it (...) to —

Agency Response:

- — contains a structural alert — and therefore a potential mutagen. ICH Q3AR and Q3BR state that in limiting the levels of impurities and degradation products due consideration should be given to factors such as toxic potential of a chemical if the chemical is a metabolite. These factors would predicate if the impurity levels proposed in the guidelines are to be recommended or not.
- The sponsor is being asked to either limit the level of to (which we consider to be a safe level for a potential mutagen) or to demonstrate that the impurity is a metabolite or is not a mutagen, in which case higher levels may be justified.

The Sponsor inquired about the basis for the — limit. Dr. Harapanhalli explained that the level is based on total daily intake (TDI). If the TDI is <100 mg, then the requirement is — . If the TDI is >100 mg, the requirement is — Alternatively, the Sponsor may evaluate genotoxicity using a p53 or SHE-cell assay. If positive, the limits must be — If not, slightly higher levels may be allowed. The Sponsor expressed their belief that a limit of — is unachievable. They obtain their — from another source who had expressed to them that achieving this level of — is unfeasible. Dr. Koble responded that this is technically and synthetically feasible and that the manufacturer has communicated as much to the Agency. The Sponsor stated that they will consult with the manufacturer and readdress this issue upon doing so. Dr. McGovern again suggested performing the genotoxicity assays. A negative result would minimize this issue.

Dr. Lee addressed biopharmaceutics item #4.

FDA Item #4:
You have used an unapproved product...for you 505(b)(2) application. Perform a relative bioavailability study and provide data that will allow the Agency to link your product to an approved oxycodone product.

Agency Response:
- This concern has been adequately addressed based on our previous communication.

Dr. Comfort addressed clinical items #1 and #2.

FDA Item # 1.
Perform an adequate and well-controlled multiple dose study...demonstrating the effectiveness of multiple doses of oxycodone HCl/ibuprofen for the proposed acute pain indication for up to 3 weeks.

Forest Response:
Combination product effectiveness over the individual components was demonstrated using the TOTPAR/SPID outcome measures over 6-hours after dosing.

Agency Response:
- The combination product difference in PR/SPID scores (Used to calculate TOTPAR/SPID) over time is small in magnitude, with significant variability, and of questionable clinical significance. In addition, the effect is not sustained beyond 3 hours, which does not support your proposed dosing regimen.
- A third non-dental pain trial (OXY-MD-07 Post-Operative Pain Study) showed no statistically significant differences between the combination product and ibuprofen alone.
- In summary, although three of four statistical endpoints were met, the clinical effect appears no better than ibuprofen alone. In addition, combining oxycodone with ibuprofen adds the significant risk profile of opioid related adverse effects with no increased clinical benefit.

Forest Response:

Division discussion (3/16, 6/16, 10/29, and 12/14/1999) resulted in agreement that the proposed label claim would be supported by successfully demonstrating superiority in two single-dose studies.

Agency Response:

- The marginal results of these clinical trials are insufficient to justify risks associated with opioid use.
- We also refer to prior discussions in which we advised that the dental pain model was not the best setting to demonstrate opioid efficacy.

Forest Response:
The Agency has previously approved (Vicoprofen/Ultracet) for treatment of acute pain based on single-dose efficacy studies...a request for multiple dose efficacy for this type of product in unprecedented and of "questionable merit" when the efficacy of oxycodone/ibuprofen vs. placebo has already been demonstrated.

Agency Response:

- The approach to analgesic development has advanced with increasing knowledge gained from the use of these products. In the 6/16/99 meeting with the Division, you were advised not to consider the Vicoprofen application as a model for approval purposes.
- The Agency no longer accepts single-dose efficacy studies as a basis for analgesic product approval. This is based upon a broad consensus stated by the Medical Community at the July 2002 Arthritic Advisory Committee Meeting where it was agreed that analgesics should be studied in clinically relevant settings according to how they are expected to be used in practice.
- Furthermore, at this Advisory Committee, there was agreement that unless there is a contraindication based on safety, formal efficacy studies of analgesics should be done in a chronic setting.
- Also, the Agency stated in the 3/16/99 meeting minutes, the 12/23/99 Clinical Review of Sponsor Questions, and as stated in the CFR §300.50(a); both components must be shown to contribute to the efficacy of the combination product. Demonstrating superiority to placebo is only part of the requirement, and as such, says nothing about the combination product efficacy when compared to ibuprofen alone.

Forest Response:
The October 1999 Guidance for Industry – Applications Covered by 505(b)(2) states that previous findings of safety and effectiveness for approved drugs (containing the same active components)...permits approval without the need to conduct unnecessary studies to reaffirm what is already established in labeling.

Agency Response:

- The 505(b)(2) approach does not relieve you of your obligation to perform supporting studies of efficacy/safety.
- The requested studies are not "unnecessary."
- As stated in CFR § 300.50(a):

  - "...Two or more drugs may be combined is a single dosage form when each component makes a contribution to the claimed effects and...is safe and effective...."
  - Based upon this, you have not adequately fulfilled the combination rule.
- Substantial evidence of clinical superiority of the combination to ibuprofen alone has not been demonstrated, as we have already discussed.

Forest Response:
The dosing interval in the proposed label is consistent with that of previously approved products containing the same active ingredients and similar PK values.

Agency Response:
- The PK data provides "time-to-steady state" information following repeated dosing, but there is no information about efficacy following repeated dosing.
- There is no clinical support for the proposed qid dosing regimen.
- A well-controlled, multi-dose study is required in order to demonstrate the effectiveness of multiple doses of the combination product and to provide a rationale for a dosing interval.

Forest Response:
The Sponsor argues that lack of sustained/consistent nociceptive pain over time confounds the interpretation of multi-dose study results. The Sponsor also states that there is no consensus regarding meaningful endpoints.

Agency Response:
- Choice of a clinically relevant study population can minimize the effects of variable reports of pain.
- There are many reliable efficacy endpoints that have been utilized in successful analgesic trials.

FDA Item #2:
You have not adequately evaluated the safety...in the population for this drug product and in the setting that reflects how it is likely to be used in practice. Perform clinical study (studies) lasting a minimum of three months demonstrating safety...in a population of patients with acute and chronic pain.

Forest Response:
Forest conducted a safety evaluation with a duration of up to 7 days...based on prior agreement with the Division (3/16/99 meeting). This was deemed adequate to support the intended use.

Agency Response:
- Short duration safety studies do not capture rare AEs and safety events associated with extended use, which is expected given the Division's experience with other oxycodone products. This position was confirmed during the July 2002 Advisory Committee Meeting.

Forest Response:
It is unreasonable to expect a Sponsor to generate data to support "likely" use of a product beyond the label recommendations.

Agency Response:

- It is known from prescribing patterns of immediate-release analgesics that patients will use these products for longer than one dose, and often longer than two weeks. It is also known that these products are often used on a chronic, intermittent basis. In order for these products to be used safely, the proper dose and dosing interval for the efficacy must be established, and safety demonstrated under those conditions of use.
- Studying this product in a limited setting has not provided adequate information to permit appropriate labeling of its safe and effective use.
- This concept was supported at the July 2002 Arthritis Advisory Committee Meeting.

Forest Response:
Forest is proposing to specify the duration of use in the Indication section of the package insert and

Agency Response:

- . are not reliable methods for limiting prescribing.

General discussion began of clinical items 1 and 2.
The Sponsor expressed their disagreement with the Agency's requirement for a safety study of at least three months duration in acute and chronic pain populations and argued that the Agency should consider the long clinical history of the components to evaluate safety. They stated that the Agency's requirement to "begin again" contradicts the spirit of 505(b)(2) and 505(j). They feel that the Agency selectively applies what we know about the safety of a product for 505(b)(2) versus 505(j) applications. Furthermore, they feel that it is unreasonable to require studies in the anticipated population, rather than the recommended population. They expressed concern that including safety data for three months of exposure in the label may suggest to the physician that the product should be used chronically.

Dr. Hertz expressed her understanding of the Sponsor's frustration but added that no reliable information can be gleaned from post marketing data as suggested by the Sponsor. The Agency requires the Sponsors of all new products to "fill in the gaps" where information is lacking on the safety of a product. It is known that both oxycodone and ibuprofen are used chronically. There is also significant concern about abuse and diversion of opioids. There must be a legitimate reason for the addition of the opioid component to the combination. The small benefit in pain relief observed with the combination may not justify the risk of introducing another potentially abusable opioid to the market. These products are frequently used over a long period of time. Therefore, the current standard is to evaluate the safety of these products over time so that the physician can understand how to prescribe this combination. If a longer term study demonstrated that the drug is not efficacious over time, than that is important information that must be put in the label. A statement that the drug has not been studied for chronic pain is not adequate. Physicians may prescribe for chronic pain anyway.

Dr. Rappaport addressed the Sponsor's comments about requirements for 505(b)(2) and 505(j) applications. He explained that a 505(j) receives a generic approval. The 505(b)(2) allows the Sponsor to rely on previous findings of safety and efficacy, but the gaps must be filled in, even if they are clinical gaps. There were clinical gaps to fill in for the oxycodone/ ibuprofen application, e.g., the efficacy of the combination. This combination is not a generic, but a new drug. The Sponsor is obligated to fulfill both the 505(b)(2) and the combination rule requirements.

The Sponsor noted that this meeting represents the third level of negotiation with the Division, beginning with Dr. Wright, then Dr. McCormick, and then Dr. Rappaport. Dr. Rappaport reminded the Sponsor that the approvable letter was written by Dr. McCormick and that her agreements with the Sponsor will be honored. The Sponsor noted that they were originally told that exposure in 500 patients was sufficient, and now are being told that this is insufficient. Furthermore, they are not convinced that there is new information to justify the new requirements or even whether the new requirements are technologically achievable. They expressed their frustration regarding how to adequately design a study to establish superiority of the combination over either placebo or the components and regarding what constitutes an acceptable magnitude of difference between the arms. Dr. Rappaport stated that this is the first time the Agency has heard concerns of this type. The Sponsor responded that they will revisit this issue and readdress it at a later time. Dr. Rappaport clarified that the reason that the drug was not approved was not due to inappropriate endpoints, etc., but due to the fact that the studies were single-dose. Single-dose administration is not how this class of drugs are used. Dr. Rappaport offered to discuss the possibility of a three-week efficacy study using a responder analysis. The Sponsor stated that their experts could not find a method to evaluate the combination beyond the acute period because pain dissipates over time. Dr. Rappaport responded that 3-weeks is not necessarily the optimum duration, but the drug should be studied in the appropriate clinical population and over an appropriate duration. He added that the post-operative study did not fail because it was in post-operative patients, but because it was also a single-dose study.

The Sponsor asked for an explanation of responder analysis. Dr. Rappaport replied that the analysis is conducted across the entire population with groups identified for which the drug works well or does not work well. The amount of rescue required, pain intensity, tolerance, and concomitant medications are some of the measures that can be combined to form the definition of a responder.

The Sponsor stated that they are not aware of any analgesic vs. placebo studies in acute pain that have shown an effect after 5-7 days. Furthermore, there is no consensus on what is an appropriate endpoint to use for pain models. Dr. Rappaport concurred that there is not a consensus on appropriate endpoints, but stated that this should not be a problem, as there are several options . that would be acceptable to the Agency. He also noted that the Division would look into the sponsor's contention that there are no data available to support successful treatment of acute pain after 5-7 days.

The Sponsor noted that Dr. McCormick agreed, in a teleconference on October 18, 2002, that the multiple dose study may demonstrate superiority over either the components or placebo. Dr.

Rappaport agreed to honor this agreement. Dr. Meyer asked whether the combination policy has been adequately met. Dr. Rappaport responded affirmatively.

Dr. Permutt noted that even if there were evidence of some contribution by each component, the rationale for the dosing interval remained unclear. The Sponsor argued that the two components do not interact, so the dosing should not be different than dosing for the individual components. Dr. Permutt replied that in the absence of a close pharmacokinetic-pharmacodynamic correlation, it was impossible to infer the dosing interval from kinetic data alone, and that in fact the effectiveness of the components after about the first three hours appears very uncertain. The combination must be tested for adequate dosing data. Dr. Rappaport expressed the need for clinical pharmacodynamic data over a reasonable multiple-dosing time period. The Sponsor stated that there exist no studies beyond 5-7 days that demonstrate efficacy of analgesics. Dr. Rappaport offered to look into this, but suggested the possibility that no one has actually evaluated an analgesic in a blinded trial over a longer period. He summarized that a reasonable approach would be to study how the drug will be used in practice. The chronic use issue is a significant one and Dr. Rappaport strongly encouraged the Sponsor to study the drug for chronic pain (e.g., 3 months). He added that the Agency may settle for a shorter study (e.g., 1 month) if the Sponsor will commit to an open label, post marketing extension study of up to 6 months.

Dr. Rappaport offered the Agency's assistance with evaluating study protocols in the future. The meeting adjourned.

Key Discussion Points:

1. Segment I (fertility) and Segment III (peri- and post-natal development) studies are required for NDA submission.
2. Carcinogenicity studies in two species may be submitted as a Phase 4 commitment, but must be underway at the time of resubmission.
3. The level of — must be — unless the Sponsor can demonstrate that the impurity is a human metabolite or is not a mutagen, in which case, the levels may be higher.
4. The Agency is requiring multiple dose studies of safety (3 months) and efficacy (e.g., 3 weeks) in appropriate clinical populations suffering from acute and chronic pain in order to provide adequate labeling and dosing information.
5. The Agency may accept a safety study of 1 month's duration with a commitment to conduct a six month, open label, post marketing extension study.
6. Efficacy of the combination may be established by demonstrating superiority over either the components or placebo.

Lisa E. Basham-Cruz, MS

Bob Rappaport, MD/concurrence

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Parinda Jani
1/16/03 04:23:27 PM

Basham-Cruz, Lisa

From:
Sent: Thursday, September 12, 2002 5:23 PM
To: bashaml@cder.fda.gov
Subject: Teleconference

Lisa,

Here's the contact information:

If there are any problems arise, please call us at number below and press "0"

Thanks,

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Andrew Friedman
Phone Number: 201-386-2117
Fax Number: 201-524-9711

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane-
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 8/15/02

COMMENTS: ***Clinical request***
Andrew,

Attached are some additional reque sts for information from the clincial reviewer.

Thanks & Best Regards,

Lisa (301-827-7420)
Please verify receipt of this fax. Thanks!

1. The 120 Day ISS Update refers to one patient receiving Ibuprofen in Oxy-MD3-96-01, that was discontinued due to AEs (Section 9.3, pg. 62, vol 4.8). You then state that inspection of this subject's CRF shows that no AE was recorded. Please provide the Patient ID number so that the reviewer can also examine this subject's CRF.

2. Section 6.1.2.2 refers to a list of allowable local, pre-op anesthetics and medications (pg. 23, Vol 58) that is provided in Appendix I.1. This appendix cannot be found. Please provide a copy of the allowable meds.

3. In Oxy-MD-06 you refer to the 4 subjects (020374, 020765, 020370, and 020254) having non-ipsilateral molar extraction. Please provide a justification for including these subjects with the ipsilateral dental surgery subjects. I.e. Are the pain levels and responsiveness to analgesics similar enough in both groups to pool these patients with the remainder of the study population?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Basham-Cruz
8/15/02 02:15:22 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Dan Gordin, PhD
Phone Number: 201-386-2025
Fax Number: 201-524-9711

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane-
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 7/30/02

COMMENTS:

Dan, Below are additional requests for clarification from the medical reviewer....

Re: NDA 21-378 Integrated Summary of Safety, Differences in quoted tables compared to values summarized from the 120 Day Safety Data Base.

Please clarify the following data mismatches:

1. ISS Update Vol. 4.8, pg. 12. Panel 1 lists study subject distribution as follows:

   Oxy & Ibu 5 & 400, Ibup 400, PBO
   N: 50 / **43 / 24** respectively

   However, analysis of the PROF120 SAS XPT file with JMP shows the following distribution of subjects:

   N: 50 / **48 / 25**

   Can you explain this discrepancy of 5 patients in the Ibuprofen 400 mg group and 1 in the placebo group?

2. ISS Update Vol. 4.8 pg. 13. Panel 1 lists the subject distribution as follows:

   Oxy & Ibu 5 & 200, Ibup 200, PBO
   N: **39 / 38 / 20** respectively

   However, analysis of the PROF 120 SAS XPT file with JMP shows the following distribution of subjects:

   N: **40 / 41 / 22**

   Can you explain this discrepancy?

3. ISS Update Vol. 4.8 pg. 17. Panel 1 lists the subject distribution as follows:

   Oxy / Ibu 5 /400, Oxy / Ibu 10 /400, Ibup 400, Oxy 5, Oxy 10, PBO
   N: 175 / 169 / **170** / 58 / 56 / **54** respectively

   However, analysis of the PROF 120 SAS XPT file with JMP shows the following distribution of subjects:

   N: 175 / 169 / **171** / 58 / 56 / **57**

   Can you explain this discrepancy?

4. ISS Update Vol. 4.8 pg. 18. Panel 1 lists the subject distribution as follows:

   Oxy / Ibu 5 /400, Oxy / Ibu 10 /400
   N: 247 / 241 respectively

   However, analysis of the PROF 120 SAS XPT file with JMP shows the following distribution of subjects:

   N: 252 / 248

Can you explain this discrepancy?

5. ISS Update Vol. 4.8 pg. 114. Table 3.1A lists the total subject distribution by treatment. Please note the discrepancies from summarizing the PROF120 SAS transport file:

Treatment	Listed Values	JMP Derived Values
Oxy/Ibu 5/200	80	**81**
Oxy/Ibu 10/200	41	41
Oxy/Ibu 5/400	910	**915**
Oxy/Ibu 10/400	527	**533**
Subtotal	**1558**	**1570**
Ibu 200	78	**81**
Ibu 400	738	**744**
Subtotal	**816**	**825**
Oxy 5	234	234
Oxy 10	113	113
Subtotal	**347**	**347**
Placebo	275	279
Total	**2996**	**3021**

The JMP calculations count each UPID once, however in the Oxy/Ibup 5 & 10/400 groups the subjects receiving mult. treatments are counted more than once. Can you explain this discrepancy between the sums 2996 and 3021?

Note: If I summarize the PROF120.XPT by UPID I get 2665 individual records when you list 2651 unique subjects (ISS Vol 4.8, Section 2.0 pg. 3). Please clarify the reason for this discrepancy.

Thanks,

Lisa Basham-Cruz

PS. Please verify receipt of this fax (direct: 301-827-7420)

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/s/

Lisa Basham-Cruz
8/5/02 10:47:38 AM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Dan Gordin, PhD
Phone Number: 201-386-2025
Fax Number: 201-524-9711

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane-
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 1 Date: 7/29/02

COMMENTS: ***Biopharm request***

Dan, Below is a request from the biopharm reviewer:

Please provide Table 9-4, gender analysis comparison (p-values) of PK parameters (page 34 of Volume 16) from Study OXY-PK-04.

Thanks & Best Regards,

Lisa (301-827-7420)
PS. Also, please verify that you received clinical questions faxed 7/23/02!!

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/s/

Lisa Basham-Cruz
7/29/02 04:37:47 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Dan Gordin, PhD
Phone Number: 201-386-2025
Fax Number: 201-524-9711

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane-
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 7/23/02

COMMENTS: ***REVISED Clinical questions***

Please disregard earlier fax!

Dan, Below are the requests from the clinical reviewer for NDA 21-378: (Additional question)

1) **The sponsor is requested to provide the following information regarding patient disposition in studies OXY-MD-05 and OXY-MD-06:**
   - **The number of subjects screened for study admission and not accepted.**

- **The number of subjects screened for study admission and accepted, but who never achieved sufficient pain levels to be randomized.**

2) **The listed patient numbers for the protocol violators in OXY-MD-06 are not found in the transport files or the paper listings. The sponsor is requested to provide correct PIDs, demographic information, treatment group, etc... for the subjects listed as protocol deviations in *Oxycodone/Ibuprofen Comparative Efficacy Study*, Vol. 58, section 10.0, pg. 37.**

   Subject numbers are: 02374, 02765, 02370, 02254, 02369, **and** 01976.

3) **The sponsor is requested to explain why subject (01796) was included in the dental pain study (OXY-MD-06) after undergoing Tubal Ligation (unapproved surgery). The sponsor is requested to provide information suggesting a similarity in pain response or pain mechanisms in these two different surgical procedures, justifying inclusion of this patient.**

Best Regards, Lisa (301-827-7420)

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/s/

Lisa Basham-Cruz
7/23/02 05:13:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories
Harborside Financial Center
Plaza 3, Suite 602
Jersey City, N.J. 07311

Attention: Robert Ashworth
Director, Regulatory Affairs

Dear Mr. Ashworth:

We received your May 17, 2002, correspondence on May 17, 2002, requesting a meeting to discuss your pending New Drug Application for oxycodone hydrochloride/ibuprofen. We considered your request and concluded the meeting is premature.

If you disagree with our decision, you may discuss the matter with Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
5/30/02 05:45:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories
Harborside Financial Center
Plaza 3, Suite 602
Jersey City, NJ 07311

Attention: M. Daniel Gordin, Ph.D.
Associate Director, Regulatory affairs

Dear Dr. Gordin:

Please refer to the teleconference between representatives of your firm and FDA on February 14, 2002. The purpose of the meeting was to discuss potential filing and review issues of your New Drug Application (NDA) for oxycodone HCl/ibuprofen.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: February 14, 2002

APPLICATION NUMBER: NDA 21-378, Oxycodone HCl/ibuprofen HCl 5/400 mg

BETWEEN:

Name:	M. Daniel Gordin, Ph.D., Associate Director, Regulatory Affairs
	Robert Ashworth, Ph.D., Senior Director, Regulatory Affairs
	Robert Jackson, Director, Project Management
	Im Abramowitz, Ph.D., Senior Director, Pharmacokinetics
Phone:	1-800-589-6988 Participant # 919315
Representing:	Forest Laboratories

AND

Name:	Judit Milstein, Regulatory Project Manager
	Cynthia McCormick, M.D., Division Director
	Gerald DalPan, M.D., Medical Officer
	Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader
	Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: Discuss potential filing and review issues of the application

BACKGROUND:

NDA 21-378 was submitted on December 20, 2002, as a 505(b)(2) application. A relative bioavailability study to support the application was conducted comparing the product with Nuprin (ibuprofen), and Roxicodone (oxycodone) IR tablet, 5 mg.

The filing date is February 18, 2002. A filing meeting was conducted on February 8, 2002, and it was noted that Roxicodone IR, 5 mg is not a listed product and therefore, this application cannot be filed. Other potential review deficiencies were identified.

The objective of this telecon was to inform the applicant of the potential refuse to file issues as well as the potential review deficiencies that were identified.

DISCUSSION:

The following deficiencies were communicated to the sponsor

Filing issue:

A relative bioavailability study was conducted with Roxicodone IR, 5 mg tablet as the reference product. This is not an approved product, and therefore, the Agency has never made a finding of safety and efficacy of oxycodone 5 mg. Demonstrating relative bioavailability to this product

will not relieve Forest Laboratories of the requirement of a full NDA. This application therefore, cannot be filed.

Forest Laboratories acknowledge that they should have referenced Percocet or Percodan as listed drugs. As an alternative to conducting another PK study, Forest Laboratories proposed to conduct only a dissolution study considering that Percodan and Percocet are recognized as AA products in the Orange Book. Forest Laboratories will submit in writing their rationale and justification for this proposed study.

A second deficiency relative to the fileability identified was the absence of data to support the proposed dosing regimen of 4 tablets/day.

Review issues:

On a preliminary review of the application, the following deficiencies were identified

1. No chronic studies were performed to assess the safety profile on the long-term use of the product. Even though the labeling indicates the short-term use of the product, IMS data suggests that the product will be used on a chronic basis.

2. In at least one of the clinical studies submitted in support of this application, the oxycodone arm effectiveness could not be distinguished from placebo.

3. Lack of data in the population/setting of intended use.

ACTION ITEMS:

Forest Laboratories will submit their rationale on why only a dissolution study is necessary for this 505(b)(2) application.

Further discussions will be held before the filing date.

POST-MEETING NOTE: A telecon was held with the sponsor on February 20, 2002, informing them that the NDA was filed by default due to an error in calculating the filing date, but that the above review issues remain and would likely affect the application's approvability. A meeting of the ALSDAC will be scheduled to discuss the adequacy of the program used to support the NDA.

Lisa E. Basham-Cruz for Judit Milstein
Regulatory Project Manager

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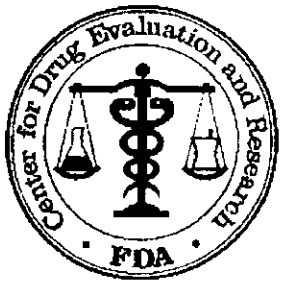
/s/

Lisa Basham
2/26/02 04:48:25 PM

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II



TO: M. Daniel Gordon, Ph.D./Forest Laboratories
Phone Number: (201) 386-2025
Fax Number: (201) 524-9711
FROM: Judit Milstein, Regulatory Health Project Coordinator

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet:6 Date:1-16-02

COMMENTS: Find enclosed request for additional information

NDA 21-378
Oxycodone HCl 5mg/Ibuprofen 400mg
Clinical Filing Review of NDA

Questions for Sponsor – January 16, 2002

1) Review of each of the data files from Study OXY—MD-05 indicates that treatment, age, gender, and race were not included in most of the data files. In addition, many entries for many variables are numerically coded, but are not accompanied by corresponding variables in the dataset that present the text name for the coded. Examples of these, for Study OXY-MD-05, are presented in the table below:

NDA 21-378 (Oxycodone 5 mg/Ibuprofen 400 mg)		
File	Description of Contents	Reviewer's Comments
DCONMED.xpt	Concomitant Medications	Age, gender, race are not listed Treatment group is not listed Entries for NONE, ROUTE and UNIT are numerically coded, and are not accompanied by corresponding columns with text entries (eg, ROUTET [for Route–Text] would have entries such as PO, SC, etc.)
DINEX.xpt	Inclusion/Exclusion Criteria	Age, gender, race are not listed Treatment group is not listed YES_NO format not in text form
DMEDHIS.xpt	Medical History	Age, gender, race are not listed Treatment group is not listed Entries for ABN, BODYSYS, and NORMAL are numerically coded, and are not accompanied by corresponding columns with text entries (eg, BODYSYST [for Body System – Text] would have entries such as Respiratory, Cardiovascular, etc.)
DMEDREC.xpt	Prior and Current Medications	Age, gender, race are not listed Treatment group is not listed Entries for CONTINUE, NONE, ROUTE, UNIT are numerically coded, and are not accompanied by corresponding columns with text entries (eg, ROUTET [for Route – Text] would have entries such as PO, SC, etc.)
DMEDRESC.xpt	Rescue Medication	Age, gender, race are not listed Treatment group is not listed Entries for NONE, RESMED, ROUTE, UNIT are numerically coded, and are not accompanied by corresponding columns with text entries (eg, ROUTET [for Route – Text] would have entries such as PO, SC, etc.)
DPE.xpt	Physical Examination	Age, gender, race are not listed Treatment group is not listed Entries for ABN, BODYSYS, and NORMAL are numerically coded, and are not accompanied by corresponding columns with text entries (eg, BODYSYST [for Body System – Text] would have entries such as Respiratory, Cardiovascular, etc.)
DPLASMA.xpt	Plasma Drug Concentrations	Age, gender, race, and site are not listed
DSURGINF.xpt	Surgical Information	Age, gender, race are not listed Treatment group is not listed
DSURGMED.xpt	Surgical Medication	Age, gender, race are not listed Treatment group is not listed Entries for MEDICATN, NA and ROUTE are numerically

NDA 21-378 (Oxycodone 5 mg/Ibuprofen 400 mg)		
File	Description of Contents	Reviewer's Comments
		coded, and are not accompanied by corresponding columns with text entries (eg, MEDICATT [for Surgical Medication – Text] would have entries such as Midazolam HCl, Atropine, etc.)
DVITALS.xpt	Vital Signs	Age, gender, race are not listed Treatment group is not listed Entries for PERIOD and TEMPFC are numerically coded, and are not accompanied by corresponding columns with text entries (eg, PERIODT [for Period – Text] would have entries such as Pre-surgery, 2 hour post dosing, etc.)
EFF.xpt	Raw post-dosing efficacy evaluation	Age, gender, race are not listed Treatment group is not listed Entries for BPAIN, GPATRAT, INTPAIN, LCOF, LOCF_FDA, NACHIEVF, NACHIEVM, PAINHG, STARTPR, and TMADOSE are numerically coded, and are not accompanied by corresponding columns with text entries (eg, TMADOSET [for Time after dosing – Text] would have entries such as 15 min, 30 min, etc.)
EFF_LOCF.xpt	Derived efficacy data	Age, gender, race are not listed Treatment group is not listed Entries for C_ONSET, C_REMED, GPATRAT, LOCF, PHG0_25, PHG0_5, PHG0_75, PHG1, PHG1_5, PHG2, PHG3, PHG4, PHG5, and PHG6 are numerically coded, and are not accompanied by corresponding columns with text entries (eg, GPATRATT [for Patient global rating – Text] would have entries such as Poor, Fair, etc.)
PROF05.xpt	Patient Profile	Entries for APAIN, ATREAT, BPAIN, HEIGHTIC, ITT, PREASON, RACE, SAF, SEX, and WEIGHTLK are numerically coded, and are not accompanied by corresponding columns with text entries (eg, PREASONT [for Primary Reason for Withdrawal - Text] would have entries such as Adverse Event(s), Insufficient Therapeutic Response, etc.)
TEAE.xpt	Adverse Events	Age, gender, race are not listed Treatment group is not listed Entries for ACTION, CHRON, CONMED, CONTINUE, NONE, OUTCOME, RELATE, SERIOUS, SEVERE, TEAE are numerically coded, and are not accompanied by corresponding columns with text entries (eg, SEVERET [for Severe – Text] would have entries such as Mild, Moderate, etc.)

Review each data file for all studies in the NDA with regard to the above issues, and provide a new set of data files that conforms to the guidance document.

2) It appears that not all raw data have been provided. For example, the ISS-Clinical datasets contain information on the duration of multiple-dose therapy, but a dataset containing the actual data as recorded on the Dosing Record CRF in Study OXY-MD-08 can not be located. Provide the location of this dataset, or submit it to the NDA if it has not already been submitted. In addition, review the datasets from all the clinical pharmacology studies and from all the clinical trials to insure that all raw data have been submitted.

3) It appears that datasets for Studies 604-001-01 and 604-002-01 have not been provided. Identify the location of the datasets for these studies in the NDA, or provide datasets for these studies.

4) The Division recognizes that Study OXY-MD-07 is not completed, and that full data from this study will be submitted at the time of the 4-month safety update. The Division also expects that all data and analyses from Study OXY-MD-08 that rely on the blinded portion of Study OXY-MD-07 (eg, treatment received during the single dose study) will be fully updated at the time of the 4-month safety update. In this regard, it appears that patient demographic data for patients who participated in both Study OXY-MD-07 and OXY-MD-08 are either not included in the PROFISS.xpt data set or are not easily identifiable in that dataset. If available at this time, provide the available demographic data for patients who participated in both OXY-MD-07 and OXY-MD-08 in the PROFISS.xpt dataset. If these data are already included in the PROFISS.xpt dataset, provide a column with a variable indicating the single-dose study in which the multi-dose study patients participated. With regard to the PROFISS.xpt file, are patients who participated in the multi-dose trial OXY-MD-08 and in any of the three lead-in single-dose studies (OXY-MD-05, OXY-MD-06, or OXY-MD-07) reported twice in that dataset, once for the single-dose participation and once for the multi-dose participation?

5) In some cases where text entries are used for values of certain variables, the text entries are not consistent. For example, the variable TRT in the PROFISS.xpt dataset (in the ISS-Clinical folder) contains multiple ways of expressing the same treatment assignment. This inconsistency, summarized in the table below, makes grouping by this variable difficult with the software used by clinical reviewers.

TRT
Ibu 200 mg
Ibu 400 mg
Ibuprofen 400 mg
ibuprofen 200 mg alone
ibuprofen 400mg
oxycodone HCL 5mg
Oxycodone HCl 5 mg
Oxycodone HCl 10 mg
Oxy/Ibu 5/200 mg
oxycodone HCL 5mg/ibuprofen 200mg
Oxy/Ibu 5/400 mg
oxycodone HCL 5mg/ibuprofen 400mg
Oxycodone HCl 5 mg / Ibuprofen 400 mg
oxycodone HCL 10mg/ibuprofen 200mg
Oxycodone HCl 10 mg / Ibuprofen 400 mg
placebo
Placebo

Provide a dataset with a single, consistent text entry for each value of a variable. Review all datasets to insure that they conform to this specification.

6) The Division wishes to clarify its understanding of the variables PID, PATNO, and SITE in the ISS-Clinical Dataset. It appears that PID is a derived variable, which combines the patient number (PATNO) and the site number (SITE). Based on a sample below, taken from the PROFISS.xpt dataset, it appears that the PID variable is not unique for each individual

participant in the clinical trials, and that the same PID has been used for two different individuals who participated in two different trials, as described in the sample below:

PROTOCOL	PID	SITE	PATNO
OXY-MD-05	10001	01	0001
OXY-MD3-96-02	10001	01	0001
604-001-01	10001	01	0001
OXY-MD-05	10002	01	0002
OXY-MD3-96-02	10002	01	0002
604-001-01	10002	01	0002
OXY-MD-05	10003	01	0003
OXY-MD3-96-02	10003	01	0003
604-001-01	10003	01	0003

Thus, to identify a unique participant, it is necessary to know both the PID and the PROTOCOL number. Please confirm that this understanding is correct. For patients who participated in one of the lead-in single-dose studies (OXY-MD-05, OXY-MD-06, or OXY-MD-07) and in the multiple-dose study (OXY-MD-08), does the PID in the lead-in study correspond to the PID in OXY-MD-08? If not, how can patient participation in a single-dose study be linked to participation in the multiple-dose study in each of the datasets? For example, Study OXY-MD-08 contains patients with PID 030347 and 030357. Since each of these PIDs is used in both OXY-MD-05 and in OXY-MD-06, how is the single-dose data to be linked to the multi-dose data in each dataset?

7) For each dataset, it appears that the electronic version of the annotated case report form, to be designated *blankcrf.pdf*, has not been provided (see *Guidance for Industry – Providing Regulatory Submission in Electronic Format – NDAs, January 1999*, Section K, Number 3 – Documentation of the datasets). Provide the *blankcrf.pdf* file for each dataset.

8) Explain why the last sentence in the first paragraph in Section 4.5 of Study Report 604-001-01 is crossed out (see NDA Volume 68, page 21 [page 12 of study report]). Similarly, explain why the last sentence in the first paragraph in Section 4.5 of Study Report 604-002-01 is crossed out (see NDA Volume 69, page 22 [page 13 of study report]).

****

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/s/

Judit Milstein
1/16/02 03:04:39 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO (Division/Office): Controlled Substance Staff HFD-009 Corinne Moody	FROM: Dr. Cynthia McCormick, HFD - 170 Project Manager: Judit Milstein 7-7440

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 7, 2002		21-378		December 20, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ibuprofen.oxycodone 5/400 mg			Open consult

NAME OF FIRM: Forest Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER (SPECIFY BELOW).

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW).

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Provide continuous advice during the review of the product.
If you have further question s call Judit Milstein, Regulatory Project Manager at 7-7440
CC: all correspondence to Judit Milstein and Aleta Crane (9B-45)

SIGNATURE OF REQUESTER: Judit Milstein	METHOD OF DELIVERY (Check one) ■ E-MAIL (DFS) HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Judit Milstein
1/7/02 12:16:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 52,310

Forest Laboratories, Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, New Jersey 07311

Attention: Daniel Gordin, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Gordin:

Please refer to the telephone conference between representatives of your firm and FDA on July 26, 2001. The purpose of the meeting was to discuss your NDA plans for oxycodone/ibuprofen.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: July 26, 2001 (10-11:30am)

Location: Conference Room "C"

Sponsor: Forest Laboratories, Inc.

Drug Name: Oxycodone/ibuprofen

Type of Meeting: Type B

Meeting Chair: Bob Rappaport, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products

Minutes Recorder: Lisa E. Basham, Regulatory Project Manager

Forest Laboratories, Inc.	Title
Ivan Gergel, M.D.	Vice President, Medical
William Byra, M.D.	Senior Director, Medical
Im Abramowits, M.D.	Senior Director, Pharmacokinetics
Robert Ashworth, Ph.D.	Senior Director, Regulatory Affairs
Doreen Morgan, Pharm.D.	Director, Regulatory Affairs
Daniel Gordin, Ph.D.	Associate Director, Regulatory Affairs
Robert Jackson	Associate Director, Project Management
Hongjie Zheng, Ph.D.	Associate Director, Biostatistics
Steven Shen, Ph.D.	Manager, Biostatistics
Edward Lakatos, Ph.D.	Senior Director, Biostatistics
Terry Fico, Ph.D.	Pharmacology
FDA	**Title**
Cynthia G. McCormick MD	Division Director
Bob Rappaport, MD	Deputy Division Director
Tom Papoian, Ph.D.	Supervisory Pharmacologist
Tom Permutt, Ph.D.	Statistics Team Leader
Gerald DalPan, M.D.	Medical Reviewer
Suzanne Thornton, Ph.D.	Pharmacology Reviewer
Sandip Roy, Ph.D.	Biopharmaceutics Reviewer
Lisa E. Basham, M.S.	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss the sponsor's proposal for submission of an NDA for oxycodone/ibuprofen.

Minutes:

Dr. Rappaport began the meeting by stating that one purpose of a pre-NDA meeting is to review the proposed application in order to avoid a refuse to file action as described in 21 CFR 314.101. The division is concerned about the lack of CMC information in the pre-NDA meeting submission and warned that the sponsor is taking a risk by not submitting their CMC proposal for FDA comment.

The meeting format focused on the questions submitted by the sponsor on June 6, 2001.

> *Question 1. Is the approach for filing the oxycodone/ibuprofen NDA as a 505(b)(2) application acceptable?*

Ms. Basham answered that this approach is acceptable. Dr. McCormick, later in the meeting, added that a 505(b)(2) application requires that the study drug be compared to a listed drug and that the indication will follow the listed drug's indication. The sponsor said that the drug will be compared to Roxicodone and Nuprin. Dr. McCormick offered that there may be more robust products with regard to labeling to use for comparison.

> *Question 2. Are the filing plans for the Pharmacology and Toxicology Section of the NDA acceptable?*

Dr. Thornton replied that the filing plan is acceptable. Phase 4 commitments for Fertility/Reproduction (Segment I) and Pre- and Post-natal studies (Segment III) will be necessary. While the proposed indication is for treatment of acute pain (treatment not to exceed 7 days), if post-marketing surveillance shows that the product is being used chronically, assessment of carcinogenic potential will be required.

Dr. McCormick commented that the clinical studies to be submitted are single-dose dental studies. The sponsor added that they are conducting an extension study in osteoarthritis patients with treatment for 7 days. Dr. McCormick stated that the label must explicitly state that the product is not intended for chronic use.

> *Question 3. Are the filing plans for Human Pharmacokinetics and Bioavailability Section of the NDA acceptable?*

Dr. Roy replied that the plan to submit the bioavailability study, the dose-proportionality study, the food effect study, and the bioequivalence study comparing the clinical trial formulation to the marketed formulation is acceptable.

> *Question 4. The content and table shells to be included in the ISS and ISE are found in Appendices 1 and 2. Does the Division agree with the proposed organization of the ISE and ISS?*

Dr. DalPan began discussion of this question by asking the rationale for the groupings described for the Integrated Summary of Efficacy (ISE), i.e. the pooling of data from studies 05 and 06 to observe subgroup effects, with the other study data considered supportive. The sponsor stated

that studies 05 and 06 are the pivotal Phase 3 studies to be considered for efficacy. Dr. McCormick responded that the Agency would consider all placebo-controlled trials in the evaluation of efficacy. The purpose of the ISE is to integrate the data from all studies to show consistency of effect, not to selectively evaluate some studies and not others. The sponsor replied that they will focus on the two pivotal studies, but will pool data from the other studies for evaluation of demographic subgroups. Dr. McCormick said that the submission should include a discussion of how the studies support each other. Dr. McCormick summarized that non placebo-controlled studies must be included in the safety database and that studies that are adequately controlled must be included in the evaluation of efficacy, with an explanation as to why they do or do not support the drug's efficacy.

Dr. DalPan conveyed the following issues with regard to the Integrated Summary of Safety (ISS):

Panel 5A/5B – non-Caucasian needs further specification.
Panel 7 – include other treatment groups, and indicate specifically if no serious adverse events occurred in them.
Panels 7, 8, 9A, 9B - In the ISS text accompanying these panels, include a clear location of the line listings and narratives for all patients in all treatment groups, with reference to individual study reports as needed.
Panel 11 – include clear cross-reference to all appropriate line listings.

> *Question 5. We propose to submit clinical datasets in SAS transport format in lieu of Case Report Tabulations. Is this acceptable?*

Dr. DalPan referred the sponsor to the Guidance for Industry, dated January, 1999, titled, *Providing Regulatory Submissions in Electronic Format –NDAs.* He summarized some key points from this guidance that, if overlooked, can limit the utility of the electronic CRTs:

- Include raw and derived data.
- Keep file sizes < 25 MB.
- Use descriptive variable names in addition to eight-character names with clear description of each variable.
- Use a consistent format for all date variables.
- Include the duration and study day in AE, concomitant medication, etc. files.
- Include treatment, age, gender, race, center/site in all files to allow for easier review of data.
- Include text, in addition to number system, for all variables.

Dr. DalPan asked if the sponsor was planning to submit patient profiles, as outlined in Section (IV)(K)(7) of the above-mentioned guidance document. The sponsor noted that it does not intend to submit such patient profiles. Dr. DalPan then inquired how safety data from the single-dose studies will be linked to safety data from the multiple-dose studies. He specifically wanted to know if individual patients retained the same number in the single-dose and multiple-dose studies. He noted that it is important to link safety data from the single-dose phase to the multiple-dose phase. Because the sponsor is not planning to provide patient profiles, the Division asked that the sponsor submit more detailed plans (e.g., sample safety data tables and listings) for linking data from the two phases. The Division will review these and determine if they are adequate.

Question 6. Are the safety data to be submitted adequate for the assessment of the safety of oxycodone/ibuprofen?

Dr. DalPan said that, based on numbers alone, the extent of exposure appears adequate. There is concern whether the elderly and young will be adequately represented, however, since molar extraction studies would predominantly enroll patients between 18-25 years old. The sponsor replied that study 06 includes patients as young as 12 years old. Originally, study 05 did, as well, but the IRB raised the inclusion age to 18. Study 08 includes both elderly and young patients. The extension study (07) includes patients up to 80 years old. The sponsor expects the data to be available by the time of the 120- day safety update.

Question 7. In regards to pediatric assessment, Forest submitted a request for a partial deferral of pediatric studies for pediatric patients <12 years of age (IND submission Number 062). Does the Division concur with this request?

The sponsor said that they were unable to cover the whole pediatric age range in the performed studies, but that they intend to study younger children in the future. Dr. McCormick said that the sponsor must submit the explanation for the lack of complete pediatric data to the NDA, and that a deferral will be granted.

Dr. McCormick made some general comments regarding the proposed indication for the drug. She clarified that the

The sponsor said that their understanding was that they would need two studies in any pain model, regardless of etiology, for a pain indication. Dr. McCormick said that the orthopedic studies need to be completed for such an indication. She added that the listed drugs may extend the indication. The issue of appropriate indication is a review issue and will be revisited at the time of review.

Regarding the lack of chemistry data, the sponsor acknowledges their omission of the data, and is comfortable with that omission. They felt that the time would be best used for discussion of other issues relevant to the NDA.

ACTION ITEMS:

The sponsor will submit a detailed description of how they plan to submit clinical data, including AEs, concomitant medications, and how they plan to link data between the single and multiple dose studies.

The NDA is expected to be submitted in November 2001.

Lisa E. Basham
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia McCormick
8/22/01 05:04:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Forest Laboratories, Inc.
Corporate Offices
909 Third Avenue
New York, NY 10022

2. TELEPHONE NUMBER *(Include Area Code)*

(201) 386-2025

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-378

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS 'NO' AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM

IF RESPONSE IS 'YES' CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO

_____
(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME

oxycodone/ibuprofen combination product

6. USER FEE I.D. NUMBER

4142

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Senior Director, Regulatory Affairs	10/22/01

FORM FDA 3397 (3/01)

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DEPARTMENT OF HE[illegible]H & HUMAN SERVICES

Di

EOP2

Food and Drug Administration
Rockville MD 20857

IND 52,310

JUL 16 1999

Forest Laboratories, Incorporated
Harborside Financial Center
Plaza 3, Suite 602
Jersey City, New Jersey 07311

Attention: Daniel T. Coleman, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Coleman:

Please refer to the teleconference between representatives of your firm and FDA on June 16, 1999. The purpose of the meeting was to discuss your development plans and to clarify what would be needed in an NDA for oxycodone hydrochloride/ibuprofen for the management of moderate to moderately severe pain.

A copy of our minutes of that teleconference is enclosed. These minutes are the official minutes of the meeting. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Debbie Fong, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

cc: Original IND 52,310
HFD-170/Div. Files
HFD-170/D. Fong/N. Chamberlin/C.P. Moody
HFD-170 C. McCormick
B. Rappaport
H. Blatt
A. D'Sa
M. Theodorakis
L. Jean
D. Brase
K. Haberny
T. Permutt
S. Wang
HFD-870/ S. Doddapaneni/R. Uppoor

Drafted by: D. Fong 6/25/99
Revised: 7/14/99 per D. Coleman (new address); 7/14/99 per C.P. Moody
Initialed by: C.P. Moody 7/14/99
Final:
Filename: 52310(Forest)MMLTR061699.doc

Meeting Minutes for Type C Teleconference

MEETING MINUTES

Meeting Date: June 16, 1999 Time: 12:30-1.30 p.m
Location: Parklawn 9B-45
IND: 52,310 Oxycodone HCl/ Ibuprofen
Sponsor: Forest Laboratories, Inc.
Indication:
Type of Meeting: Type C meeting (teleconference to clarify NDA requirements)
Meeting Chair: Cynthia G. McCormick, M.D.
Minutes Recorder: Debbie Fong/ Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Harold Blatt, D.D.S.	Medical Reviewer	HFD-170
Michael Theodorakis, Ph.D.	Senior Chemistry Reviewer	HFD-170
David Brase, Ph. D.	Pharmacology Reviewer	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Reviewer	HFD-870
Debbie Fong, Pharm.D.	Regulatory Project Manager	HFD-170
Indira Kumar	Regulatory Project Manager	HFD-170
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Sue-Jane Wang, Ph.D.	Biostatistics Reviewer	HFD-170

Forest's Attendees:	Titles:
Im Abramowitz, Ph.D.	Senior Director, Pharmacokinetics
Dan Coleman, Ph.D.	Manager, Regulatory Affairs
Karen Fleshman, Ph.D.	Assistant Director, Regulatory Affairs
Ivan Gergel, M.D.	Executive Director, Medical
Julie Kilbane, R.N., M.B.A.	Director, Project Management
Barry Levine, M.D.	Director, Medical
Larry Olanoff, M.D., Ph.D.	Executive Vice President, Scientific Affairs
Ross Rocklin, M.D.	Senior Director, Medical
Keith Rotenberg, Ph.D.	Executive Director, Regulatory Affairs & Quality Operations
Jia-Yeong Tsay, Ph.D.	Director, Biostatistics
Edward Yau, Ph.D.	Director, Toxicology

Meeting Objective: The primary objective of this meeting was to respond to the firm's April 27, 1999 meeting request for clarification on a clinical development plan and what is required for their NDA. Their proposed indication for the combination oxycodone HCl/ ibuprofen tablet product is

Introduction: The firm had a telecon with the Division on January 29, 1997 to discuss the clinical development plans for oxycodone/ ibuprofen. Forest discontinued their trials in 1997. Then on August 13, 1998, Forest informed the Agency that they had received notification of clinical

protocol violations in study OXY-MD3-96-01-000 being conducted by
[redacted] site. This Division met with the sponsor on March 16, 1999, to discuss reinitiation of the sponsor's proposed Phase 3 clinical development plan. This plan was not accepted by this Division. On March 30, 1999, the sponsor proposed three trials to study safety and efficacy in two pain models. After Forest's meeting request dated April 27, 1999, they elaborated on toxicology questions on May 18, 1999. On June 14, 1999, Forest faxed in their current list of questions, referencing the Vicoprofen SBA.

FIRM'S QUESTIONS:

Clinical Issues:

1. At the March 16, 1999 meeting with the Division, Forest proposed a clinical development program that was similar to a program previously agreed upon by Forest and the Division based on a teleconference of January 29, 1997. The Division rejected the proposed program, instead requesting additional studies. On review of the Agency's Basis for the Approval of Vicoprofen® (see attached summary points from Vicoprofen SBA), Forest finds that the program proposed earlier and also presented in a submission of March 30, 1999 is in fact more rigorous than what was accepted for approval of Vicoprofen. This program is reiterated below (please refer to June 14, 1999 fax) with a minor modification (i.e., deletion of the 5 mg oxycodone group from Study 3). Is this program acceptable to the Division for the desired claim (relief of moderate to moderately severe pain)?

   Division Response: Dr. McCormick stated that the Vicoprofen application is an outlier and should not be considered a typical application for approval purposes. The Division of Anti-Inflammatory Drugs, Analgesic, and Ophthalmologic Drug Products concurs with this Division that data on a specific dose ratio must be replicated in two studies. A dose-ranging design should be worked into the two studies. A six-arm study, including arms of 5/400 mg oxycodone/ibuprofen (single tablet), 10/400 mg oxycodone/ibuprofen (two 5/200 mg tablets), 400 mg ibuprofen, 10 mg oxycodone, 5 mg oxycodone, and placebo, will allow testing of both combination strengths against the individual components and placebo.

   Discussion: The sponsor reviewed previous studies conducted, including Phase 2 studies that did not show statistically significant differences between ibuprofen and the combination product. The sponsor stated that these studies were inadequately powered to detect differences. Dr. McCormick emphasized that we cannot hypothesize what could have resulted from those studies. Data from these studies can only be used to support the safety database

   Dr. McCormick reiterated that data on each dosage ratio must be replicated in two studies. That is, one dose ratio cannot be analyzed in one study, while a second dose ratio is analyzed in the second study. If this latter approach was implemented, patients could not be properly informed when to use which product for various situations.

   Two replicated studies will also provide a safety comparison.

2. If Forest were to perform the three clinical studies above (please refer to June 16, 1999 fax) (one study in dental pain and two studies in either orthopedic or general surgery), would all three studies have to demonstrate statistical separation between the ibuprofen and the combination product (oxycodone/ibuprofen) treated groups for the primary endpoints, or would it be sufficient to demonstrate statistical separation for the study in dental pain and for one study in alternate pain condition with confirmatory numerical trends in the complimentary study?

   Division response: If one study is unsuccessful, it will be described in the labeling. However, two successful studies with replicated results will support approval for the intended claim.

   Discussion: The sponsor stated that they are willing to accept the risk involved in excluding

3. In our letter dated March 30, 1999, we stated that we are planning to include an extension multiple-dosing period (3 to 7 days) for safety assessment in 300 patients. These patients would be enrolled from Studies 1, 2, and 3. We request reconsideration of the 500-patient requirement stated by the Division at the March meeting since recent multiple dose safety experience with a similar product, Vicoprofen (ibuprofen/hydrocodone combination, NDA 20-716 approved September 1997), was limited to 300 patients.

   Division response: Dr. McCormick stated that a multiple-dose toxicity study is needed to assess additive toxicity in addition to additive efficacy in terms of combination products Three-hundred patients are insufficient to assess this. We would probably still file the application with less than 500 patients, however a smaller database could be problematic The sponsor was reminded that products have recently either been pulled from the market or given onerous labeling due to safety concerns. It is a new combination product, and more data is preferable. If we don't feel comfortable with the safety data submitted, it could impact upon our decision to approve or not approve the application.

   Discussion: Dr. McCormick concurred with the sponsor that patients from the multiple-dose and pharmacokinetic studies will contribute to the safety database. Thus, the sponsor may be able to capture up to 500 patients for the safety database. The sponsor stated that they would capture as many patients as they can, i.e. 300-500 patients.

Toxicology Issues:

4. Has the Division set forth the requirements for general toxicology studies for an NDA application upon further review of the prior studies conducted on this combination product? Specific issues, which were proposed in the letter of May 18, are listed in "Nonclinical Issues" handout (attached).

   Does the Division concur that:

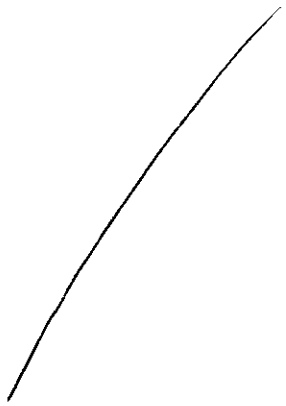
   a) The 28-day Dog Tox Study does not need to be repeated?

b) Segment I and III studies are not required?
c) A genotox battery will not be required?
d) 2-year carcinogenicity studies will not be required?

Division response and discussion: The sponsor confirmed that they have licensed the rights to the product, including data from Dupont. Dr. Brase stated that the 28-day dog study does not need to be repeated. However, he has concerns regarding the statistically significant 5.4-fold increase in the incidence of fecal occult blood for the high-dose combination compared with ibuprofen alone, which is paralleled by a decrease in hematocrit observed at day 33 in dogs receiving the high-dose combination treatment. This finding must be added to the Investigator's Brochure and future labeling, because the abnormality is unexpected, based on the pharmacology of the individual components of the product.

Data from Segments I-III reproductive toxicity studies, genotoxicity studies, and carcinogenicity studies are required. Dr. McCormick informed the sponsor that due to a lack of satisfactory preclinical data on the individual components of the product, we plan to bring data from all three types of studies to the Pharmacology and Toxicology Coordination Committee (PTCC). The sponsor should submit data they have from Dupont on Segment II reproductive toxicity studies. The sponsor thought that carcinogenicity studies were not required when the product is intended for acute use only. Dr. McCormick said that it is better for the sponsor to state the findings from carcinogenicity studies in their labeling.

The sponsor was advised that the use of any literature references would make their NDA submission a 505(b)(2) application.



Discussion: The sponsor asked several additional questions regarding biopharmaceutic requirements. Dr. Doddapaneni, in response to these questions, reiterated that they would have to conduct a multiple-dose study. A population pharmacokinetic approach could be utilized The sponsor will also need to conduct food effect studies, since the product will be intended for use with food to decrease gastrointestinal toxicity. The sponsor does not need to conduct pediatric pharmacokinetic studies, since they do not plan to label their product for use in patients less than 12 years old.

The sponsor asked if they could change their intended labeling from moderate to moderately severe pain, to moderate to severe pain. Dr. McCormick said that would depend on what types of patients are enrolled in their clinical studies, how their entry criteria are defined, and how pain is measured in the clinical studies. The sponsor asked if sub-group analysis was satisfactory. Dr. McCormick felt that additional information was needed in order to respond completely to that question. She told the sponsor they should submit their proposal in writing to the Division.

OTHER DISCUSSION FOR MEETING:

Chemistry: Dr. Theodorakis asked the sponsor how they plan to conduct stability testing for the ——— The sponsor responded that such testing would be done according to ICH guidelines, ———

The meeting was adjourned by Dr. McCormick.

Action Items:

- The firm will take the information discussed in this meeting under advisement and attempt to address the FDA concerns.
- FDA will provide the sponsor with a copy of the meeting minutes.
- FDA will provide the sponsor with recommended statements concerning the one-month dog toxicity study to be included in the Investigator's Brochure and future labeling.

Minutes Prepared By: Debbie Fong, Pharm.D. Debbie Fong

Minutes Concurred By Chair: Cynthia McCormick, M D. Cynthia McCormick MD

cc: Original IND 52,310

HFD-170/Div. Files
HFD-170/D. Fong/N. Chamberlin/C.P. Moody
HFD-170 C. McCormick
B. Rappaport
H. Blatt
A. D'Sa
M. Theodorakis
L. Jean
D. Brase
K. Haberny
T. Permutt
S. Wang
HFD-870/ S. Doddapaneni/R. Uppoor

Drafted by: D. Fong 6/25/99
Revised: 6/30/99 and 7/2/99 per D. Brase, L. Jean; 7/6/99 per H. Blatt and S. Doddapaneni; 7/15/99 per B. Rappaport; 7/16/99 per C. McCormick
Initialed by: C.P. Moody 7/14/99 cpm 7-16-99
Final:

File name: 52310MTG(Forest)061699.DOC

DEPARTMENT OF HEALTH & HUMAN SERVICES

IND 52,310

Type C

Food and Drug Administration
Rockville MD 20857

Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022-4731

APR 15 1999

Attention: William Woolever
Assistant Director, Regulatory Affairs

Dear Mr. Woolever:

Please refer to the meeting between representatives of your firm and FDA on March 16, 1999. The purpose of the meeting was to discuss reinitiating your proposed Phase III clinical development program and clarify what would be required in an NDA for the combination product oxycodone/ibuprofen.

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc: Original IND 52,310
HFD-170/Div. Files
HFD-170/Chamberlin\ C Moody
HFD-170 C McCormick
B Rappaport
H Blatt
M Theodorakis
D Brase
L Jean
A Dsa
S Calderon
HFD-870 /S Doddapaneni
R Uppoor

Drafted by: N.Chamberlin 4-14-99
Revised: 4-15-99 nc
Initialed by: C. P. Moody 4-15-99 cpm 4-15-99
Final:
filename: 52310ltr316.doc

Meeting Minutes

MEETING MINUTES

Meeting Date: March 16, 1999 Time: 9:30-11:00 a.m.
Location: Parklawn, 3rd Floor, Conference room C
IND: 52, 310 Oxycodone HCl/ Ibuprofen
Sponsor: Forest Laboratories, Inc.
Type of Meeting: General Program Overview
Meeting Chair: Cynthia G. McCormick, M.D.
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Harold Blatt, D.D.S.	Medical Reviewer	HFD-170
Michael Theodorakis, Ph.D.	Senior Chemistry Reviewer	HFD-170
Albinus D'Sa, Ph. D.	Chemistry Team Leader	HFD-170
David Brase, Ph. D.	Pharmacology Reviewer	HFD-170
Dou Huey Jean, Ph.D.	Pharmacology Team Leader	HFD-170
Silvia Calderon, Ph.D.	CSET Team and Drug Abuse Liability Reviewer	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Reviewer	HFD-870
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170

Forest's Attendees:	Titles:
Im Abramowitz, Ph.D.	Senior Director, Pharmacokinetics
Gilbert Adelstein, Ph.D.	Director, Regulatory Affairs, CMC
Ivan Gergel, M.D.	Executive Director, Medical
Julie Kilbane	Director, Program Management
Barry Levine, M.D.	Director, Medical
Charles Lindamood III, Ph.D.	Senior Director, Pharmacology/Toxicology
Lawrence Olanoff, M.D., Ph.D.	Executive Vice President, Scientific Affairs
Keith Rotenberg, Ph.D.	Executive Director, Regulatory Affairs & Quality Operations
Jia-Yeong Tsay, Ph.D.	Director, Biostatistics
William Woolever	Assistant Director, Regulatory Affairs
Ross Rocklin	

Meeting Objective: The primary objective of this meeting was to respond to the firm's January 12, 1999 meeting request for information about reinitiating a proposed Phase III clinical development program. Their proposed indication is [redacted] for the combination oxycodone HCl/ ibuprofen tablet product.

Introduction: Regulatory Background was provided in the firm's briefing package. Firm had a telecon with the Division on January 29, 1997 to discuss the clinical development plans for oxycodone/ ibuprofen. Forest discontinued their trials in 1997. Then on August 13, 1998 Forest

informed the Agency that they had received notification of clinical protocol violations in study OXY-MD3-96-01-000 being conducted site.

Pharmacokinetics: Sponsor presented the four PK studies in which it claimed to show that oxycodone and ibuprofen had similar PK profiles. However, Cmax was lower and Tmax was longer in the tested combination versus Nuprin which was fast acting. Dr. Doddapaneni asked if oxycodone was affecting the absorption. The firm responded that they did not think so and that Dupont's Medipren has a slower dissolution. The firm concluded that there was no PK interaction between oxycodone and ibuprofen and that the two dosage level combinations were equivalent to ibuprofen.

Clinical: Sponsor summarized their clinical development plans.

The firm stated that their phase II Dupont dental model sample size was not large enough to discriminate efficacy. In their high dose and low dose studies, the firm stated that both discriminated from placebo. These were used for the initial dose-response information, the 400 mg ibuprofen gives the full therapeutic analgesic response and the oxycodone 5 mg was equal to 60 mg codeine and used to enhance the NSAID analgesic effect.

In the phase III study of oxycodone 5mg /ibuprofen 400 mg combination for treatment of moderate to severe pain, the primary efficacy endpoints were TOTPAR and SPID, and the secondary endpoints were global assessments, etc. The sponsor stated that upon receiving notification of clinical protocol violations in study OXY-MD3-96-01-000 being conducted by — at two different sites, it was stopped and they could not not use one site's information. In the single dose study, the patients did not receive rescue medication. Study–02 dental study was only partially completed.

The firm talked about the studies it proposed to conduct.

FIRM'S QUESTION:

1. **Does the Division agree that the development plan as described in the Briefing Book Section 2.3, sufficiently support the proposed analgesic claim, assuming that at least one study for each pain model demonstrates a statistically significant benefit of the combination product compared to ibuprofen alone?**

   Dr. McCormick concurred with the sponsor's decision that it would not be appropriate to use this opioid/ibuprofen fixed combination in chronic use.

   Dr. McCormick said that the sponsor needs to show that each component contributes to the efficacy in the painful conditions under study. The dental study looked at both components while the ortho study only looked at oxycodone. She commented that the sponsor needs to establish the ratio and components that contribute to efficacy. She urged the sponsor to modify their proposed studies.

   Dr. Permutt commented that it is a difficult issue showing that the ratio of ibuprofen/ oxycodone are the ones that will be needed. He also noted that dosage ratio ranging across studies is a problem.

Dr. McCormick asked the sponsor to think about what they know about the drug, how it behaves, and what the dose would be. The sponsor responded that they learned the 200 mg ibuprofen was not an effective dose.

Dr. Permutt asked the firm what dose would they recommend for

Dr. Permutt stated that we must be able to label it.

The firm commented that it appears to have received different guidance before. Dr. McCormick responded that the combination drug product policy has to be met. Their proposal for a combination product used as an analgesic,

, based on the sponsor's proposal.

2. Is the Division in agreement with the statistical plan for the analysis of the proposed clinical studies in the Briefing Book, Section 2.4?

Dr. Permutt commented that the plan was brief and in general on the right track. However, he agreed that we could review the detailed protocols prior to initiating studies to help them.

Dr. Permutt commented that the primary outcome measurement was appropriate to use SPID and TOTPAR, and be aware that analysis at the end time points as a secondary outcome would be very important for single dose analgesic. He noted that we cannot be committed to agree that they would win on TOTPAR/SPID, because we look at the total time course. He noted that they need both components to contribute at each time point, which could potentially be a problem if they have different time courses of action. Sums of pain relief appear to be the right way to do this. In addition, he referred them to look at the guidelines and the way other Anti-inflammatory agents were studied. There is not a need for statistical significance at each time point. Dr. McCormick commented that there would be a problem when individual time points contradict the sum total. The sponsor responded that they thought the time points were similar and would look to secondary parameters to see the general trend.

3. Based on the results of the completed pharmacokinetic studies performed with the combination formulation of oxycodone HCl / ibuprofen, is the Division in agreement that these pharmacokinetic studies are sufficient for the approval and labeling of the combination product?

Dr. McCormick asked the sponsor what formulation and dosage were used. Dr. Doddapaneni noted that in the 97-01 biostudy, they used 2 ibuprofen tablets and there appeared to be a formulation effect.

Dr. Doddapaneni noted that the sponsor had conducted single dose studies and asked them what dosing interval they would recommend. The firm answered, every 6 hours, with a maximum of 4 doses. Dr. Doddapaneni suggested they study it for determining the dosing recommendation because the t ½ of oxycodone is 3.5 to 4 hours.

Dr. Doddapaneni suggested that the sponsor do a multidose study. Dr. McCormick stated that if they are planning to dose the product over several days, then we need the data from a multidose study. The firm asked if doing a PK study for 3 to 4 days would be adequate. The opioid tolerant question would need to be addressed in the clinical product.

Dr. Doddapaneni asked the firm if the product would be used with food, due to the ibuprofen component. He recommended that the sponsor conduct a food study, unless they can show that the food effect is due to the drug substance.

4. Would the Division designate the combination product - oxycodone HCl / ibuprofen as a Schedule III or Schedule II Controlled Substance?

   Dr. Calderon noted that there are no provisions in the law to allow for changing from Schedule II for the combination. The sponsor would have to prove that ibuprofen limits the amount of drug abuse and extractability of oxycodone, and would have to compare it to other products in Schedules II and III.

5. Pediatrics- the firm is currently looking at 16 years.
   It was suggested that the sponsor look at younger patients at least 12 years and provide a pediatric study proposal for a written request for PK and safety studies in children for exclusivity in a condition likely to get an efficacy response in children.

OTHER DISCUSSION FOR MEETING:

Chemistry: Dr. D'Sa asked the sponsor if the formulation was changed from that used in the clinical trials. The firm responded that the coating was changed for cosmetic reasons and did not affect the function of the film coating.

Pharmacology: The sponsor did not provide any pre-clinical issues in the briefing package; however, upon reviewing the recent annual reports, the Agency had the following suggestions for the sponsor:

- The Agency would like the sponsor to provide the final study reports of all preclinical studies it intends to use to support their clinical development to the IND.

- In the 28-day dog toxicity study, the high dose of ibuprofen was 20 mg/kg, while the MRHD for Motrin is 3200 mg (approximately 64 mg/kg/day) in divided doses. Therefore, the dog study was not conducted at high enough doses and is not considered a valid toxicology study.

The sponsor needs to repeat the 28-day dog study at higher doses, including the toxicokinetics measurements to determine exposure to both drugs, as well as the active metabolite oxymorphone.

- The sponsor needs to conduct a standard battery of genotoxicity tests of the combination of oxycodone:ibuprofen in the ratio it intends to market.

- The sponsor needs to conduct studies of fertility (segment I), prenatal and postnatal development including maternal function (segment III), including toxicokinetics, ideally before initiating phase III clinical trials. Such is required for a new chemical entity.

- ICH guidelines require carcinogenicity studies for drugs having chronic indications.

- Dr. Jean asked the sponsor to see if the combination product has any increased GI side effects and provide the Agency with the data.

The sponsor responded that they had conducted 28-day rat and dog studies using the dose ratio of the proposed market product. It was noted that the dose was not high enough in the dogs.

Dr. Jean noted that the ICH guidelines generally require 28-day studies, but since the intended use of this product would be for only a few days to 1 week, they could do a 2-week study instead. However, she noted that if the drug were to be used over 2 weeks, then they would have to do a 28-day study. She stressed that it is important to obtain the toxicokinetic parameters in the study.

The sponsor had expressed concern that they were a small company with limited resources and that the agency was now being more rigorous in their requirements on old drugs to be used in combination for only 7 days.

Dr. Brase responded that we don't expect any surprises from this combination, but we don't have the data. Dr. McCormick told the sponsor that she would get back to them on this.

Conclusions:

- Pharmacokinetics reviewer requested the sponsor to conduct a food study, if they cannot show that the food effect is due to the drug substance.

- Pharmacokinetics reviewer requested a multiple dose study in normal volunteers.

- Proposed indication would be for acute only, so the chronic pain study would not be required.

- The proposed product would be Schedule II, unless sponsor provides a proposal to change this.

- Agency recommended for pediatrics use that the sponsor decrease the study's age inclusion criteria to 14 or 12, and pharmacokinetic safety information is needed for under 12 years of age. Dr. McCormick commented that ideally the Agency prefers to get pediatric pharmacokinetics data at time of the NDA or shortly after the drug is approved.

- Need to repeat the 28-day toxicology study in the dogs using an appropriate high dose.

- The sponsor needs to conduct a battery of genotoxicity tests of the combination of oxycodone:ibuprofen in the ratio it intends to market.

- The sponsor was told that they need to conduct studies of fertility (segment I), prenatal and postnatal development including maternal function (segment III), including toxicokinetics. Dr. McCormick agreed that the division would check on this since old drugs were being used in this new combination.

- **Clinical trials would need replication of effect. Dr. McCormick stated that the firm should do 4 studies to get the data that they need and replicate within the painful conditions studied, assuming that different ratios of ibuprofen and oxycodone are required for different conditions as the sponsor has proposed.**

- The sponsor needs to show that both components contribute to efficacy of the combination product.

- Dr. McCormick encouraged the sponsor to explore the efficacious dose and ratio.

- Safety data would be obtained in the multiple dosing over short term in the open label study of 3 to 7 days duration (continuing administration after the first dose).

- Dr. McCormick noted that the recommended ICH numbers for the safety data base of 1500 patients would not be required for this drug, and she recommended that they obtain 500 in the 3 to 7 days study.

- The Agency recommended that the sponsor submit the protocols for the FDA to comment on the design and that it would respond in a timely manner.

Action Items:

- The firm will take the information discussed in this meeting under advisement and attempt to address the FDA concerns.

- FDA will provide the sponsor with a copy of the meeting minutes.

Minutes Prepared By: N. Chamberlin, Pharm.D. Nancy Chamberlin

Minutes Concurred By Chair: C. McCormick, M.D. Cynthia M McCormick MD

CC: IND 52,310

HFD-170/Division Files

HFD-170/Chamberlin
HFD-170 C McCormick
B Rappaport
M. Scheinbaum
M Theodorakis/D'Sa
Brase/Jean
Permutt
C Moody
HFD-870 /S Doddapaneni
R Uppoor

Reviewed: M.Theodorakis and D'Sa on 4-14-99

Drafted by: N.Chamberlin 4-8-99
Revised: 4-14-99 per HB, 4-14-99 per SC and Suresh, 4-14-99 per Lucy and David, 4-15-99nc, 4-15-99 per Cynthia
Initialed by: C. P. Moody 4-15-99
Final:

FILE NAME: 52310MTG316.DOC

Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022

OXYCODONE HCl / IBUPROFEN

NDA #21-378

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

1 Pediatric Population

Approximately 240 pediatric patients between the ages of 13-17 years were exposed to the oxycodone HCl/ibuprofen combination product for the evaluation of safety. Furthermore, approximately 80 of these 240 patients were exposed to multiple doses of oxycodone HCl/ibuprofen with an average duration of exposure of 4 days (range 1-8 days).

In terms of addressing the remaining age groups, pursuant to the Pediatric Rule, Forest Laboratories, Inc. submitted a proposal to conduct a pharmacokinetic study to address the pediatric age group 7 to 12 years and requested the Agency to issue a Written Request (IND Serial No. 077 submitted on August 29, 2001).

At the Pre-NDA meeting (Date: July 26, 2001), the Division indicated that a deferral would be granted for the remaining age groups and to include a deferral request in the NDA which follows.

1. **Is the indication for a life-threatening condition that occurs in the pediatric population?**

   Oxycodone HCl/ibuprofen 5/400 mg is a narcotic/analgesic combination product that will be indicated for the relief of acute, moderate to severe pain. Acute, moderate to severe pain is not a life-threatening condition.

2. **What ages are included in your deferral request?**

   The ages that are included in the deferral request are based on the FDA pediatric rule and include neonates, infants, and children 2-6 years.

3. **Reason for not including the entire pediatric population in the studies or in the deferral request:**

   In the current core trials (Studies OXY-MD-05, -06, and -08) the enrollment of pediatric patients was restricted by the decisions of many study center's individual IRBs to limit the enrollment of pediatric patients due to potential safety concerns related to doses of oxycodone $\geq$ 5 mg and to the possibility of pediatric patients being randomized to the placebo arm which many considered unethical (Letters from investigators previously submitted in IND Submission No. 59). In addition, since the design of clinical studies to assess relief of pain for efficacy involves subjective measures, such as VAS and onset and offset of pain utilizing stopwatches, which requires a patient to understand how to assess their pain, the ability of a child $\leq$ 12 years old to measure a response to oxycodone/ibuprofen therapy for the determination of efficacy may be limited by these protocol specified procedures.

4. **Reasons for deferring pediatric studies:**

   A deferral is requested for pediatric patients < 7 years of age for the following reasons:

   - The completed safety and efficacy clinical trials (Studies OXY-MD-05, OXY-MD-06) and extension trial (Study OXY-MD-08) which include adults and a robust number of pediatric patients between the ages of 13-17 are provided in this NDA submission.
   - A proposal was made to the Division on August 29, 2001 to conduct a pharmacokinetic study in the pediatric population aged 7 to 12 years.
   - Before attempting studies in younger patients, it is desired to confirm the safety and efficacy findings in adults and adolescents and thus, deferral of studying patients < 7 is requested until additional overall experience with the drug has been gained.

5. Have pediatric drug development plans been submitted to the Agency?

Information was submitted to support the Pediatric Study Request and a detailed protocol summary of the proposed pharmacokinetic study was submitted to the Agency on August 29, 2001 (IND Serial No. 077).

The pharmacokinetics of oxycodone HCl/ibuprofen are linear. Based on the General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biologic Products (November 1998), Forest proposed to conduct a single center, single dose, open-label, pharmacokinetic trial in children 7 to 12 years old.

The objective of the proposed pharmacokinetic study will be to assess subject tolerability of oxycodone HCl/ibuprofen and to compare the pharmacokinetics of oxycodone and ibuprofen following a single dose regimen in children 7 to 12 years old and adult subjects.

6. Suggested deferred date for submission of studies

A final study report based on the results of the proposed pharmacokinetic study in the 7 to 12 year olds will be available approximately 9 months after completion of the study.

A further clinical study in children < 7 years of age will be considered after additional overall experience with the oxycodone HCl/ibuprofen 5/400 mg product has been gained in adults and adolescents and after completion of the comparative pharmacokinetic study in the 7 to 12 year old pediatric group.

4.5.4 Drug Product Manufacturing, Packaging and Analytical Testing Sites

4.5.4.4 Commercial Manufacturing Site

The drug product will be manufactured by:

FOREST PHARMACEUTICAL, INC.
Plant # 2
5000 Brotherton Road
Cincinnati, OH 45209

Forest Laboratories, Inc.
321 Prospect Street
Inwood, NY 11096

4.5.4.2 Commercial Packaging Site

The drug product will be packaged in bottles, unit dose and labeled at:

FOREST PHARMACEUTICAL, INC.
Plant # 2
5000 Brotherton Road
Cincinnati, OH 45209

4.5.4.3 Analytical Testing Sites

The drug product release testing will be conducted at:

FOREST PHARMACEUTICAL, INC.
Plant # 2
5000 Brotherton Road
Cincinnati, OH 45209

Forest Laboratories, Inc.
321 Prospect Street
Inwood, NY 11096

The commercial drug product stability testing will be conducted at:

FOREST PHARMACEUTICAL, INC.
Plant # 2
5000 Brotherton Road
Cincinnati, OH 45209

Forest Laboratories, Inc.
321 Prospect Street
Inwood, NY 11096

Clinical release and NDA stability testing was conducted at:

FOREST LABORATORIES, INC. (CLINICAL RELEASE TESTING)
320 Prospect Street
Inwood, NY 11096
Note: R & D laboratory has since relocated to:
49 Mall Drive
Commack, NY 11725

FOREST LABORATORIES, INC. (NDA STABILITY TESTING)
220 Sea Lane
Farmingdale, NY 11735