INTERNATIONAL REGULATORY BUSINESS CONSULTANTS, L.L.C.

*Ira R. Berry, President*

August 18, 2003

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
12420 Parklawn Drive (Room 1-23)
Rockville, MD 20857

**RE: SUITABILITY PETITION**

Dear Madam/Sir:

Enclosed are four copies of this Suitability Petition filed by the undersigned under 21 CFR 314.93.

It is requested that the Commissioner makes a determination that the drug product described hereinafter is suitable for consideration as an Abbreviated New Drug Application (ANDA) under 21 CFR 314.93(b).

Sincerely,
INTERNATIONAL REGULATORY BUSINESS CONSULTANTS, L.L.C.

Ira R. Berry

Enclosure: Four (4) copies
Certified Mail – Return Receipt Requested

2003P-0398

CP1

*Providing scientific and regulatory consultant services to the global pharmaceutical, nutritional and medical devices and diagnostics products industries*

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# Suitability Petition

Petition Filed By:

International Regulatory Business Consultants, L.L.C.
2115 Millburn Avenue, Suite 108
Maplewood, NJ 07040

Proposed Product:

Oral Capsule Dosage Form Containing
Hydrocodone Bitartrate 5 mg/ Butalbital 50 mg/ Caffeine 40 mg/ Acetaminophen 325mg

# Table of Contents

# Suitability Petition

International Regulatory Business Consultants, L.L.C. submits this Suitability Petition under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 355 (j)(2)(C), which authority has been delegated to the Commissioner of Food and Drugs (Commissioner) under CFR §5.10. Petitioner requests the Commissioner to make a determination that the drug products hereinafter described are suitable for consideration as an Abbreviated New Drug Application (ANDA) under CFR §314.93 (b).

## A. Action Requested

International Regulatory Business Consultants, LLC requests a determination that a drug product containing hydrocodone bitartrate 5 mg, butalbital 50 mg, caffeine 40 mg, and acetaminophen 325 mg in capsule form for oral administration is suitable for evaluation under an ANDA.

Fioricet® w/ Codeine (codeine phosphate 30 mg, butalbital 50 mg, caffeine 40 mg, and acetaminophen 325 mg) is listed in the Orange Book as the reference listed drug (See Attachment 1). The hydrocodone bitartrate 5 mg, butalbital 50 mg, caffeine 40 mg, and acetaminophen 325 mg product substitutes the use of hydrocodone bitartrate 5 mg for the 30 mg of codeine phosphate. The remaining actives and strengths are the same. We request the Commissioner to grant the hydrocodone bitartrate 5 mg, butalbital 50 mg, caffeine 40 mg, and acetaminophen 325 mg capsule suitable for submission as an ANDA.

We also request the Commissioner to grant a waiver from the requirements of the pediatric study for a change in actives from codeine phosphate to hydrocodone bitartrate on the basis that these active ingredients are currently approved by the Food and Drug Administration at the same strengths and all for the same disease conditions. We understand the Agency's desire to seek information regarding the use of this drug in various pediatric populations. However, in this case, the approved product labeling already includes uses and dosing instructions for the most significant patient population. We propose that the concept of a standardized dosage adjustment for safety and efficacy, which is the usual goal of pediatric studies, is not relevant to this drug. In accordance with 21 CFR 314.55(c) the Commissioner may grant full or partial waiver of the study requirements on his own initiative **or** at the request of the applicant.

## B. Statement of Grounds

## 1. Hydrocodone Bitartrate, USP Replaces Codeine Phosphate, USP

The Federal Food, Drug and Cosmetic Act allows an ANDA applicant to petition the FDA for permission to file an ANDA for a drug product in which one active ingredient is suitable for substitution of another active ingredient in a drug listed product with the same therapeutic effect. See 21 CFR 314.93 (b). The hydrocodone bitartrate for the indications of moderate to severe pain and codeine phosphate from the indicated RLD at 6 codeine to 1 hydrocodone ratio are of the same therapeutic class and both are expected to produce the same therapeutic effect. Therefore, the exchange on the 30 mg of codeine from the RLD is equivalent to 5 mg of hydrocodone (See Attachment 2). Further, hydrocodone bitartrate has been previously approved in listed drug products (See Attachment 3).

The legal basis under which this application proceeds is promulgated in the CFR Section noted above, which allows the Commissioner to accept a generic drug application for a drug which differs in dosage strength from the pioneer or reference drug product. The petitioner is not aware of any information that would be unfavorable to the granting of the requested action.

## 2. Identification of Reference Listed Drug (RLD)

Attached is the labeling for the RLD product to which we are comparing the proposed drug which substitutes hydrocodone bitartrate 5 mg for codeine phosphate 30 mg (See Attachments 1 and 4).

Application No.

020232

(Strength) Name of Drug:

(30 mg codeine phosphate, USP, 50 mg butalbital, USP, 40 mg caffeine, USP, 325 mg acetaminophen, USP) Fioricet® with Codeine

Company

Watson Pharmaceuticals, Inc.

Note that on March 2003, the applicant holder name changed from Novartis to Watson (See Attachment 5). When the Watson label is available, the appropriate changes if any will be made to the generic label.

## 3. Labeling Differences

Attached are copies of the proposed generic labeling in draft form (See Attachment 6) and copies of the reference drug labeling (See Attachment 4). Please note that the final design for the product container label and name have not been established and will be established once the manufactured for client is identified. Additionally, the label does not have the expiration and lot number printed directly on the label, it will be printed during packaging.

The following is a description of the differences between the proposed generic product and the RLD package inserts.

**PACKAGE INSERT**

1. Remove Novartis Logo
2. Replace "**Fioricet® w/Codeine** (*butalbital, acetaminophen, caffeine, and codeine phosphate)*" trade name to the generic name of "Hydrocodone Bitartrate, Butalbital, Caffeine, and Acetaminophen"
3. Replace "codeine phosphate" with "hydrocodone bitartrate"

## DESCRIPTION

A. Replace the trade name with the generic name indicated

B. Replace "codeine phosphate" with "hydrocodone bitartrate" and their descriptions

C. Replace the dosage for "30 mg" with "5 mg"

**FROM:**

**DESCRIPTION**
Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is supplied in capsule form for oral administration.

Each capsule contains:
codeine phosphate, USP.....30 mg
butalbital, USP.....50 mg
caffeine, USP.....40 mg
acetaminophen, USP.....325 mg

Codeine phosphate [morphine-3-methyl ether phosphate (1:1) (salt) hemihydrate, $C_{18}H_{24}NO_7P$, anhydrous mw 397.37], is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, $C_{11}H_{16}N_2O_3$, mw 224.260), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$, mw 194.19), is a central nervous system stimulant.

Acetaminophen (4'-hydroxyacetanilide, $C_8H_9NO_2$, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic.

*Active Ingredients:* codeine phosphate, USP, butalbital, USP, caffeine, USP, and acetaminophen, USP.

*Inactive Ingredients:* black iron oxide, colloidal silicon dioxide, D&C Red #7 (calcium lake), D&C Red #33, FD&C Blue #1, FD&C Blue #1 (aluminum lake), gelatin, magnesium stearate, pregelatinized starch, red iron oxide, sodium lauryl sulfate, and titanium dioxide.

*May also include:* benzyl alcohol, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

**TO THE FOLLOWING:**

**DESCRIPTION**
The hydrocodone bitartrate, butalbital, caffeine, and acetaminophen product is supplied in capsule form for oral administration.

Each capsule contains:
hydrocodone bitartrate, USP.....5 mg
butalbital, USP.....50 mg
caffeine, USP.....40 mg
acetaminophen, USP.....325 mg

Hydrocodone bitartrate ($C_{18}H_{21}NO_3C_4H_6O_6$, Morphinan-6-one, 4, 5α-epoxy-3-methoxy-17-methyl-, (5 ), [R-(R*,R*)] – 2,3-dihydroxybutanediote (1:1), hydrate (2.5)) is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, $C_{11}H_{16}N_2O_3$, mw 224.260), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$, mw 194.19), is a central nervous system stimulant.

Acetaminophen (4'-hydroxyacetanilide, $C_8H_9NO_2$, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic.

*Active Ingredients:* hydrocodone bitartrate, USP, butalbital, USP, caffeine, USP, and acetaminophen, USP.

*Inactive Ingredients:* FD&C Blue #1, gelatin, magnesium stearate, talc, and titanium dioxide.

## CLINICAL PHARMACOLOGY

A. Replace the trade name with the generic name indicated

B. Remove both sentences "Fioricet® consists..... 325 mg. The role...understood."

| FROM: | TO THE FOLLOWING: |
|---|---|
| | Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding. |
| **Pharmacokinetics**<br>The behavior of the individual components is described below. | **Pharmacokinetics**<br>The behavior of the individual components is described below. |
| *Codeine*<br>Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.<br><br>The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.<br><br>At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours. | *Hydrocodone Bitartrate*<br>Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites. |
| *See OVERDOSAGE* for toxicity information. | *See OVERDOSAGE* for toxicity information. |

**INDICATIONS**

A. Replace the trade name with the generic name indicated

B. Replace "codeine" with "hydrocodone"

**CONTRAINDICATIONS**

A. Replace the trade name with the generic name indicated

B. Replace "codeine" with "hydrocodone"

**WARNINGS**

A. Replace "codeine" with "hydrocodone"

B. Replace the trade name with the generic name indicated

**PRECAUTIONS**

A. Replace the trade name with the generic name indicated

B. Replace "codeine" with "hydrocodone"

C. Replace the trade name with "this product" in the ***Pregnancy Category C:*** Section

D. Replace the trade name with "this product" in the **Nursing Mothers** Section

E. Replace the first paragraph with "Safety and effectiveness in geriatric patients have not been established." in the **Geriatric Use** Section

**ADVERSE REACTIONS**

A. Replace the trade name with the generic name indicated

B. Replace "codeine" with "hydrocodone"

**DRUG ABUSE AND DEPENDENCE**

A. Replace the trade name with "This product"

B. Replace "codeine" with "hydrocodone"

**OVERDOSAGE**

A. Replace the trade name with "this product"

B. Replace "codeine" with "hydrocodone"

a. Toxic doses (for adults)

i. Replace "codeine: toxic dose 240 mg" with "hydrocodone: toxic dose 40 mg"

**DOSAGE AND ADMINISTRATION**

A. No Change

**HOW SUPPLIED**

A. Replace the trade name with the generic name indicated

B. Replace "codeine phosphate" with "hydrocodone bitartrate"

C. Removed "Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936" and Replace with "Manufactured for: XXXXXX" and "Manufactured by: XXXXX"

D. Add Novartis trademark statement

**FROM:**

**HOW SUPPLIED**
**Fioricet® with Codeine**
**(butalbital, acetaminophen, caffeine, and codeine phosphate)**

Dark blue, opaque cap with a grey, opaque body. Cap is imprinted twice in light-blue with "FIORICET" and "CODEINE". Body is imprinted twice with four-head profile "" in red.

Bottle of 100.....(NDC 0078-0243-05)

***Store and Dispense***
Below 30°C (86°F); tight container.

*Levophed is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07963

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T2002-70

89017701

**TO THE FOLLOWING:**

**HOW SUPPLIED**
**Hydrocodone Bitartrate, Butalbital, Caffeine, and Acetaminophen**
**Capsules**

Dark blue, opaque cap with a light blue, opaque body. Cap is imprinted with "XXXXX". Body is imprinted with "325".

Bottle of 100.....(NDC XXXX-XXXX-XX)

***Store and Dispense***
Below 30°C (86°F); tight container.

*Levophed is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

**Fiorinal is a registered Trademark of Novartis Pharmaceuticals.

Manufactured for:
XXXXXXXXX
XXXXXXXXXX

Manufactured by:
XXXXXXXXXX
XXXXXXXX

**Rx Only**

## C. Environmental Impact

International Regulatory Business Consultants, L.L.C., hereby requests a categorical exclusion from the requirement of preparing an environmental assessment. As provided in 21 CFR 25.31, neither an environmental assessment nor an environmental impact statement is required. To the best of the petitioner's knowledge, no extraordinary circumstances exist that may significantly affect the human environment as discussed under 21 CFR 25.21.

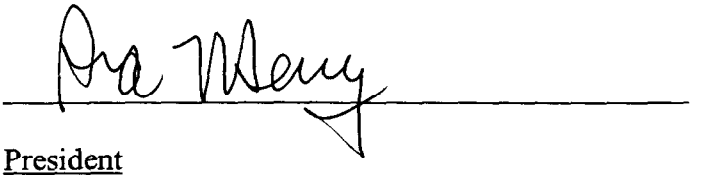
## D. Economic Impact

As provided in 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

## E. Certification

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

Typed Name: Mr. Ira R. Berry

Signature: 

Title: President

Name of Petitioner: International Regulatory Business Consultants, L.L.C.

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