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CITIZEN PETITION

PETITION TO REQUEST A CHANGE FROM A LISTED DRUG

Date: September 20, 2003

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

PETITION FILED BY:

**Anabolic Laboratories, Inc.
Irvine, CA 92614-6502**

PROPOSED PRODUCTS:

**Oral dosage forms containing
300 mg Acetaminophen/ 5 mg Hydrocodone
300 mg Acetaminophen/ 7.5 mg Hydrocodone
300 mg Acetaminophen/ 10 mg Hydrocodone**

2003P.0436

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Introduction

The undersigned submits this petition under provisions of Section 505(j)(2)(C) of the Food, Drug and Cosmetic Act ("FDCA") as implemented by 21 CFR §314.93 and according to Part §10.20 of the same title. The petitioner requests the Commissioner of Food and Drugs to make a determination that the drug products described hereinafter, with a slightly different strength than the listed drugs, are suitable for marketing under an Abbreviated New Drug Application ("ANDA") because:

- a) Investigations are not necessary to show the safety and effectiveness of the proposed drugs or any of the active ingredients or the strength; and
- b) There are no active ingredients which may not be adequately evaluated for approval as safe and effective on the basis of the information to be submitted in an abbreviated application.

Action Requested

The petitioner requests the Commissioner of Food and drugs to make a determination that a drug product containing a combination of 300 mg of Acetaminophen with 5 mg of Hydrocodone Bitartrate, or 300 mg of Acetaminophen with 7.5 mg of Hydrocodone Bitartrate, or 300 mg of Acetaminophen with 10 mg of Hydrocodone Bitartrate is suitable for evaluation under an ANDA.

Statement of Grounds

Pain of multiple etiologies remains a substantial problem for many patients. Multimodal analgesic combinations, such as Acetaminophen ("APAP") and Hydrocodone ("HCB"), can provide a method to improve pain treatment by offering improved pain relief and minimized adverse effects.

Several multimodal pain treatments combine a centrally acting opiate, such as Hydrocodone or Codeine, with a peripherally acting analgesic such as

Acetaminophen. In 2002, according to NDCHealth, APAP/HCB combinations were one of the top 200 drugs prescribed based on 3.05 billion prescriptions analyzed. Acetaminophen/Codeine was not in the top 200, which probably reflects the belief among physicians that HCB is more effective at lower doses with some reporting that 5 mg of HCB is equivalent to 30 mg of Codeine when given orally.¹

A review article² summarizes several studies of fixed dose analgesic combinations that suggest the combinations are more effective than either the individual active ingredients alone. Also, the review points out that both HCB and Codeine are morphine-like pro-drugs metabolized by the cytochrome P-450 isoenzyme 2D6.

Acetaminophen used alone does not produce the same pain relief as when used in combination with either HCB or Codeine. However, there is a safety issue, recognized by FDA, concerning Acetaminophen, which is the risk of dose-related hepatic toxicity. As a matter of fact, FDA has proposed that a warning to this effect be included on labeling of drug products containing Acetaminophen. As a consequence, physicians are increasingly requesting the dose of Acetaminophen be reduced in pain relief drug combinations in order to reduce the probability of patient's developing hepatic toxicity. This is more likely in cases where patients are automanipulate their prescribed pain medication containing Acetaminophen. Consequently, lowering the dosage of Acetaminophen in combinations also containing HCB would benefit the United States patient population.

Section 505(j)(2)(C) of the FDCA directs FDA to approve a petition requesting a change from a listed drug as suitable for evaluation under an ANDA unless FDA finds that investigations must be conducted to show the safety and effectiveness of the strength of the proposed drug product that differs from the strength of the listed drug product. The petitioner considers that new

¹ Narconon International; www.narconon.org

² Barkin, R.L., Acetaminophen, Aspirin, or Ibuprofen in Combination Analgesic Products, *Am. J. Therapeutics* 8, 433-442 (2001)

investigations should not be necessary to evaluate the safety and effectiveness of the proposed drug product because dosages of both the proposed Acetaminophen and HCB ingredients are currently approved as safe and effective in several listed prescription drug products.

The following are listed as reference drugs ("RLD") by FDA in *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"):

Table 1: Reference Listed Drugs

Application Number	Description	Strength	Company
040148	Acetaminophen/ HCB	325 mg/10 mg	Watson Pharma
	Acetaminophen/ HCB	325 mg/7.5 mg	
040099	Acetaminophen/ HCB	325 mg/5 mg	
85055	Acetaminophen/ Codeine Phosphate	300 mg/60 mg	Ortho McNeil Pharmaceuticals
	Acetaminophen/ Codeine Phosphate	300 mg/30 mg	
	Acetaminophen/ Codeine Phosphate	300 mg/15 mg	
	Acetaminophen/ Codeine Phosphate	300 mg/7.5 mg	

The most current labeling for the listed drugs containing Acetaminophen/Hydrocodone (325 mg/5 mg) was approved on July 13, 1999 while the labeling for the alternate strengths was approved May 11, 2000 ; those for the listed drugs containing Acetaminophen/Codeine were approved on May 7, 1991. Copies of labeling for these listed drugs are provided in an attachment to this petition. Also, a copy of a draft label for the proposed drugs is provided in an attachment to this petition.

Acetaminophen has been in clinical use in the United States since the 1950s, while the combinations listed above were approved by FDA after review of safety and effectiveness data in 1982 (Codeine) and 1997 (HCB). Accordingly, there does not appear to be safety issues with either proposed active ingredient at the strengths proposed. Also, since Acetaminophen has been approved by FDA as effective for pain relief at levels of 300 mg in combination with Codeine and since Hydrocodone is considered more effective than Codeine at the same strengths, the petitioner considers there can be no effectiveness issues. Moreover, a reduced strength of Acetaminophen in combination with HCB (the most widely prescribed pain relief treatment drug combination) will improve patient safety while maintaining the same effectiveness of the listed drug.

Environmental Impact

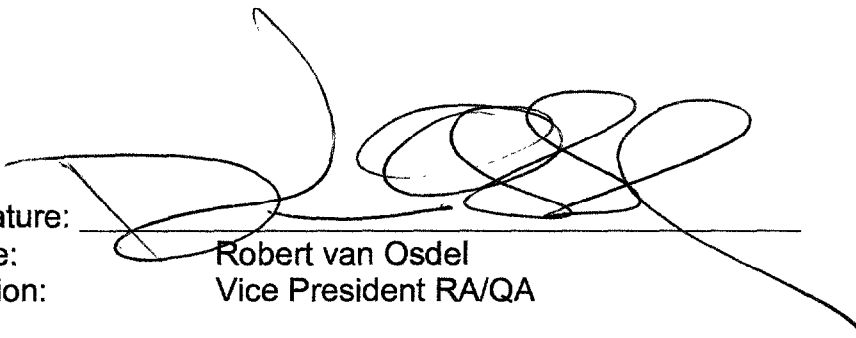
The petitioner requests a categorical exclusion from the requirement of preparing an environmental assessment. As provided in 21 CFR §25.31, neither an environmental assessment nor an environmental impact statement is required. To the best of the petitioner's knowledge, no extraordinary circumstances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

Economic Impact

As provided in 21 CFR §10.30(b), the petitioner agrees to submit economic impact information only if requested by the Commissioner of Food and Drugs following review of the petition.

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 the petitioner which are unfavorable to the petition.


Signature: _____
Name: Robert van Osdel
Position: Vice President RA/QA

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