

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 40-445

Name: Metaxalone Tablets, 800 mg

Sponsor: Sandoz, Inc.

Approval Date: March 31, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-445

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-445

APPROVAL LETTER



ANDA 040445

Sandoz Inc.
Attention: Marcy Macdonald
Director, Regulatory Affairs
4700 Sandoz Drive
Wilson, NC 27893

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Metaxalone Tablets, 800 mg, an amendment for which was received on November 4, 2004.¹

Reference is also made to your amendments dated November 8, 2001; June 19, June 21, July 16, October 24, November 15, and December 4, 2002; January 7, 2003; May 10, November 1, and December 15, 2004; September 6, 2006; February 2, 2007; January 26, August 29, 2008; and November 23, December 8, December 23, 2009; January 14, January 27 (2 submissions), and March 9, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Metaxalone Tablets, 800 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Skelaxin Tablets of King Pharmaceuticals, Inc. (King). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

¹ ANDA 040445 was submitted on August 31, 2001 for a 400 mg. strength which was later withdrawn.

The reference listed drug (RLD) upon which you have based your ANDA, King's Skelaxin Tablets, 800 mg, is subject to periods of patent protection. The following patents and their expiration dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
6,407,128 (the '128 patent)	December 3, 2021
6,683,102 (the '102 patent)	December 3, 2021
7,122,566 (the '566 patent)	February 6, 2026

With respect to all three patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Metaxalone Tablets, 800 mg, under this ANDA. You notified the agency that Sandoz complied with the requirements of section 505(j)(2)(B) of the Act, and litigation for infringement of the '128 and '102 patents was brought against Eon Labs (now Sandoz) within the statutory 45-day period in the United States District Court for the Eastern District of New York [King Pharmaceuticals, Inc. v. Eon Labs, Inc., Civil Action No. 04-5540]. You have also notified the agency that the court decided that the '128 and '102 patents are invalid; therefore, under section 505(j)(5)(B)(iii) your ANDA is eligible for approval.²

With respect to 180-day generic drug exclusivity for Metaxalone Tablets, 800 mg, the agency has concluded that Sandoz was the first ANDA applicant to submit a substantially complete ANDA for Metaxalone Tablets, 800 mg, with paragraph IV certifications to the '128 and '102 patents. The agency notes that Sandoz failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. We have determined, however, that this was caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application was filed. Namely, Sandoz submitted its amendment for the 800 mg strength on November 4, 2004, and during the entire time the ANDA was under review, the

² You also notified the agency that litigation for infringement of the '566 patent was brought against Sandoz in the United States District Court for the District of New Jersey [King Pharmaceuticals Inc., King Pharmaceuticals Research and Development Inc., Pharmaceutical IP Holding Inc. v. Sandoz Inc., Civil Action No. 08-CV-05974-GEB-JJH]. Although this litigation is ongoing, because the '566 patent was listed after submission of your ANDA, litigation with respect to it creates no statutory stay of approval of your ANDA.

agency had pending before it a citizen petition that created a review of the appropriate labeling for generic metaxalone in light of certain patent-protected language in the labeling of the RLD.

Therefore, with this approval, the agency has determined that Sandoz is eligible for 180 days of generic drug exclusivity for Metaxalone Tablets, 800 mg. Generic drug exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, begins to run from the date of commercial marketing identified in that section. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "**Miscellaneous Correspondence - SPL for Approved ANDA 040445**".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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

/s/

ROBERT L WEST
03/31/2010
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-445

LABELING


Colors:



Artwork for
Metaxalone Tablets, 800 mg x 100 Tablets

L8917
Issued 01/08
Label Size: 2" x 5-1/4"
Prepared by: (b) (6)
Date: 01/25/08



 SANDOZ	Regulatory Affairs	Wilson, NC
Approved by:	Signature:	Date:
(b) (6)		

Colors:



Artwork for Metaxalone Tablets, 800 mg x 1000 Tablets

L8931
Issued 01/08
Label Size: 3" x 6"
Prepared by: (b) (6)
Date: 01/25/08

Exp. Date: Lot No.: NO VARNISH	<p>USUAL DOSAGE: The recommended dose for adults and children over 12 years of age is one tablet (800 mg) three to four times a day. See accompanying literature for complete prescribing information.</p> <p>Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].</p> <p>This is a bulk package. Dispense contents in a tight container with a child-resistant closure, as required.</p> <p>Issued 01/08 L8931</p>	<p>NDC 0185-0448-10</p> <h2 style="margin: 0;">Metaxalone Tablets</h2> <h3 style="margin: 0; background-color: green; color: white; padding: 2px 5px;">800 mg</h3> <p>Rx only</p> <p>1000 Tablets</p> <p> SANDOZ</p>	<p>Each tablet contains: Metaxalone 800 mg</p> <p>KEEP TIGHTLY CLOSED.</p> <p>KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.</p> <p>Sandoz Inc. Princeton, NJ 08540</p>	FOR PLACEMENT ONLY BAR CODE
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SANDOZ		Regulatory Affairs	Wilson, NC
Approved by:	Signature:		Date:
(b) (6)			



Isa 10/09



04-48

SANDOZ

Metaxalone
Tablets

Rx only

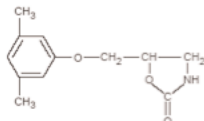
Metaxalone Tablets

Rx only

DESCRIPTION

Metaxalone tablets are available as an 800 mg tablet.

Chemically, metaxalone is 5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone. The empirical formula is $C_{12}H_{15}NO_3$, which corresponds to a molecular weight of 221.25. The structural formula is:



Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Each tablet contains 800 mg metaxalone and the following inactive ingredients: corn starch, alginic acid, acacia, sodium starch glycolate, magnesium stearate and FD&C red No. 40 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Pharmacokinetics

The pharmacokinetics of metaxalone have been evaluated in healthy adult volunteers after single dose administration of metaxalone tablets under fasted and fed conditions at doses ranging from 400 mg to 800 mg.

Absorption: Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions. Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of metaxalone tablets from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C_{max}) and area under the curve (AUC). Dose proportionality at doses above 800 mg has not been studied. The absolute bioavailability of metaxalone is not known.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers are shown in Table 1.

Table 1: Mean (%CV) Metaxalone Pharmacokinetic Parameters					
Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC ₀₋₁₂ (ng·h/mL)	$T_{1/2}$ (h)	CL/F (L/h)
400 ¹	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800 ²	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

¹Subjects received 1x400 mg tablet under fasted conditions (N=42)

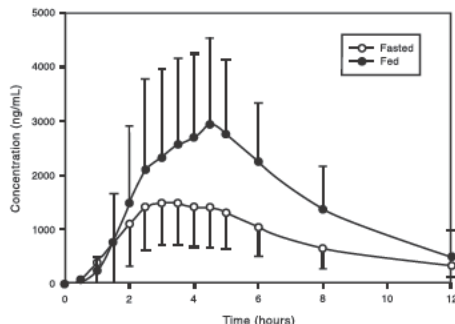
²Subjects received 2x400 mg tablets under fasted conditions (N=59)

Food Effects: A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg metaxalone tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age = 23.5 ± 5.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 177.5% and increased AUC (AUC₀₋₁₂, AUC₀₋₂₄) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.3 h versus 3.3 h) and terminal half-life was decreased (2.4 h versus 9.0 h) under fed conditions compared to fasted.

In a second food effect study of similar design, two 400 mg metaxalone tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22

females), ranging in age from 18 to 50 years (mean age = 25.6 ± 8.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 193.6% and increased AUC (AUC₀₋₁₂, AUC₀₋₂₄) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.9 h versus 3.0 h) and terminal half-life was decreased (4.2 h versus 8.0 h) under fed conditions compared to fasted conditions. Similar food effect results were observed in the above study when one metaxalone 800 mg tablet was administered in place of two metaxalone 400 mg tablets. The increase in metaxalone exposure coinciding with a reduction in half-life may be attributed to more complete absorption of metaxalone in the presence of a high fat meal (Figure 1).

Figure 1. Mean (SD) Concentrations of Metaxalone following an 800 mg Dose under Fasted and Fed Conditions



Distribution, Metabolism and Excretion: Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution ($V/F \sim 800$ L) and lipophilicity ($\log P = 2.42$) of metaxalone suggest that the drug is extensively distributed in the tissues. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. Hepatic Cytochrome P450 enzymes play a role in the metabolism of metaxalone. Specifically, CYP1A2, CYP2D6, CYP2E1, and CYP3A4 and, to a lesser extent, CYP2C8, CYP2C9, and CYP2C19 appear to metabolize metaxalone.

Metaxalone does not significantly inhibit major CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Metaxalone does not significantly induce major CYP enzymes such as CYP1A2, CYP2B6, and CYP3A4 in vitro.

Pharmacokinetics in Special Populations

Age: The effects of age on the pharmacokinetics of metaxalone were determined following single administration of two 400 mg tablets (800 mg) under fasted and fed conditions. The results were analyzed separately, as well as in combination with the results from three other studies. Using the combined data, the results indicate that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age.

The bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers of varying age is shown in Table 2.



USC 10/09



04-48

Metaxalone
Tablets

Rx only

Table 2: Mean (%CV) Pharmacokinetics Parameters Following Single Administration of Two 400 mg Metaxalone Tablets (800 mg) under Fasted and Fed Conditions

	Younger Volunteers		Older Volunteers			
Age (years)	25.6 ± 8.7		39.3 ± 10.8		71.5 ± 5.0	
N	59		21		23	
Food	Fasted	Fed	Fasted	Fed	Fasted	Fed
C _{max} (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)	3168 (43)	3680 (59)
T _{max} (h)	3.0 (39)	4.9 (48)	3.0 (40)	8.7 (91)	2.6 (30)	6.5 (67)
AUC _{0-t} (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	20482 (37)	23797 (45)	24340 (48)
AUC _∞ (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	20815 (37)	24194 (44)	24704 (47)

Gender: The effect of gender on the pharmacokinetics of metaxalone was assessed in an open label study, in which 48 healthy adult volunteers (24 males, 24 females) were administered two metaxalone 400 mg tablets (800 mg) under fasted conditions. The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL versus 1335 ng/mL) and AUC_∞ (17884 ng·h/mL versus 10328 ng·h/mL). The mean half-life was 11.1 hours in females and 7.6 hours in males. The apparent volume of distribution of metaxalone was approximately 22% higher in males than in females, but not significantly different when adjusted for body weight. Similar findings were also seen when the previously described combined dataset was used in the analysis.

Hepatic/Renal Insufficiency: The impact of hepatic and renal disease on the pharmacokinetics of metaxalone has not been determined. In the absence of such information, metaxalone tablets should be used with caution in patients with hepatic and/or renal impairment.

INDICATIONS AND USAGE

Metaxalone tablets are indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Known hypersensitivity to any components of this product.

Known tendency to drug induced, hemolytic or other anemias.

Significantly impaired renal or hepatic function.

WARNINGS

Metaxalone tablets may enhance the effects of alcohol and other CNS depressants.

PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Taking metaxalone tablets with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Information for Patients).

Information for Patients

Metaxalone tablets may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

Drug Interactions: The sedative effects of metaxalone tablets and other CNS

depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. Therefore, caution should be exercised with patients who take more than one of these CNS depressants simultaneously.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of metaxalone has not been determined.

Pregnancy: Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers: It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children 12 years of age and below have not been established.

ADVERSE REACTIONS

The most frequent reactions to metaxalone include:

CNS: drowsiness, dizziness, headache and nervousness or "irritability";

Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions are:

Immune System: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia, hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants and have been reported with this class of drug in combination with alcohol.

When determining the LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

Treatment

Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day.

HOW SUPPLIED

Metaxalone Tablets are supplied as follows:

800 mg: rose-colored, capsule-shaped tablets, debossed "E 448" on one side and scored on the other side and supplied as:

NDC 0185-0448-01 bottles of 100

NDC 0185-0448-10 bottles of 1000

Dispense contents in a tight, light-resistant container as defined in the USP with a child-resistant closure, as required.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Sandoz Inc.
Princeton, NJ 08540

OS7750

MF0448ISS10/09

Issued 10/09

MG #17653

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-445

LABELING REVIEWS

This labeling approval summary supersedes the labeling approval summary dated 1/7/2003.

APPROVAL SUMMARY #2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-445

Dates of Submission: January 26, 2008 and November 1, 2004

Applicant's Name: Sandoz Inc. (formerly Eon Labs, Inc.)

Established Name: Metaxalone Tablets, 800 mg

APPROVAL SUMMARY

CONTAINER LABELS – Bottles of 100's and 1000's:

Satisfactory in FPL as of the January 26, 2008 e-submission.

PROFESSIONAL PACKAGE INSERT:

Satisfactory in FPL as of the January 26, 2008 e-submission.

Revisions needed post-approval:

In the DESCRIPTION section, revise the first sentence to read, "Metaxolone is available as an 800 mg tablet for oral administration."

Patent Data – NDA 13-217

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6407128	December 3, 2021	U-189	Enhancement of the bioavailability of the drug substance.	IV	None

Exclusivity Data– NDA 13-217

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: Skelaxin®

NDA Number: 13-217

NDA Drug Name: Skelaxin® (metaxalone) Tablets

NDA Firm: King Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement: November 24, 2006; NDA 13-217/S-046

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

FOR THE RECORD:

The following comments are from the previous reviewer:

FOR THE RECORD:

1. This review was based on the labeling for Skelaxin® Tablets: Approved on November 24, 2006; NDA 13-217/S-046.

2. Patent Data – NDA 13-217

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6407128	December 3, 2021	U-189	Enhancement of the bioavailability of the drug substance.	IV	None

Exclusivity Data– NDA 13-217

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature between 15 to 30°C (59 to 86°F)

ANDA: Store at (b) (4)

NDA: Dispense in a well-closed container.

ANDA: This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP. With a child-resistant closure, (as required).

Note that requested revisions to the storage/temp conditions were made to be in accord with comments from Dr. Rich Adams.

4. Product Line:

The innovator markets their product in two strengths (400 mg and 800 mg). They are packaged in bottles of 100 and 500 tablets.

The applicant proposes to market their product (b) (4) tablets.

5. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See **pgs 0556 in volume B. 1.3**)

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page 0054, Vol B. 1.1.**

7. Container/Closure (See page 0380 in Vol. B. 1.3)

Containers: HDPE

Closure: CRC closures for 100 count bottles and non-CRC for the (b) (4) 1000 count bottles.

8. All manufacturing will be done by Eon Laboratories, Inc. (page 0205 in vol. B. 1.2)

9. The drug product submitted for this ANDA is scored as is the RLD's drug product.

10. APPLICANT ADDRESS AND CONTACT INFORMATION

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893
Dietrich Bartel

(252)234-2212

11. BIOEQUIVALENCE

The following information was extracted from the 11/9/2007 bioequivalence review:

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute for Eon Labs Inc. on its metaxalone 800 mg tablet have been found acceptable to the Division of Bioequivalence.
2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.5% SLS in water at temp, 37°C + 0.5°C using the USP apparatus II (paddle) at 100 rpm. The test product should meet the following specification: NLT (b)(4) % (Q) of metaxalone in the dosage form is dissolved in 60 minutes.
3. Division of Bioequivalence deems the test product Metaxalone Tablet 800 mg, manufactured by Eon/Sandoz to be bioequivalent to the reference product, Skelaxin®, 800 mg Tablet manufactured by Jones Pharma Inc/ King Pharms.

12. The firm has withdrawn the 400 mg tablet.

Date of Review: September 30, 2008

Dates of Submission: January 26, 2008 and November 1, 2004

Primary Reviewer: Postelle Birch-Smith, Pharm.D.

Team Leader: John Grace

CC:

ANDA: 40-445
Review

Following this page, 4 pages withheld in full - (b)(4), draft labeling

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

/s/

Postelle Birch-Smith
9/30/2008 02:57:36 PM
LABELING REVIEWER

John Grace
10/1/2008 11:23:34 AM
LABELING REVIEWER

This approval summary supersedes the labeling approval summary dated 1/26/08 and 11/1/04.

APPROVAL SUMMARY #3
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 040445

Dates of Submission: November 23, 2009

Applicant's Name: Sandoz Inc. (formerly Eon Labs, Inc.)

Established Name: Metaxalone Tablets, 800 mg

APPROVAL SUMMARY

CONTAINER LABELS – Bottles of 100's and 1000's:

Satisfactory in FPL as of the January 26, 2008 e-submission.

PROFESSIONAL PACKAGE INSERT:

Satisfactory in FPL as of the November 23, 2009 e-submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No.

What is the RLD on the 356(h) form: Skelaxin®

NDA Number: 013217

NDA Drug Name: Skelaxin® (metaxalone) Tablets

NDA Firm: King Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement: October 31, 2008; NDA 013217/S-053

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? No.

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels.

FOR THE RECORD:

The following comments are from the previous reviewer:

FOR THE RECORD:

1. This review was based on the labeling for Skelaxin® Tablets: Approved on October 31, 2008; NDA 013217/S-053.

2. Patent Data – NDA 013217

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6407128	December 3, 2021	U-189	Enhancement of the bioavailability of the drug substance.	IV	None

Exclusivity Data– NDA 013217

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

UPDATE (12/8/09):**Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
013217	003	6407128	Dec 3, 2021			U-189	
013217	003	6683102	Dec 3, 2021			U-189	
013217	003	7122566	Feb 6, 2026			U-915	

Exclusivity Data

There is no unexpired exclusivity for this product.

The Sandoz pending ANDA includes Paragraph IV certifications to all three patents currently listed in the Orange Book in connection with Skelaxin®, namely, U.S. Patent Nos. 6,407,128 (the '128 patent), 6,683,102 (the '102 patent), and 7,122,566 (the '566 patent). Sandoz's ANDA does not include any "(viii) statements" that seek to omit patent-protected labeling information in the labeling of the RLD.

Final approval of the Sandoz ANDA is not delayed by any non-patent exclusivity periods or by the 180-day exclusivity rights of a generic competitor. Final ANDA approval is also not delayed by any litigation stays resulting from lawsuits pursuant to receipt of notices of Sandoz Paragraph IV certifications. With regard to the '128 and '102 patents, the 30-month litigation delays of final ANDA have long expired. As stated and documented in the Sandoz Patent Amendment dated June 26, 2009, the last notice of Paragraph IV certification was received on November 9, 2004. Moreover, as also stated and documented in that Patent Amendment, the federal district court held, on January 20, 2009, that all claims of both patents are invalid.

The '566 patent did not issue until October 17, 2006, long after the Sandoz ANDA was submitted to FDA and accepted for substantive review.¹ Thus, no litigation stay is available with regard to the '566 patent. See 21 U.S.C. § 355(j)(5)(B)(iii) (as amended by MMA § 1101(a)(2)(A)(ii)(I), applicable to patent information submitted to FDA for Orange Book listing on or after August 18, 2003, see MMA § 1101(c)(3)).

3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature between 15 to 30°C (59 to 86°F)

ANDA: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

NDA: Dispense in a well-closed container.

ANDA: Dispense in tight, light-resistant containers as defined in the USP with a child-resistant closure, as required.

Note that requested revisions to the storage/temp conditions were made to be in accord with comments from Dr. Rich Adams.

4. Product Line:

The innovator markets their product in two strengths (400 mg and 800 mg). They are packaged in bottles of 100 and 500 tablets.

The applicant proposes to market their product (b) (4) tablets.

Update (11/23/09): The innovator markets their product in 800 mg packages in bottles of 100 and 500 tablets.

The applicant proposes to market their product as 800 mg packages in bottles of 100 and 1000 tablets.

5. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See **pgs 0556 in volume B. 1.3**)

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page 0054, Vol B. 1.1.**

7. Container/Closure (See page 0380 in Vol. B. 1.3)

Containers: HDPE

Closure: CRC closures for 100 count bottles and non-CRC for the 1000 count bottles.

8. All manufacturing will be done by Eon Laboratories, Inc. (page 0205 in vol. B. 1.2)

9. The drug product submitted for this ANDA is scored as is the RLD's drug product.

10. APPLICANT ADDRESS AND CONTACT INFORMATION

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893
Dietrich Bartel
(252)234-2212

11. BIOEQUIVALENCE

The following information was extracted from the 11/9/2007 bioequivalence review:

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute for Eon Labs Inc. on its metaxalone 800 mg tablet have been found acceptable to the Division of Bioequivalence.
2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.5% SLS in water at temp, 37°C + 0.5°C using the USP apparatus II (paddle) at 100 rpm. The test product should meet the following specification: NLT (b)(4) % (Q) of metaxalone in the dosage form is dissolved in 60 minutes.
3. Division of Bioequivalence deems the test product Metaxalone Tablet 800 mg, manufactured by Eon/Sandoz to be bioequivalent to the reference product, Skelaxin®, 800 mg Tablet manufactured by Jones Pharma Inc/ King Pharms.

12. The firm has withdrawn the 400 mg tablet.

Date of Review: December 8, 2009

Dates of Submission: November 23, 2009

Primary Reviewer: Burhan Nour

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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

/s/

BURHAN A NOUR
12/08/2009

JOHN F GRACE
12/08/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-445

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 3 (three)
2. ANDA # 40-445
3. NAME AND ADDRESS OF APPLICANT
Sandoz, Inc.
227-15 North Conduit Avenue
Laurelton, NY 11413
Tel: 718-276-8600
4. LEGAL BASIS FOR SUBMISSION
RLD: Skelaxin® tablets (Metaxalone Tablets) 800 mg, NDA 13-217 manufactured by Jones Pharma, Inc.
Patent IV certification
Eon Labs acknowledges that US patent # 6407128 and US patent # 6683102 associated with NDA 13-217 for Skelaxin® tablets, 800 mg. The patent will expire on December 3, 2021.
Eon Labs certify under Section 505 (j) (2) (A) (vii) (IV) of the federal food, drug and cosmetic act that US patent # 6407128 and US patent # 6683102 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Metaxalone Tablets 800 mg, for which this application is submitted.
Exclusivity
There is no exclusivity associated with NDA 13-217 Skelaxin® tablets, 400 mg and 800 mg.
5. SUPPLEMENT(s)
None
6. PROPRIETARY NAME
None
7. NONPROPRIETARY NAME
Metaxalone Tablets, 400 mg and 800 mg
8. SUPPLEMENT(s) PROVIDE(s) FOR:
None
9. AMENDMENTS AND OTHER DATES:
Date of submission: August 31, 2001
Acceptable for filing: November 7, 2001
Bio amendment: June 19, 2002
Minor amendment: June 21, 2002
Telephone amendment: October 24, 2002
Telephone amendment: November 15, 2002
Telephone amendment: December 4, 2002

Major amendment: November 1, 2004
(new strength was submitted for 800 mg tablets)
Acceptable for filing (800 mg strength): 12/28/04
Correspondence (change of ownership): 7/21/05
10. PHARMACOLOGICAL CATEGORY
As an adjunct to rest, physical therapy, and other measures to the relief of discomforts associated with acute, painful musculoskeletal conditions.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
RLD: Skelaxin® tablets (Metaxalone Tablets) 400 mg, and 800 mg NDA 13-217 manufactured by Carnrick Laboratories, Division of Elan Pharmaceuticals.

DMF

(b) (4)

Manufacturer:

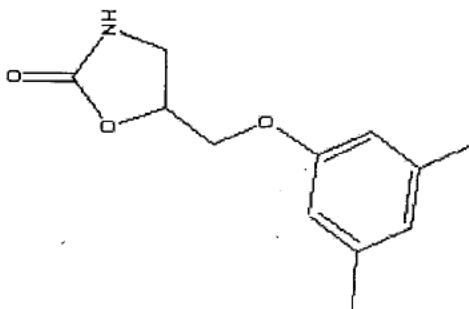
(b) (4)

(b) (4)

13. DOSAGE FORM
Tablet
14. POTENCY
400 mg and 800 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name: 5-[(3,4-dimethylphenoxy) methyl]-2-oxazolidinone



16. RECORDS AND REPORTS

None

17. COMMENTS

This application is not approvable.

(b) (4)

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

19. REVIEWER:

Liang-Lii Huang, Ph.D.
Endorsed by James Fan

DATE COMPLETED:





Nov 15, 2005
Nov 15, 2005

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-445APPLICANT: Sandoz, Inc.DRUG PRODUCT: Metaxaone Tablets, 400 mg and 800 mg

The deficiencies below represent MINOR deficiencies.

A. Deficiencies:

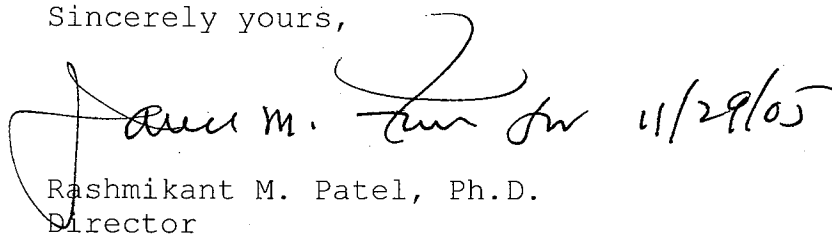
1. Please establish both the (b) (4)

Please provide an updated
(b) (4)
2.  (b) (4)
Please reconcile these differences.
3. Please revise the (b) (4)

for the drug product.
4.  (b) (4)
data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.
2. Your Labeling information is pending review. Deficiencies, if any, will be communicated to you separately.

3. Bioequivalence deficiencies were communicated to you via facsimile on May 9, 2005. You should address the issues in the May 9 communication prior to or concurrent with your response to this communication.

Sincerely yours,

 11/29/05

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 40-445

ANDA DUP 40-445

DIV FILE

Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/Liang-Lii Huang, Ph.D./11/15/05;11/17/05 *L Huang 11/29/05*HFD-627/James Fan, Team Leader /11/15/05;11/17/05 *James 11/29/05*

HFD-617/ Ann Vu, Project Manager /11/17/05; 11/18/05

V:\FIRMSNZ\SANDOZ\LTRS&REV\40445 rev3.doc

November 17, 2005 *W 11/30/05*

CHEMISTRY REVIEW - not APPROVABLE

1. CHEMISTRY REVIEW NO. 4 (four)
2. ANDA # 40-445
3. NAME AND ADDRESS OF APPLICANT
Sandoz, Inc.
4700 Sandoz Drive
Wilson, NC 27893
Tel: 303-438-4599
4. LEGAL BASIS FOR SUBMISSION
RLD: Skelaxin® tablets (Metaxalone Tablets) 800 mg, NDA 13-217 manufactured by Jones Pharma, Inc.
Patent IV certification
Eon Labs acknowledges that US patent # 6407128 and US patent # 6683102 associated with NDA 13-217 for Skelaxin® tablets, 800 mg. The patent will expire on December 3, 2021.
Eon Labs certify under Section 505 (j)(2)(A)(vii)(IV) of the federal food, drug and cosmetic act that US patent # 6407128 and US patent # 6683102 are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Metaxalone Tablets 800 mg, for which this application is submitted.
Exclusivity
There is no exclusivity associated with NDA 13-217 Skelaxin® tablets, 400 mg and 800 mg.
5. SUPPLEMENT(s)
None
6. PROPRIETARY NAME
None
7. NONPROPRIETARY NAME
Metaxalone Tablets, 800 mg
8. SUPPLEMENT(s) PROVIDE(s) FOR:
None
9. AMENDMENTS AND OTHER DATES:
Date of submission: August 31, 2001
Acceptable for filing: November 7, 2001
Bio amendment: June 19, 2002
Minor amendment: June 21, 2002
Telephone amendment: October 24, 2002
Telephone amendment: November 15, 2002
Telephone amendment: December 4, 2002
Major amendment: May 10, 2004
(New strength was submitted for 800 mg tablets)
Acceptable for filing (800 mg strength): 12/28/04
Correspondence (change of ownership): 7/21/05
Amendment: February 02, 2007
Sandoz submitted a withdrawal letter to the Agency on September 6, 2006, withdrawing the 400 mg

strength of the drug product. Their responses to the OGD's deficiency comments therefore only address the 800 mg strength.

Telephone amendment: August 29, 2008

Compliance with USP <467> requirements for residual solvents

Telephone amendment: 12/23/09

Telephone amendment: 1/14/10

Telephone amendment: 1/27/10

Site withdrawal telephone amendment: 1/27/10

Telephone amendment: March 9, 2010

10. PHARMACOLOGICAL CATEGORY

As an adjunct to rest, physical therapy, and other measures to the relief of discomforts associated with acute, painful musculoskeletal conditions.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

RLD: Skelaxin® tablets (Metaxalone Tablets) 800 mg NDA 13-217 manufactured by Carrick Laboratories, Division of Elan Pharmaceuticals.

DMF (b) (4)

Manufacturer: (b) (4)

(b) (4)

13. DOSAGE FORM

Tablet

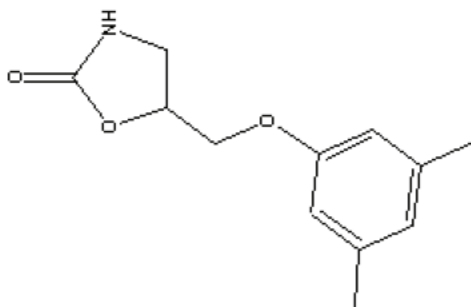
14. POTENCY

800 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name: 5-[(3,4-dimethylphenoxy) methyl]-2 oxazolidinone

MW 221.25 muscle relaxant



16. RECORDS AND REPORTS

None

17. COMMENTS

This application is approvable.

The drug substance and drug product meet the ICH limits.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

19. REVIEWER:

Liang-Lii Huang, Ph.D.

Endorsed by James Fan

DATE COMPLETED:

January 27, 2010

January 27, 2010

Following this page, 25 pages withheld in full - (b)(4)

cc:

ANDA 40-445
ANDA DUP 40-445
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/Liang-Lii Huang, Ph.D./12/8/09; 1/27/10

HFD-627/James Fan, Team Leader /12/8/09; 1/27/10

HFD-617/T. Tran, Project Manager /12/8/09; 1/27/10

V:\Chemistry Division I\Team 3\FIRMSNZ\SANDOZ\LTRS&RVS\40445 rev4.doc

January 27, 2010

CHEMISTRY REVIEW – APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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/s/

LIANG LII HUANG
03/12/2010

TRANG Q TRAN
03/15/2010

JAMES M FAN
03/18/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-445

BIOEQUIVALENCE REVIEWS

MAY 4 2005

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-445
Drug Product Name	Metaxalone tablet
Strength	400 and 800 mg
Applicant Name	Eon Labs, Inc.
Address	Laurelton, New York
Submission Date(s)	1 November 2004
Amendment Date(s)	None
Reviewer	J. Lee
First Generic	N
File Location	V:\firmsam\Eon\ltrs&rev\40445N1104.doc

I. Executive Summary

This submission pertains to metaxalone 800 mg and 400 mg tablets. The sponsor has previously (b) (4)

and introduced an 800 mg tablet. At the time of the original submission, the 800 mg Skelaxin® had not yet been approved.

The present submission includes one fasting and one fed BE study on the 800 mg tablet. The fasting study is a single-dose, two-way crossover study using 60 healthy normal male and female volunteers given a dose of 800 mg. The results (point estimate, 90% CI) of the fasting BE study are LAUCt of 97.2, 91.2-103%; LAUCi of 96.9, 91.0-103%; and LCmax of 92.9, 84.1-103%.

The fed BE study is a single-dose two-way crossover study using 60 healthy normal male and female volunteers given a dose of 800 mg. The results (point estimate, 90% CI) of the fed BE study are LAUCt of 103, 96.5-109; LAUCi of 99.6, 94.2-105 and LCmax of 92.6, 81.4-105.

Dissolution testing data was submitted using the DBE interim method. The dissolution specification was met, however, the (b) (4) (b) (4) The sponsor should provide an explanation for this.

From the bioequivalence view point, this application is incomplete.

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III. Submission Summary

A. Drug Product Information

Test Product	Metaxalone tablet
Reference Product	Skelaxin [®] tablet
RLD Manufacturer	Jones Pharma Inc. (subsidiary of King Pharmaceuticals)
NDA No.	13-217
RLD Approval Date	13 Aug 1962 (400 mg); 30 Aug 2002 (800 mg)
Indication	Relief of discomforts associated with acute, painful musculoskeletal conditions

B. PK/PD Information

Bioavailability	Not known, per PDR
Food Effect	There is a significant increase in C _{max} ; also an increase in AUC
T_{max}	3.3 hrs (fasted); 4.3 hrs (fed)
Metabolism	Hepatic
Excretion	Renal
Half-life	9.2 hrs ± 4.8 hrs (fasted); 2.4 hrs ± 1.2 hrs (fed)
Relevant OGD or DBE History	The two bio-studies contained in this submission represent the <u>second</u> set of bio-studies for this application. Previously, the sponsor had (b) (4)

This submission contains those new bio-studies. Since, at the time of the original submission, an 800 mg metaxalone tablet had not yet been approved, the original bio-studies were conducted on the 400 mg tablet. Presently, however, the 800 mg Skelaxin® is the designated RLD and the new bio-studies have been conducted using the 800 mg strength tablets.

Agency Guidance	None
Drug Specific Issues (if any)	Fasted and fed bio-studies are currently recommended for this drug product.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	y	1
Single-dose fed	y	1
In vitro dissolution	y	2
Waiver requests	y	1

D. Pre-Study Bioanalytical Method Validation

	Metaxalone
Analyte name	Metaxalone
Internal Standard	(b) (4)
Method description	RP-HPLC/UV; organic extraction
QC range	30 to 6000 ng/ml
Standard curve range	10 to 7500 ng/ml
Limit of quantitation	10 ng/ml
Average recovery of Drug (%)	105.7
Average Recovery of Int. Std (%)	101.8
QC Intraday precision range (%)	0.75 to 3.85%
QC Intraday accuracy range (%)	85.0 to 99.9%
QC Interday precision range (%)	2.04 to 5.89%
QC Interday accuracy range (%)	100 to 104%
Bench-top stability (hrs)	5 hr 52 min
Stock stability (days)	12
Processed stability (hrs)	50
Freeze-thaw stability (cycles)	4
Long-term storage stability (days)	133
Dilution integrity	Y
Specificity	Y
SOPs submitted	Y
Bioanalytical method is acceptable	Y

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R04-0159
Study Design	2 treatment, 2 period, 2 sequence
No. of subjects enrolled	60
No. of subjects completing	60
No. of subjects analyzed	60
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 37 Female: 23
Test product	Metaxalone tablet
Reference product	Skelaxin® tablet
Strength tested	800 mg
Dose	1 x 800 mg

Summary of Statistical Analysis		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	97.2	91.2; 103
AUC _∞	96.9	91.0; 103
C _{max}	92.9	84.1; 103

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6									
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis				
	Actual number		% of total assays		Actual number		% of total assays		
	T	R	T	R	T	R	T	R	
pharmacokinetic fit	3	3	0.13	0.13	3	3	0.13	0.13	
no IS response	21	1	0.88	0.04	-	-	-	-	
poor chromatography	-	3	-	0.13	-	-	-	-	
instrument malfunction	5	1	0.21	0.04	-	-	-	-	
processing error	-	2	-	0.08	-	-	-	-	
Total	29	10	1.2	0.42	3	3	0.13	0.13	

Did use of recalculated plasma concentration data change study outcome? No
The 90% confidence intervals were still acceptable when original values for the PK repeats were used.

2. Single-dose Fed Bioequivalence Study

Study No.	R04-0160
Study Design	Two treatment, two period, two sequence
No. of subjects enrolled	60
No. of subjects completing	58
No. of subjects analyzed	58
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 37 Female 23
Test product	Metaxalone tablet
Reference product	Skelaxin® tablet
Strength tested	800 mg
Dose	1 x 800 mg

Summary of Statistical Analysis		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	103	96.5; 109
AUC _∞	99.6	94.2; 105
C _{max}	92.6	81.4; 105

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 17								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
pharmacokinetic fit	4	-	0.17	-	4	-	0.17	-
no IS response	1	3	0.04	0.13	-	-	-	-
poor chromatography	1	1	0.04	0.04	-	-	-	-
instrument malfunction	-	3	-	0.13	-	-	-	-
Total	6	7	0.26	0.30	4	-	0.17	-

Did use of recalculated plasma concentration data change study outcome? No.
The 90% confidence intervals were the same when original values for the PK repeats were used.

F. Formulation

The test product formulation is detailed in Table 1 of the Appendix.

G. In Vitro Dissolution (DBE interim)

USP apparatus II (paddle) @ 100 rpm
900 ml of 0.5% SLS in water
NLT (b) (4) dissolved in 60 minutes

H. Waiver Request(s)

Strengths for which waivers requested	400 mg
Regulation cited	21 CFR 320.22 (d)(2)
Proportional to strength tested in vivo (yes or no)	(b) (4)
Dissolution is acceptable (yes or no)	(b) (4)
Waiver granted (yes or no)	N

I. Deficiency Comments

1.



(b) (4)

J. Recommendations

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute for Eon Labs Inc. on its metaxalone 800 mg tablet have been found acceptable to the Division of Bioequivalence.
2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.5% SLS in water at 37°C using

USP XXVII apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

Not less than (b) (4) % of the labeled amount of the drug in the tablet is dissolved in 60 minutes

3. The waiver request for the 400 mg tablet will not be granted at this time due to comment #1.

The sponsor should address comment #1.

R. Lee 5-3-05
J. Lee, Branch II

GJP Singh 5-3-05
GJP Singh, Ph.D., Team Leader, Branch II

Dale P. Conner 5/4/05
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	R04-0159
Study Title	A relative bioavailability study of 800 mg metaxalone tablets under fasting conditions
Clinical Site	PRACS Institute, Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	per I - 28 Mar 04; per II - 4 Apr 04
Analytical Site	PRACS Institute
Analytical Director	(b) (6)
Analysis Dates	19 Apr 04 - 6 May 04
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	39 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metaxalone	Skelaxin®
Manufacturer	Eon Labs, Inc.	Jones Pharma Inc.
Batch/Lot No.	RDW00470	ES803121A
Manufacture Date	Feb, 2004	N/A
Expiration Date	N/A	Apr, 2005
Strength	800 mg	800 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4) dosage units	N/A
Production Batch Size	(b) (4) dosage units	N/A
Potency	99.5%	99.1%
Content Uniformity (mean, %CV)	99.6% (0.5%)	99.3% (1.1%)
Dose Administered	1 x 800 mg	1 x 800 mg
Route of Administration	Oral	Oral

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB - subj #1, 3, 5-8, 14, 15, 17, 20, 24, 25, 27, 30, 31, 33-36, 38, 41, 43, 45, 46, 50, 51, 53, 57, 58, 60 BA - subj #2, 4, 9-13, 16, 18, 19, 21-23, 26, 28, 29, 32, 37, 39, 40, 42, 44, 47-49, 52, 54-56, 59
Blood Sampling Times	0 (pre-dose) 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 30 and 36 hrs
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	Cool centrifuged; plasma stored at $\leq -20^{\circ}\text{C}$
IRB Approval	Y
Informed Consent	Y
Subjects Demographics	See Table 1
Length of Fasting	10 hrs prior to dosing
Length of Confinement	Through the 24 hr blood draw
Safety Monitoring	Vital signs measured pre-dose and at 12 and 24 hrs post-dose

Comments on Study Design: none

b) Clinical Results

Table 1 Demographics of Study Subjects

Age (yrs)		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	93.3
Mean	22.4	Mean	165	18-40	98.3	Male	62	Afr. Amer.	
SD	5.5	SD	828	41-64	1.7	Female	38	Hispanic	1.7
Range	18-42	Range	117-217	65-75				Asian	5
				>75				Others	

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
none			

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
headache, fatigue	3	2
stomachache	0	1
sore throat	0	1
Total:	2	4

Table 4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
taking of ibuprofen for cramps	1	

Comments on Dropouts/Adverse Events/Protocol Deviations: All adverse events were mild in nature. The protocol deviation would not compromise outcome or validity of study in the opinion of the clinical investigators.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

QC Conc. (ng/ml)	30.0 - 6000
Inter day Precision (%CV)	3.4 - 6.6%
Inter day Accuracy (%)	101 - 102%
Cal. Standards Conc. (ng/ml)	10.0 - 7500 (7 pts)
Inter day Precision (%CV)	0.64 - 5.6%
Inter day Accuracy (%)	99.5 - 101%
Linearity Range (r^2)	≥ 0.9992

Comments on Study Assay Quality Control: none

Any interfering peaks in chromatograms?	N
Were 20% of chromatograms included?	Y
Were chromatograms serially or randomly selected?	serial

Comments on Chromatograms: none

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
090-01	13 Jun 02	Sample Re-analysis

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Y
Did recalculation of plasma concentrations change the study outcome?	N
Does the reviewer agree with the outcome of the repeat assays?	Y
If no, reason for disagreement	

Summary/Conclusions, Study Assays: acceptable

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC _{0-t}	(ng*hr)/ml	13277	53	13445	46	1.00
AUC _∞	(ng*hr)/ml	14396	55	14551	46	0.99
C _{max}	ng/ml	1450	55	1562	51	0.93
T _{max}	hr	4.64	35	4.04	54	1.15
T _{1/2}	hr	8.21	44	8.78	49	0.94
K _{el}	1/hr	0.10	39	0.10	47	1.00

Table 9 Geometric Means and 90% Confidence Intervals

Parameter	Test		Reference		T/R	90% CI
	Mean	%CV	Mean	% CV		
AUC _{0-t}	11821	5.1	12167	4.9	0.97	91.2; 103
AUC _∞	12740	5.1	13147	4.9	0.97	91.0; 103
C _{max}	1262	7.5	1358	7.8	0.93	84.1; 103

Table 10 Additional Study Information

Root mean square error, AUC	0.2041
Root mean square error, Cmax	0.3234
Ke and AUCi determined for how many subjects?	all
Do you agree or disagree with firm's decision?	Y
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	2
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	N

Comments on Pharmacokinetic Analysis: There was one subject (#30, per II, ref) who had a zero hour sample concentration >5% of his Cmax. That subject was excluded from the statistical analyses.

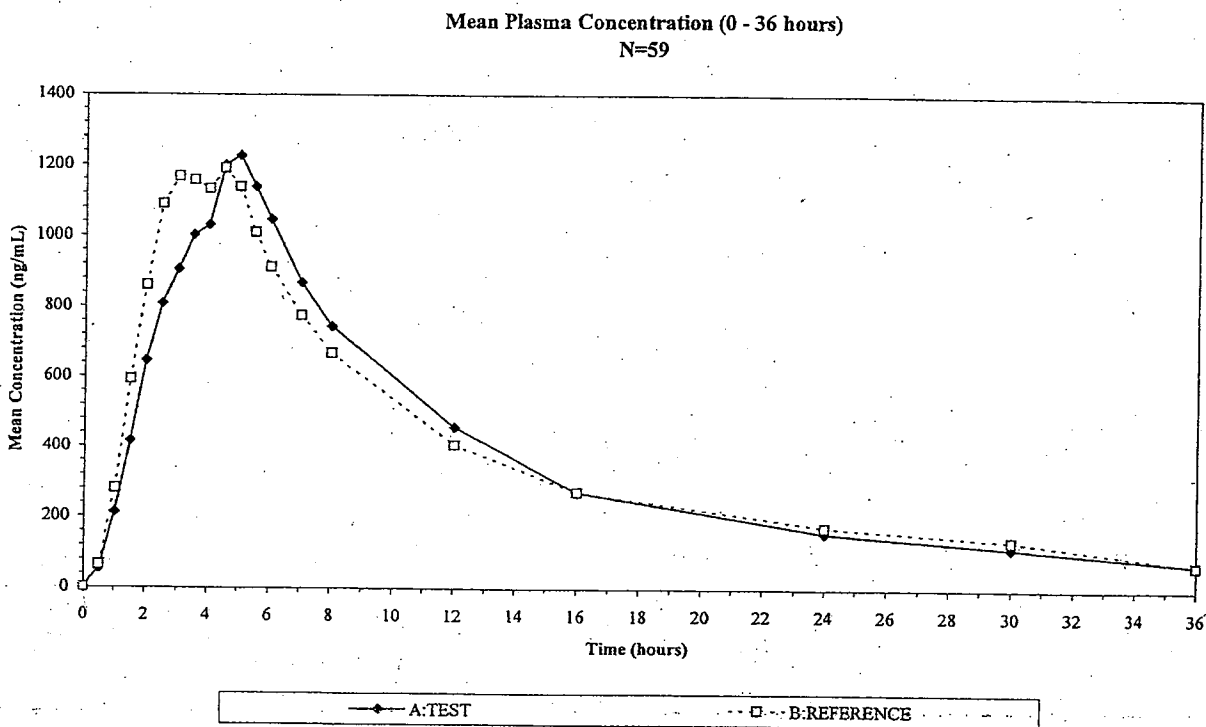
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: acceptable

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Mean Drug Levels (ng/ml)					
Trt A (Eon)					
Time (hr)	N	Mean	Std Dev	CV	T/R
0	59	0	0		
0.5	59	54.4	69.2	127.1	0.84
1	59	211.5	249.6	118.0	0.76
1.5	59	415.9	404.8	97.3	0.70
2	59	646.3	541.5	83.8	0.75
2.5	58	808.5	627.8	77.6	0.74
3	59	906.0	637.7	70.4	0.78
3.5	59	1002.3	627.2	62.6	0.87
4	59	1030.7	655.2	63.6	0.91
4.5	59	1199.4	711.2	59.3	1.01
5	59	1227.0	721.2	58.8	1.08
5.5	59	1139.1	658.9	57.8	1.13
6	59	1046.5	625.3	59.8	1.15
7	59	868.3	554.7	63.9	1.12
8	59	744.3	474.9	63.8	1.11
12	59	457.2	292.0	63.9	1.13
16	59	271.0	191.8	70.8	1.00
24	59	156.2	106.1	67.9	0.90
30	59	116.5	106.0	91.0	0.85
36	59	72.4	96.1	132.8	1.02

Trt B (Skelaxin)					
Time (hr)	N	Mean	Std Dev	CV	
0	59	0.2	1.9	768.1	
0.5	59	64.5	93.9	145.5	
1	59	279.6	329.9	118.0	
1.5	59	593.4	635.1	107.0	
2	59	860.5	744.7	86.5	
2.5	59	1089.7	836.0	76.7	
3	59	1167.3	816.3	69.9	
3.5	59	1157.3	752.3	65.0	
4	59	1132.7	700.6	61.9	
4.5	59	1190.8	713.8	59.9	
5	59	1138.4	669.0	58.8	
5.5	59	1009.7	585.3	58.0	
6	59	912.2	550.7	60.4	
7	59	775.2	558.6	72.1	
8	59	668.0	521.1	78.0	
12	59	405.9	274.2	67.5	
16	59	271.6	160.0	58.9	
24	59	172.8	119.4	69.1	
30	59	136.8	93.2	68.1	
36	59	70.9	58.1	81.9	

**Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
(800 mg)**



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	R04-0160
Study Title	A relative bioavailability study of 800 mg metaxalone tablets under non-fasting conditions
Clinical Site	PRACS Institute, Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	Per I - 14 Mar 04; per II - 21 Mar 04
Analytical Site	PRACS Institute
Analytical Director	(b) (6)
Analysis Dates	25 Mar 04 - 12 Apr 04
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	30 days

Treatment ID	Test Product	Reference Product
Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Metaxalone	Skelaxin®
Manufacturer	Eon Labs, Inc.	Jones Pharma Inc.
Batch/Lot No.	RDW00470	ES803121A
Manufacture Date	Feb, 2004	N/A
Expiration Date	N/A	Apr, 2005
Strength	800 mg	800 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4) dosage units	N/A
Production Batch Size	(b) (4) dosage units	N/A
Potency	99.5%	99.1%
Content Uniformity (mean, %CV)	99.6% (0.5%)	99.3% (1.1%)
Dose Administered	1 x 800 mg	1 x 800 mg

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB - subj #4, 7, 8-10, 13, 15, 18, 19, 21-24, 27-30, 32, 36, 37, 39-41, 43, 48, 49, 53, 56, 57, 59 BA - subj#1-3, 5, 6, 11, 12, 14, 16, 17, 20, 25, 26, 31, 33-35, 38, 42, 44-47, 50-52, 54, 55, 58, 60
Blood Sampling Times	0 (pre-dose) 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 30 and 36 hrs
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	cool centrifuged; plasma stored at $\leq -20^{\circ}\text{C}$
IRB Approval	Y
Informed Consent	Y
Subjects Demographics	See Table 12
Length of Fasting before Meal	overnight
Length of Confinement	through the 24 hr blood draw
Safety Monitoring	vital signs measured pre-dose and at 12 and 24 hrs post-dose
Standard FDA Meal Used?	Y

Comments on Study Design: none

b) Clinical Results

Table 12 Demographics of Study Subjects

Age (yrs)		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	89
Mean	24.8	Mean	162	18-40	95	Male	62	Afr. Amer.	3
SD	6.5	SD	28	41-64	5	Female	38	Hispanic	5
Range	18-45	Range	105-223	65-75				Asian	3
				>75				Others	

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
26	personal reasons	I	N
43	personal reasons	prior to per II check-in	N

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
dry throat	-	1
headache	2	1
fatigue	1	-
Total	3	2

Table 15 Protocol Deviations

Subjects #33 and 55 took OTC medications to relieve cramps and cold symptoms. In the opinion of the clinical investigators, the medication use was not expected to compromise the outcome or validity of the study.

Comments on Adverse Events/Protocol Deviations: All adverse events were mild/moderate in nature.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

QC Conc. (ng/ml)	30.0 - 6000
Inter day Precision (%CV)	1.6 - 3.9%
Inter day Accuracy (%)	92.6 - 99.0%
Cal. Standards Conc. (ng/ml)	10.00 - 7500 (7 pts)
Inter day Precision (%CV)	0.72 - 3.30%
Inter day Accuracy (%)	92.7 - 104%
Linearity Range (r^2)	≥ 0.9976

Comments on Study Assay Quality Control: none

Any interfering peaks in chromatograms?	N
Were 20% of chromatograms included?	Y
Were chromatograms serially or randomly selected?	serial

Comments on Chromatograms: OK

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
090-01	13 Jun 02	Sample Re-analysis

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Y
Did recalculation of plasma concentrations change the study outcome?	N
Does the reviewer agree with the outcome of the repeat assays?	Y
If no, reason for disagreement	

Summary/Conclusions, Study Assays: acceptable

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC _{0-t}	(ngxhr)/ml	18016	47	17913	61	1.01
AUC _∞	(ngxhr)/ml	17944	41	18905	58	0.95
C _{max}	ng/ml	1901	63	2206	83	0.86
T _{max}	hr	12.56	61	12.37	69	1.02
T _{1/2}	hr	4.31	41	4.85	50	0.89
K _{el}	1/hr	0.1913	44	0.1781	47	1.07

Table 20 Geometric Means and 90% Confidence Intervals

Parameter	Test		Reference		T/R	90% CI
	Mean	%CV	Mean	% CV		
AUC _{0-t}	16102	5.1	15692	5.2	1.03	96.5; 109
AUC _∞	16784	4.7	16850	5.0	1.00	94.2; 105
C _{max}	1567	8.8	1692	9.7	92.6	81.4; 105

Table 21 Additional Study Information

Root mean square error, AUC	0.1971
Root mean square error, C _{max}	0.4149
Ke and AUC _i determined for how many subjects?	54 for trt A; 56 for trt B
Do you agree or disagree with firm's decision?	Y
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	1
-first measurable drug concentration as C _{max}	none
Were the subjects dosed as more than one group?	N

Comments on Pharmacokinetic Analysis: Possibly due to the fact that AUC_{inf} could only be calculated for 54 subjects out of the 58 subjects completing the study (trt A), AUC_{inf} is smaller than AUC for the arithmetic mean pharmacokinetic parameters.

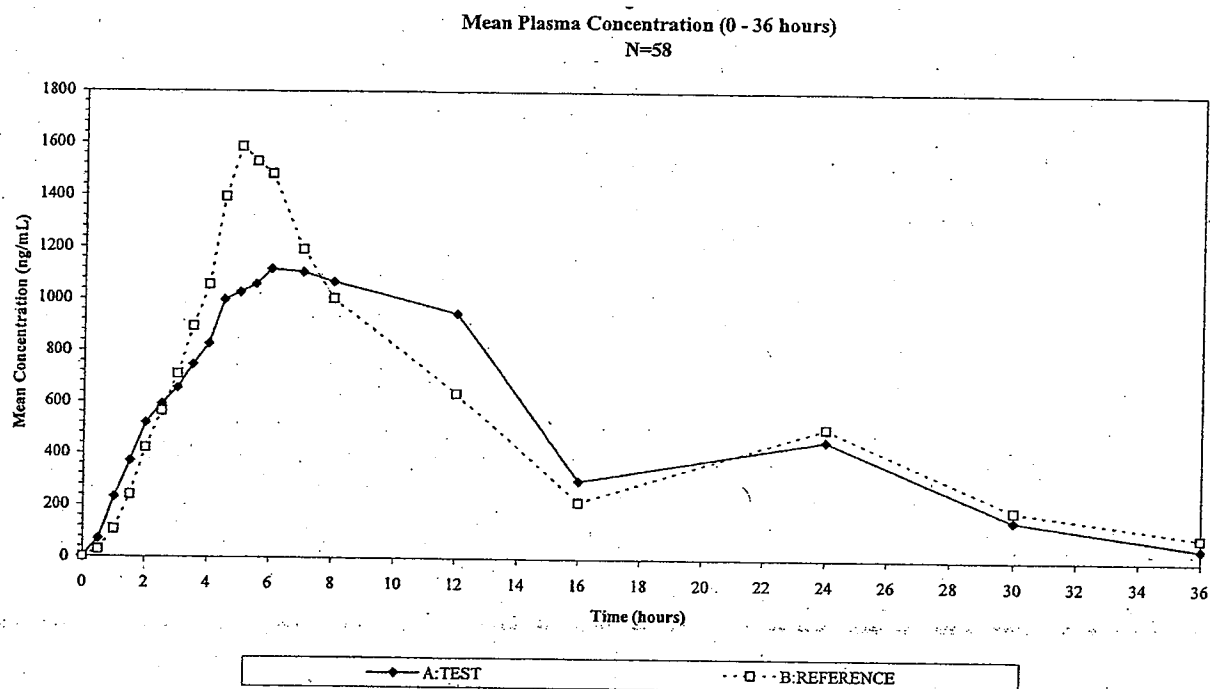
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: acceptable

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Mean Drug Levels (ng/ml)					
Trt A (Eon)					
Time (hr)	N	Mean	Std Dev	CV	T/R
0	58	0.27	2.1	761.6	.
0.5	58	70.1	84.2	120.2	2.47
1	58	231.7	244.3	105.5	2.16
1.5	58	370.3	371.7	100.4	1.55
2	58	518.4	511.9	98.8	1.23
2.5	58	592.6	501.4	84.6	1.05
3	58	655.5	533.9	81.5	0.92
3.5	58	746.2	664.9	89.1	0.83
4	58	826.7	821.8	99.4	0.78
4.5	58	996.7	1037.3	104.1	0.72
5	58	1026.0	1006.1	98.1	0.65
5.5	58	1057.5	1002.0	94.7	0.69
6	58	1116.1	1018.2	91.2	0.75
7	58	1104.8	1071.2	97.0	0.93
8	58	1067.3	999.1	93.6	1.06
12	58	946.4	685.6	72.4	1.49
16	58	300.3	235.6	78.5	1.38
24	58	457.3	693.9	151.7	0.90
30	56	155.4	388.4	250.0	0.81
36	58	51.2	104.3	203.6	0.55

Trt B (Skelaxin)				
Time (hr)	N	Mean	Std Dev	CV
0	58	0	0	.
0.5	58	28.4	48.6	171.2
1	58	107.3	151.1	140.9
1.5	58	239.5	338.4	141.3
2	58	420.4	592.0	140.8
2.5	58	563.8	777.9	138.0
3	58	709.4	1049.7	148.0
3.5	58	894.3	1315.9	147.1
4	58	1055.2	1498.0	142.0
4.5	58	1394.0	1739.1	124.8
5	58	1585.8	1867.9	117.8
5.5	58	1530.0	1745.2	114.1
6	58	1482.4	1659.9	112.0
7	58	1191.8	1318.5	110.6
8	58	1003.4	1082.4	107.9
12	57	636.8	701.0	110.1
16	58	218.4	258.8	118.5
24	58	506.7	650.0	128.3
30	58	193.0	226.2	117.2
36	58	93.8	116.4	124.1

**Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study
(800 mg)**



B. Formulation Data

	400 MG		800 MG	
COMPONENT	Amount per Tablet, mg	% w/w	Amount per Tablet, mg	% w/w
Metaxalone	(b) (4)		800.0	86.39
Acacia, NF	(b) (4)		(b) (4)	
FD & C Red # 40 Aluminum Lake				
Corn Starch, NF				
Alginic Acid, NF				
(b) (4)				
Sodium Starch Glycolate, NF	(b) (4)		(b) (4)	
Magnesium Stearate, NF				
Total Tablet Weight	(b) (4)		926.0	100.00

metaxalone 800 mg - rose-colored, capsule-shaped tablets. Debossed "E448" on one side and scored on the other side.

(b) (4)

Skelaxin® 800 mg - oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other.

Skelaxin® 400 mg - pale rose tablet, inscribed with 8662 on the scored side and "C" on the other.

C. Dissolution Data

Table 1

IN - VITRO DISSOLUTION TESTING

Method Ref.:	DBE interim	Medium:	water w/0.5% SLS
USP 27 Apparatus:	II	Volume:	900 mL
RPM:	100	Tolerance:	NLT (b) (4) in 60 min.
No. Units Tested:	12	Assay Method:	UV
Reference Drug:	Skelaxin® tablet		

Sampling Times (Minutes)	Test Product:			Ref Product:		
	Lot No.: (b) (4)			Lot No.: ES40349A, exp. 10/2006		
	Strength: 400 mg			Strength: 400 mg		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
15	(b) (4)					
30						
45						
60						
75						

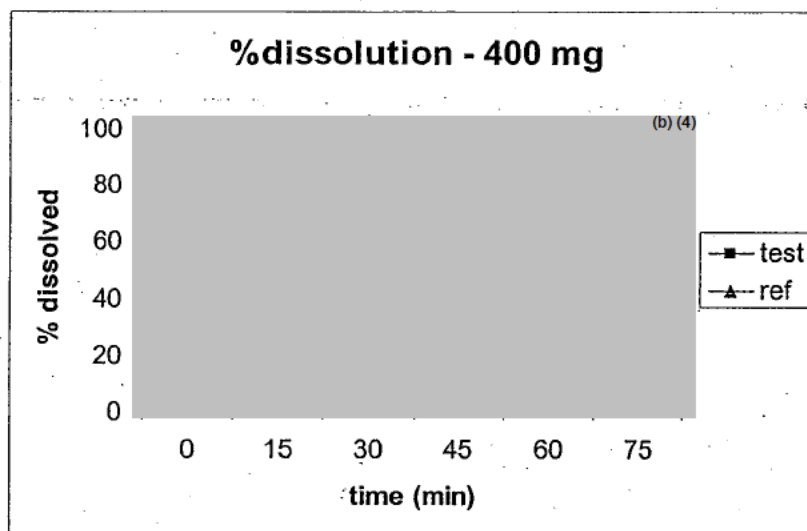
(b) (4)

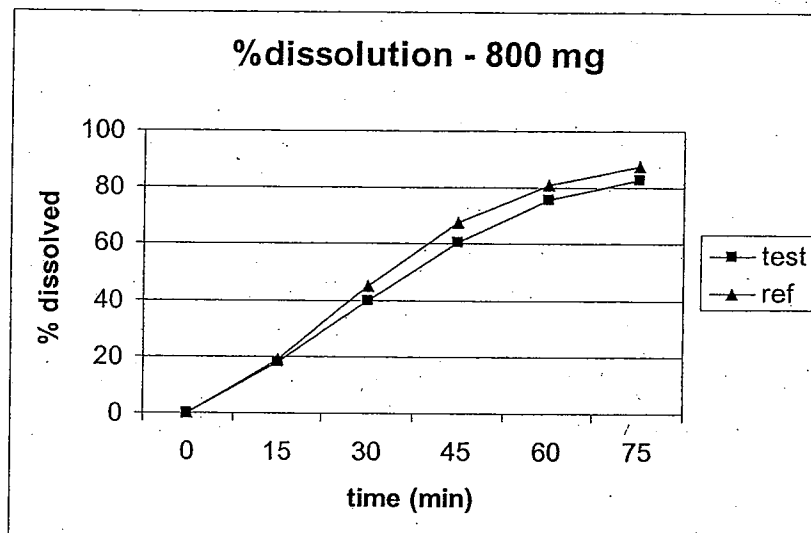
Sampling Times (Minutes)	Test Product: Lot No.: RDW00470 Strength: 800 mg			Ref Product: Lot No.: ES803121A, exp. 4/2005 Strength: 800 mg		
	Mean (%)	Range	% CV	Mean (%)	Range	% CV
15	17.9	(b) (4)	8.8	19.0	(b) (4)	5.4
30	39.8	(b) (4)	10	45.2	(b) (4)	3.3
45	60.8	(b) (4)	9.3	68.0	(b) (4)	2.9
60	75.6	(b) (4)	5.2	81.0	(b) (4)	2.6
75	83.1	(b) (4)	2.9	87.8	(b) (4)	2.4

$$f_2(T_2:R_2)=65.83$$

$$f_2(T_1:T_2)=44.05 \quad f_2(R_1:R_2)=79.17$$

Figure 3 Dissolution Profiles






D. Consult Reviews


N/A

E. SAS Output

Fasted study

metaxalone	 Metaxfs8.txt
------------	---

Fed study

metaxalone	 Metaxfd8.txt
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BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 40-445

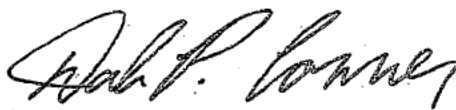
APPLICANT: Eon Labs Inc.

DRUG PRODUCT: Metaxalone tablets; 400 mg and 800 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:



Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-445
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements:

HFD-655/Reviewer *R.P. 5-3-05*
HFD-655/Bio Team Leader *WJB 5-3-05*
HFD-617/Project Manager
HFD-650/Dale Conner *MC 5/4/05*

V:\firmsam\Eon\ltrs&rev\40445N1104.doc

BIOEQUIVALENCE - DEFICIENCIES

Submission Date: 1 Nov 04_n

1. FASTING STUDY (STF)

Strengths: 800 mg

Clinical: PRACS Institute
Analytical: same

Outcome: AC

2. FOOD STUDY (STP)

Strengths: 800 mg

Clinical: PRACS Institute
Analytical: same

Outcome: AC

7. DISSOLUTION WAIVER (DIW)

Strengths: 400 mg

Outcome: IC

Outcome Decisions:

AC - Acceptable

WC - Without Charge

UN - Unacceptable

IC - Incomplete

WinBio Comments

Fasted & fed studies are acceptable. Waiver incomplete for the
400 mg tablet pending appropriate explanation for (b) (4)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40445		
Drug Product Name	Metaxalone Tablet		
Strength(s)	Originally for 800 mg and 400 mg (400 mg is being withdrawn)		
Applicant Name	Originally Eon now Sandoz		
Address	506 Carnegie Center, Princeton NJ 08540		
Applicant's Point of Contact	Sadie Ciganek		
Contact's Telephone Number	609-627-8728		
Contact's Fax Number	609-627-8673		
Original Submission Date(s)	Aug 31, 2001		
Submission Date(s) of Amendment(s) Under Review	Sept 6, 2006 (withdrawal of the 400 mg Tablet)		
Reviewer	Surendra Shrivastava		
Study Number (s)	Not applicable		
Study Type (s)	Not Applicable		
Strength (s)	Not Applicable		
Clinical Site	Not applicable		
Clinical Site Address	Not applicable		
Analytical Site	Not applicable		
Analytical Site Address	Not applicable		
OUTCOME DECISION	ACCEPTABLE		

1 EXECUTIVE SUMMARY

Sandoz/Eon has ANDA 40445 for the 800 mg and 400 mg Tablets. The RLD (NDA 13217) is the 800 mg Skelaxin® tablet from Jones Pharma Inc a subsidiary of Kings Pharms. To accept both strengths the DBE requires acceptable single dose, BE studies (fasting and fed) on the 800 mg Tablet, acceptable data as per the 21 CFR 320.22 (d)(2) on the 400 mg Tablet.

As per our last review of submission dated November 1, 2004, the firm had submitted:

- i) Acceptable BE studies (fasting and fed) on the 800 mg Tablet.
- ii) (b) (4) formulations for the 800 mg and 400 mg metaxalone tablets.
- iii) Incomplete comparative dissolution testing.

(b) (4)

In this submission, the firm has elected to withdraw the 400 mg Tablet without prejudice. This means that the firm has submitted acceptable BE requirements for the 800 mg Tablet. Thus, the ANDA 40445 (only for the 800 mg Tablet) is complete and acceptable to DBE without any deficiencies.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

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3 SUBMISSION SUMMARY

(Please see V:\firmsam\Eon\ltrs&rev\40445N1104.doc)

3.1 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Not applicable	
Single-dose fed	Not applicable	
Steady-state	Not applicable	
In vitro dissolution	Not applicable	
Waiver requests	Not applicable	
BCS Waivers	Not applicable	
Clinical Endpoints	Not applicable	
Failed Studies	Not applicable	
Amendments	Yes	1

3.2 Formulation

Location in appendix	V:\firmsam\Eon\ltrs&rev\40445
If a tablet, is the RLD scored?	Yes
If a tablet, is the test product biobatch scored	Yes
Is the formulation acceptable?	FORMULATION ACCEPTABLE
If not acceptable, why?	Not applicable

3.3 In Vitro Dissolution

Location of DBE Dissolution Review	V:\firmsam\Eon\ltrs&rev\40445
Source of Method (USP, FDA or Firm)	FDA
Medium	0.5% SLS in water
Volume (mL)	900
USP Apparatus type	II (paddle)
Rotation (rpm)	100
DBE-recommended specifications	NLT ^{(b) (4)} (Q) in 60 minutes
If a modified-release tablet, was testing done on ½ tablets?	Not applicable
F2 metric calculated?	For the 800 mg Tablet (T vs. R = 65.83)
If no, reason why F2 not calculated	Not applicable
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	Not applicable

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	Other Strength	F2 metric for test	F2 metric for RLD
Not applicable			

3.4 Waiver Request(s)

Strengths for which waivers are requested	Not Applicable
Proportional to strength tested in vivo?	
Is dissolution acceptable?	
Waivers granted?	Not applicable
If not then why?	The firm withdrew the lower strength

3.5 Deficiency Comments

None

3.6 Recommendations

Standard BE Studies

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute for Eon Labs Inc. on its metaxalone 800 mg tablet have been found acceptable to the Division of Bioequivalence.
2. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.5% SLS in water at temp, 37°C + 0.5°C using the USP apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

NLT (b) (4) (Q) of metaxalone in the dosage form is dissolved in 60 minutes.

3. Division of Bioequivalence deems the test product Metaxalone Tablet 800 mg, manufactured by Eon/Sandoz to be bioequivalent to the reference product, Skelaxin®, 800 mg Tablet manufactured by Jones Pharma Inc/ King Pharms.

3.7 Comments for Other OGD Disciplines

Discipline	Comment
	none

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-445

APPLICANT: Sandoz (Eon)

DRUG PRODUCT: Metaxalone Tablet 800 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that you will conduct the dissolution testing in 900 mL of 0.5% SLS in water at temp, 37°C + 0.5°C using the USP apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

NLT ((b) (4) %) (Q) of metaxalone in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

3.8 Outcome Page

ANDA: 40445

Completed Assignment for 40445 ID: 786

10/30/2007 2:55:42 PM

Reviewer: Shrivastava, Surendra

Date

Completed:

Verifier: Shriniwas Nerurkar

Date Verified: 10/30/2007

Division: Division of Bioequivalence

Description: Metaxalone Tablets Sandoz (Previously Eon)

Productivity:

<i>ID</i>	<i>Date Entered</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
786	9/6/2006	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

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

/s/

Surendra P. Shrivastava
11/6/2007 09:27:30 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
11/6/2007 09:40:23 AM
BIOPHARMACEUTICS

Barbara Davit
11/9/2007 02:28:39 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 40-445

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

August 31, 2001

Gary J. Buehler
Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Concur.
18/11/01
RTF
Standish
17-OCT-2001



**RE: Original ANDA
Metaxalone Tablets, 400 mg**

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, enclosed is an original Abbreviated New Drug Application for Metaxalone Tablets, 400 mg. This application consists of the following volumes:

- Volume 1 Debarment, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, dissolution profiles, signed disclosure statement, certificates of analysis, and components and composition.
- Volume 2 Raw material control data, manufacturing and packaging records including Executed Batch Record.
- Volume 3 Container/closure information, finished product controls, methods validation, stability data, and environmental impact statement.
- Volume 4 through 8 Bioequivalence study summary and test results. (Also included is one diskette containing the raw data).

A full table of contents precedes each appropriately paginated volume.

We have also enclosed three (03) copies of analytical methods validation package in a separate volume.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the District Field Office, Jamaica, New York.

G. Buehler

August 31, 2001

Page 1 of 2

Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact me at (718) 276-8600, extension 330.

Sincerely,
Eon Labs Manufacturing, Inc.

A handwritten signature in cursive script, reading "Sadie M. Ciganek", is written over a horizontal line.

Sadie M. Ciganek
Vice President, Regulatory Affairs

ANDA 40-445

OCT 17 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated August 31, 2001, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Metaxalone Tablets, 400 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

It appears that your proposed

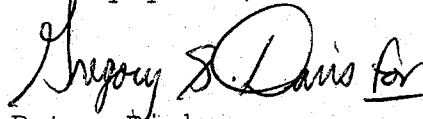
(b)(4)

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Saundra T. Middleton
Project Manager
(301) 827-5862

Sincerely yours,



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-⁴⁴⁵~~455~~

cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-615/MBennett

Endorsement: HFD-615/GDavis, Chief, RSE G. Davis 17-07-2001 date
HFD-615/SMiddleton, CSO S. Middleton date 12/12/01
Word File
V:\FIRMSAM\EON\LTRS&REV\40445.RTF
F/T File EEH 10/15/01
ANDA Refuse to Receive!



Eon Labs

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 949-3120

November 2, 2001

Ms. Sandra Middleton
Project Manager
Regulatory Support Branch
Office of Generic Drugs, HFD-615
Center for Drug Evaluation and Research
7500 Standish Place
Metro Park North II
Rockville, MD 20857

ORIG AMENDMENT

N/Ac

- GENERAL CORRESPONDENCE -

Re: Metaxalone Tablets, 400 mg
ANDA 40-445

Dear Ms. Middleton:

Reference is made to the **Refusal-to-Receive** letter dated October 17, 2001 for Metaxalone Tablets, 400 mg, **ANDA 40-445**. The letter raised concerns about the

[Redacted]

- [Redacted]

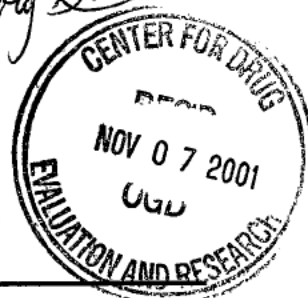
- [Redacted]

*11/26/01.
All Forming
talked at the
pharm. and stated
that they seem to
be sufficient info.
for consult.*

Will send for consult.

*11/29/01
Ack for filing
505(j)(2)(A)
S. Middleton*

*Concurrence
Hugory B. L...*



(b) (4)

* (b) (4)
**

(b) (4)

in Eon Labs Metaxalone product .

• (b) (4)

to FDA, Regulatory Support Branch (Ms. Sandra Middleton) for review if required.

Based on the information submitted herein, are requesting that our Abbreviated New Drug Application for Metaxalone Tablets, 400 mg be accepted for filing since (b) (4)

(b) (4)

If you require further information, do not hesitate to let either myself know at (718) 276-8607 x 235, or Ms. Sadie Ciganek at (718) 276-8607 x 330. We will provide the necessary assistance to resolve this matter as quickly as possible.

Sincerely,
Eon Labs Manufacturing, Inc.

Enna Krivitsky
Enna Krivitsky
Manager Regulatory Affairs

ANDA 40-445

NOV 30 2001

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to Receive" letter dated October 17, 2001 and your amendment dated November 2, 2001.

NAME OF DRUG: Metaxalone Tablets, 400 mg

DATE OF APPLICATION: August 31, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 7, 2001

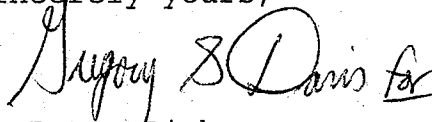
We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,



Wm Peter Rickman
Acting Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-445

cc: DUP/Jacket

Division File

HFD-82

Field Copy

HFD-330

HFD-610/R.West

HFD-610/P.Rickman

HFD-615/MBennett

Endorsements: HFD-615/GDavis, RSB

HFD-615/SMiddleton, CSO

Word Document

V:\FIRMSAM\EON\LTRS&REV\40445.ACK

F/T by StM 11/29/01

ANDA Acknowledgment Letter!

JD 30-NOV-2001
date

date 11/29/01

Food and Drug Administration
Rockville MD 20857

MAR 1 2004

ANDA for Metaxalone Tablets

Dear Applicant:

This letter is to inform you that the FDA has determined that labeling corresponding to the use (U-189) listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for U. S. Patent number 6,407,128 (the '128 patent) may be carved out of the metaxalone labeling. Previously, the FDA may have informed you that such omission would not be permitted. A preliminary decision not to permit omission of this labeling was challenged by an ANDA applicant. The applicant has submitted information and analysis that has persuaded FDA that the fed-state bioavailability information may be carved out of the metaxalone labeling without rendering the drug less safe or effective for the remaining conditions of use. Therefore, FDA has concluded that you may submit proposed labeling that omits the use (U-189) described in the Orange Book. Should you adopt this approach, you must accompany this submission with a "section viii statement" to the '128 patent, pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (Act)

The listed drug at issue is Elan's Skelaxin (metaxalone) Tablets, NDA 13-217.¹ Metaxalone is approved by FDA for use "as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions." The '128 patent is listed for Skelaxin in the Orange Book. It is identified as a use patent. The use claimed by the patent is listed in the Orange Book as "enhancement of the bioavailability of the drug substance" (U-189). The question presented to the agency was whether a section viii statement with respect to the '128 patent would be permitted. A section viii statement asserts that the labeling in the ANDA does not include any use claimed by the use patent. Section 505(j)(2)(A)(viii); 21 CFR 314.94(a)(12)(iii). A section viii statement is only appropriate when an applicant can carve information protected by the use patent out of the labeling for the product proposed in the ANDA.

ANDA Applicants May Omit from Labeling Method of Use Information Claimed by a Patent if the Omission Will Not Render the Drug Less Safe and Effective

The regulatory principles governing FDA's decision on this matter are well established. FDA has authority to approve ANDAs that omit labeling carried by the listed drug, when such labeling is protected by patent or exclusivity. The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Section 505(j)(2)(A)(i). The Act also requires that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug" Section

¹ This NDA is now owned by Jones Pharma, Inc., a subsidiary of King Pharmaceuticals, Inc.

505(j)(2)(A)(v). The Act specifies two exceptions to this requirement. ANDA labeling may differ from that of the listed drug because changes from the listed drug were approved pursuant to an ANDA suitability petition, or because the drugs are produced or distributed by different manufacturers. Section 505(j)(2)(A)(v).

The Act specifically contemplates that an innovator company may submit to FDA patents claiming an approved method of using a drug and that ANDA applicants may omit from proposed labeling methods of use covered by those patents. Sections 505(b)(1) and (c)(2) of the Act state that innovators may submit patents to FDA that claim the approved drug "or method of using such drug." If a method-of-use patent listed by the innovator does not claim a use for which an ANDA applicant is seeking approval (because it is omitted from the proposed ANDA labeling), the ANDA applicant may submit a "section viii statement" to FDA that it is not seeking approval for a use claimed by a listed patent. Section 505(j)(2)(A)(viii). The statutory provisions addressing patent listing and section viii statements use the same "method of use" terminology, and effectively mirror one another; a method of use claimed by a patent is also a method of use that an ANDA applicant may propose to carve out of labeling.

FDA regulations further describe the differences that are permitted between the proposed labeling in the ANDA and the listed drug. 21 CFR 314.94, "Content and format of an abbreviated application," provides:

Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.*

21 CFR 314.94(a)(8)(iv)(emphasis added). The courts have upheld FDA's authority to approve generic drugs with labeling that omits information protected by exclusivity, *Bristol-Myers v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), and information protected by patent, *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002); *aff'd Purepac Pharm. Co. v. Thompson*, Nos. 02-5410 & 03-5121, 2004 WL 76594 (D.C. Cir. Jan. 20, 2004).

The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 CFR 314.127(a)(7). Whether a particular ANDA proposing labeling that

omits protected information may be approved depends upon the specific drug product and the labeling at issue. Therefore, whether FDA could approve a metaxalone ANDA that omits certain method of use information from the labeling depends upon whether the agency concludes that the drug will remain safe and effective for all the conditions of use that would remain in the label.

ANDA Applicants May Omit Labeling Related to Fed-State Bioavailability from Metaxalone Labeling

The agency has reviewed the labeling for Skelaxin, and determined that information related to the "enhancement of the bioavailability of the drug substance," may be omitted from the labeling for metaxalone products proposed in ANDAs, without rendering those drug products less safe or effective for the conditions of use that would remain in the label.

Metaxalone is approved by FDA only for use "as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions." The mode of action of metaxalone has not been clearly identified, but may be related to its sedative properties. The drug has been marketed for approximately 40 years, and is considered to have a favorable safety profile. Until recently, Skelaxin had no information in its labeling related to the effect of administration of the drug with food.

In 2001, Elan conducted a food effect study with metaxalone, and submitted the results to FDA in a labeling supplement. In June 2002, FDA approved changes to the Clinical Pharmacology section of the Skelaxin labeling to incorporate information from the food effect study.² It is this pharmacokinetic information that an applicant seeks to delete from its labeling as corresponding to the use claimed in the '128 patent. The bioavailability data submitted by Elan did not result in new Dosing and Administration labeling information for Skelaxin. Nor did it result in any changes to the warnings, precautions, or contraindications in the Skelaxin labeling

The pharmacokinetic information submitted by Elan and included in the labeling demonstrated that administration of metaxalone with a high fat meal enhances drug absorption. See attached Skelaxin labeling. The Skelaxin label includes pharmacokinetic information from dosing following a standardized high fat meal. The results from this study showed that food statistically significantly increased the rate (C_{max}), and extent of absorption (AUC_{0-t} , AUC_{inf}) of metaxalone. The approved Skelaxin labeling further acknowledges that "[t]he clinical relevance of these effects is unknown."³

The agency's assessment of whether pharmacokinetic information may be omitted from metaxalone labeling without rendering the drug less safe or effective for the remaining uses focused on whether information about enhanced fed-state bioavailability was necessary to the

² Elan did not receive three years of exclusivity for this labeling change under section 505(j)(5)(D)(iii) or (iv) because bioavailability studies are not clinical studies that qualify for exclusivity. 21 CFR 314.108(a).

³ If Elan had conducted clinical trials to demonstrate a clinical effect arising from the difference in fed- and non-fed-state bioavailability, the inclusion of such information in labeling might have been considered necessary for the safe and effective use of metaxalone. No such study has been submitted.

safe and effective use of the drug. The agency looked specifically at the relationships between bioavailability and efficacy, and bioavailability and the occurrence of known adverse events, particularly drowsiness.

FDA has concluded that omission of information regarding fed-state bioavailability will not negatively affect the safe use of metaxalone. On May 31, 2002, FDA approved an addition to the Skelaxin Clinical Pharmacology labeling that stated "Given the magnitude of the plasma level changes following a high fat meal, Skelaxin tablets should be administered on an empty stomach." The agency had approved this information because it was concerned about enhanced bioavailability and increased adverse events. However, no related changes were made to the Dosing and Administration portion of the labeling. After discussions with Elan and additional review of the available information, the agency later concluded that there were insufficient data to support a correlation between enhanced drug concentrations and increased adverse events. The label was further revised in June 2002, to remove information regarding dosing on an empty stomach, and to state that the clinical effect of the increased bioavailability is unknown.

Because the clinical effect of the increased bioavailability is unknown, omission of fed-state bioavailability information from the labeling will not render the drug less safe for its approved uses. There are no data to support an increase in adverse events related to increased drug concentrations. Even if it were reasonable to conclude that increased bioavailability relates to an increase in adverse events, the labeling already adequately addresses the primary CNS (central nervous system) adverse events by way of the caution that "SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants." This caution applies to use of metaxalone without reference to the conditions of administration.

The Skelaxin labeling provides no information that links variations in bioavailability to the effectiveness of the drug. In fact, as noted above, the approved labeling specifically states that the clinical relevance of the food effect is unknown. Thus, because the clinical effect of increased bioavailability is unknown, omission of information on this characteristic of the drug will not affect the effective use of metaxalone.

Finally, FDA notes that metaxalone has a long history of safe use. It has been marketed for decades without dosing adjustment information related to fed-state administration. Few adverse event reports have been entered into the Adverse Event Reporting System. Based upon the data available to the agency, there is no reason to believe that metaxalone will not continue to be safe and effective for use as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions.

For the reasons described above, FDA has concluded that an ANDA applicant may delete from its labeling information on fed-state bioavailability claimed by the '128 patent because metaxalone products with such labeling will be no less safe or effective for all of the remaining conditions of use.

If you have further questions regarding this issue, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert L. Test / for". The signature is fluid and cursive, with a large "R" at the beginning and a slash followed by "for" at the end.

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

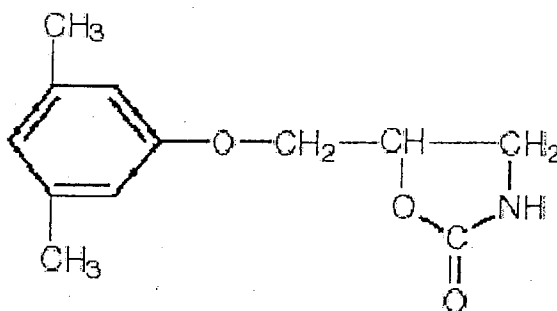
Attachment: Skelaxin Labeling

cc: Jones Pharma, Inc.
Daniel E. Troy, OCC

SKELAXIN® (Metaxalone)

DESCRIPTION

SKELAXIN® (metaxalone) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone

SKELAXIN (metaxalone) is available as a 400 mg round, pale rose tablet and an 800 mg oval, pink scored tablet.

CLINICAL PHARMACOLOGY

The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Pharmacokinetics: In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), a single 400 mg SKELAXIN (metaxalone) tablet was administered under both fasted and fed conditions.

Under fasted conditions, mean peak plasma concentrations (C_{max}) of 865.3 ng/mL were achieved within 3.3 \pm 1.2 hours (S.D.) after dosing (T_{max}). Metaxalone concentrations declined with a mean terminal half-life ($t_{1/2}$) of 9.2 \pm 4.8 hours. The mean apparent oral clearance (CL/F) of metaxalone was 68 \pm 34 L/h.

In the same study, following a standardized high fat meal, food statistically significantly increased the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$, AUC_{inf}) of metaxalone from SKELAXIN tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 115.4%, respectively. The mean T_{max} was also increased to 4.3 \pm 2.3 hours, whereas the mean $t_{1/2}$ was decreased to 2.4 \pm 1.2 hours. This decrease in half-life over that seen in the fasted subjects is felt to be due to the more complete absorption of metaxalone in the presence of a meal resulting in a

better estimate of half-life. The mean apparent oral clearance (CL/F) of metaxalone was relatively unchanged relative to fasted administration (59 ± 29 L/hr). Although a higher C_{max} and AUC were observed after the administration of SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

In another single center, randomized four-period crossover study in 59 healthy volunteers (37 males, 22 females), the rate and extent of metaxalone absorption were determined after the administration of SKELAXIN tablets under both fasted and fed conditions. Under fasted conditions, the administration of two SKELAXIN 400 mg tablets produced peak plasma metaxalone concentrations (C_{max}) of 1653 ng/mL 3.0 \pm 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with mean terminal half-life ($t_{1/2}$) of 8.0 \pm 4.6 hours. The mean apparent oral clearance (CL/F) of metaxalone was 66 \pm 34 L/hr. Except for a 17% decrease in mean C_{max} , these values were not statistically different from those after the administration of one SKELAXIN 800 mg tablet.

In the same study, the administration of two SKELAXIN 400 mg tablets following a standardized high fat meal showed an increase in the mean C_{max} , and the area under the curve ($AUC_{0-\infty}$) of metaxalone by 194% and 142%, respectively. A high fat meal also increased the mean T_{max} to 4.9 \pm 2.3 hours but decreased the mean $t_{1/2}$ to 4.2 \pm 2.5 hr. The effect of a high fat meal on the absorption of metaxalone from one SKELAXIN 800 mg tablet was very similar to that on the absorption from two SKELAXIN 400 mg tablets in quality and quantity. The clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from SKELAXIN tablets is not known. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. The impact of age, gender, hepatic, and renal disease on the pharmacokinetics of SKELAXIN (metaxalone) has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment and in the elderly.

INDICATIONS AND USAGE

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Known hypersensitivity to any components of this product.
Known tendency to drug induced, hemolytic, or other anemias.
Significantly impaired renal or hepatic function.

WARNINGS

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

PRECAUTIONS

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Information for Patients

SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

Drug Interactions

SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of metaxalone has not been determined.

Pregnancy

Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children 12 years of age and below have not been established.

ADVERSE REACTIONS

The most frequent reactions to metaxalone include:

CNS: drowsiness, dizziness, headache, and nervousness or "irritability";

Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions are:

Immune System: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia; hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with this class of drugs, particularly in combination with antidepressants and/or alcohol.

When determining the LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

Treatment - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is two 400 mg tablets (800 mg) or one 800 mg tablet three to four times a day.

HOW SUPPLIED

SKELAXIN (metaxalone) is available as a 400 mg pale rose tablet, inscribed with 8662 on the scored side and "C" on the other. Available in bottles of 100 (NDC 0086-0062-10) and in bottles of 500 (NDC 0086-0062-50).

SKELAXIN (metaxalone) is also available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 59075-068-10) and in bottles of 500 (NDC 59075-068-50).

Store at Controlled Room Temperature, between 15° C and 30° C (59° F and 86° F).

Rx Only

Revised: August, 2002

November 1, 2004

Gary J. Buehler, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MAJOR AMENDMENT

N/AC
RECEIVED

NOV 04 2004

OGD / CDER

**RE: Major Amendment to ANDA 40-445
Metaxalone Tablets, 400 mg and 800 mg**

Dear Mr. Buehler:

Pursuant to 21 CFR 314.96 and 21 CFR 314.120, and referencing OGD's letters to Eon Labs dated December 3, 2002 and March 6, 2003, this filing constitutes a Major Amendment to Eon Labs' Abbreviated New Drug Application for Metaxalone Tablets, 400 mg, ANDA # 40-445.

In accord with the FDA letter of March 6, 2003, this Major Amendment contains CMC information supporting (b) (4) drug product, fasting and fed bioequivalence studies performed on the 800 mg test product and the Reference Listed Drug, and new labeling to add the 800 mg strength. We also propose a new manufacturing site for these drug products.

Since the supporting information for these changes is substantial, this amendment has been formatted with ANDA sections. The complete volume contents are outlined in the Table of Contents and correspond to the following:

- Volume 1 Basis of submission, patent and exclusivity certifications, Section 505(j)(2)(A) information, labeling, bioequivalence data, request for waiver, dissolution profiles, signed disclosure statement, certificates of analysis, components and composition, and raw material control data.
- Volume 2 Facility descriptions, cGMP certification, contract labs, and blank and executed manufacturing and packaging records.
- Volume 3 Container/closure information, finished product controls, methods validation, stability data, environmental impact statement, and debarment certification.

Mr. G. Buehler

November 1, 2004

1 of 3

Volumes 4 through 11 Bioequivalence study summary and test results. (Also included are two CD-ROMs containing the raw data).

Draft labeling is provided in electronic format (as PDF and DOC files on diskette).

A full table of contents precedes each appropriately paginated volume.

We have also enclosed three (3) copies of the analytical methods validation package in separate volumes.

Please note that we are including new "Paragraph IV" patent certifications (to U.S. Patents 6,407,128 and 6,683,102) for the 800 mg strength of the drug product.

The following is an update to the legal status of the 400 mg strength of the drug product with regard to both patents, since "Paragraph IV" certifications have already been filed for the 400 mg strength:

U.S. Patent 6,407,128: A complaint has been filed by Elan Corporation, plc, against Eon Labs, Inc. as described in the Patent Amendment to this ANDA dated January 15, 2003.

U.S. Patent 6,683,102: A "Paragraph IV" certification was filed to this patent on February 10, 2004. We hereby certify to the FDA that, in accordance with 21 CFR 314.95(b), **Patent Certification Notice** for U.S. Patent 6,683,102 has been provided to the patent holder, Elan Corporation, plc, and to the holder of the approved NDA 13-217, Jones Pharma, Inc. (subsidiary of King Pharmaceuticals, Inc.) for the reference listed drug, Skelaxin® as defined in 21 CFR 314.95(a). Further, the notices have met the content requirements under 21 CFR 314.95(c). Copies of the return receipts are provided in Section III-Patents/Exclusivity of this filing. We also hereby notify the FDA that a complaint has been filed by Elan Corporation, plc, against Eon Labs, Inc. in the U.S. District Court for the Eastern District of New York, Civil Action No. 03-CV-0006, on Jan. 2, 2003 and amended on Feb. 11, 2004.

In addition to the archival and review copies, we are submitting a certified true copy of the chemistry, manufacturing and controls data to the FDA District Field Office, Atlanta, Georgia.

Subsequent amendments or supplements containing chemistry, manufacturing and controls data will also be submitted to the District Field Office.

If there are any comments or questions about this application, please contact either Mr. Dietrich Bartel at (252) 234-2212 or Mr. Steve Brown, Director, Regulatory Affairs at (252) 234-2224.

Sincerely,

A handwritten signature in cursive script, reading "Dietrich Bartel", is written over a horizontal line.

Dietrich Bartel
Assistant Director, Regulatory Affairs
Eon Labs, Inc.

MEMORANDUM

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

DATE : November 29, 2004

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)



SUBJECT: Examination of the bioequivalence study submitted with an ANDA 40-445 for Metaxalone Tablets, 400 mg and 800 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv). The new strength is 800 mg.

Eon Labs. Inc. has submitted ANDA 40-445 for Metaxalone Tablets, 400 mg and 800 mg. The ANDA contains a certification pursuant to 21 USC 355(j)(5)(B)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Eon Labs. Inc. on November 01, 2004 for its Metaxalone product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

Telecon Record

Date: 12/9/04

ANDA: 40-445

Firm: Eon Labs, Inc.

Drug: Metaxalone Tablets, 400mg and 800mg

FDA Participants: Iain Margand

Industry Participants: Dietrich Bartel

Phone: 252-234-2212

Agenda:

1. Iain requested the following:

Please provide a Field Copy Certification with original signature.

Please provide a contact person for the API manufacturer or their U.S. agent.

Provide cGMPs for outside firms used in this application.

Provide a protocol for the Stability of Finished Dosage Form.

AC

December 15, 2004

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

RE: **TELEPHONE AMENDMENT** – ANDA 40-445
Metaxalone Tablets, 400 mg and 800 mg

Dear Mr. Buehler:

Pursuant to Section 505(j) of the federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR 314.96(a), this submission constitutes a Telephone Amendment to ANDA 40-445. It is being filed in response to a telephone communication from Mr. Iain Margand of the OGD, to Eon Labs, Inc. on December 9, 2004. The OGD telephone request for information referenced the MAJOR AMENDMENT filed on November 1, 2004.

The following is provided in response to the request:

1. As in all prior OGD filings, the Field Copy cover letter with **the** original signature was sent with the actual Field Copy. The Archival and Review Copies of the ANDA contain a copy only.
2. The U.S. agent and contact name for the API manufacturer, (b) (4), is:



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OGD / CDER

3. cGMP certificates are provided for all outside contract manufacturers listed in Part X of the Major Amendment (**Attachment 1**). Internal sites are covered by certifications in Part IX of the ANDA and Major Amendment.
4. Protocols are provided for all stability studies performed on both strengths of the drug product and provided in Part XVI of the Major Amendment (**Attachment 2**).

We certify that an identical copy of this submission is also being filed to the FDA Atlanta District Office, 60 Eight St. NE, Atlanta, GA 30309.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., by telephone at (252) 234-2212.

Yours truly,



Dietrich Bartel
Assistant Director, Regulatory Affairs,
Eon Labs, Inc.

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 40-445

FIRM NAME **Eon Labs, Inc.**

DRUG NAME Metaxalone Tablets, 400 mg and 800 mg

DOSAGE FORM **Tablets**

SUBJ: Request for examination of: Bioequivalence Study and Request for Waiver

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
<input checked="" type="checkbox"/>	Study meets statutory requirements
<input type="checkbox"/>	Study does NOT meet statutory requirements
	Reason:
<input checked="" type="checkbox"/>	Waiver meets statutory requirements
<input type="checkbox"/>	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: ☒ COMPLETE ☐ INCOMPLETE

Reviewed by:

Sheryl Gunther Date: 12/20/2004
Sheryl Gunther
Reviewer

Moheb H. Makary Date: 12/20/2004
Moheb Makary
Team Leader
Acting

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Assay Methodology	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Procedure SOP	<input type="checkbox"/>	<input checked="" type="checkbox"/>			Referenced but not provided.
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Study Results Ln/Lin	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Adverse Events	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
IRB Approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Dissolution Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Pre-screening of Patients	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Chromatograms	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Consent Forms	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Original	Copy of original	
Composition	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary of Study	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Individual Data & Graphs, Linear & Ln	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
PK/PD Data Disk Submitted)	<input checked="" type="checkbox"/>	<input type="checkbox"/>			EDR
Randomization Schedule	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Protocol Deviations	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Discussed in clinical summaries
Clinical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			PRACS Institute, Ltd., Fargo, ND 58104
Analytical Site	<input checked="" type="checkbox"/>	<input type="checkbox"/>			PRACS Institute, Ltd., 4666 Amber Valley Parkway, Fargo, ND 58104

Study Investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Medical Records	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Clinical Raw Data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Test Article Inventory	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
BIO Batch Size	<input checked="" type="checkbox"/>	<input type="checkbox"/>			(b) (4) tablets
Assay of Active Content Drug	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Test: 99.5% Reference: 99.1%
Content Uniformity	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Test: 99.6% (0.5% CV) Reference: 99.3% (1.1% CV)
Date of Manufacture	<input checked="" type="checkbox"/>	<input type="checkbox"/>			2/2004
Exp. Date of RLD	<input checked="" type="checkbox"/>	<input type="checkbox"/>			4/2005
BioStudy Lot Numbers	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Test: RDW00470 Reference: ES803121A
Statistics	<input checked="" type="checkbox"/>	<input type="checkbox"/>			
Summary results provided by the firm indicate studies pass BE criteria	<input checked="" type="checkbox"/>	<input type="checkbox"/>			For both the fasting and non-fasting studies, summary results for AUC0-t, AUCinf, and Cmax for metaxalone pass 90% CI criteria.
Waiver requests for other strengths / supporting data	<input checked="" type="checkbox"/>	<input type="checkbox"/>			For the 400 mg strength

Additional Comments regarding the ANDA:

The firm has submitted single-dose fasting and non-fasting BE studies to assess the bioequivalence of its Metaxalone Tablets, 800 mg versus the RLD, Skelaxin® Tablets, 800 mg. For both studies, summary results for AUC0-t, AUCinf, and Cmax for metaxalone pass 90% CI criteria of 80-125%. DIW is requested for the 400 mg strength. The 800 mg strength carries a first generic designation.

The firm previously submitted

(b) (4)

(b) (4)

The current submission contains a

(D) (4)

ANDA 40-1445 Final Check List for Branch Chief

- N/A 1) Check letter date and stamp date of ANDA vs. drafted letter.
- ✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.
- N/A 3) Check for gross errors in letter.
- N/A 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- N/A 5) Check address and contact person on letter vs. 356h.
- ✓ 6) Check for any t-cons and verify date and correspondence date.
- ✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- ✓ 8) Check for any comments or problems raised by reviewer on Check List.
- ✓ 9) If first generic, copy BE review and file. (*860mg only*)
- ✓ 10) Sign Check List.
- ✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. *Skelaxin 860mg*
- ✓ 12) Check for MOU patents
- ✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- ✓ 14) Review Basis for Submission. *Skelaxin 13217*
- ✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. *PIV to '1298 & '102*)
- ✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- ✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.
- ✓ 18) Pull USP information. (USP yes ✓no)
- ✓ 19) Final Grammar review on letter.
- ✓ 20) Verify information in OGD Patent Tracking System.
- ✓ 21) EES slip.
- ✓ 22) Document in record book.

Signature *Marchi H. Simon* date *28 Dec 2004*

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 40-445 FIRM NAME: EON LABS

RELATED APPLICATION(S): NA

First Generic Product Received? YES ~~ON 800 MG~~

DRUG NAME: METAXALONE

DOSAGE FORM: TABLETS, 400 MG AND 800 MG
(NEW STRENGTH 800 MG)

Bio Assignments:

☒ BPH

☐ BCE

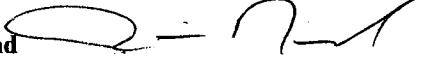
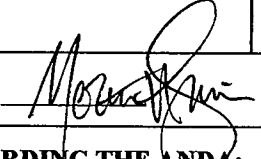
☐ BST

☐ Micro Review

Random Queue: 4

Chem Team Leader: Gill, Dave PM: Sarah Park Labeling Reviewer: Debbie Catterson

Letter Date: NOVEMBER 01, 2004		Received Date: NOVEMBER 04, 2004	
Comments: EC- 1+1=2 YES On Cards: YES			
Therapeutic Code: 2010100 MUSCLE RELAXANTS			
Archival Format: PAPER		Sections I (356H Sections per EDR Email)	
Review copy: YES		E-Media Disposition: YES SENT TO EDR	
Not applicable to electronic sections			
Field Copy Certification (Original Signature) YES			
Methods Validation Package (3 copies PAPER archive)		YES	
(Required for Non-USP drugs)			
Cover Letter YES		Table of Contents YES	
PART 3 Combination Product Category		N Not a Part3 Combo Product	
(Must be completed for ALL Original Applications)		Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Iain Margand 		Recommendation:	
Date 12/28/04		<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE to RECEIVE	
Supervisory Concurrence/Date: 		Date: 24 Dec 2004	
ADDITIONAL COMMENTS REGARDING THE ANDA:			
See T-con dated 12/9/04			
Top 200 Drug Product:			

Sec. I	Signed and Completed Application Form (356h) YES (Statement regarding Rx/OTC Status) RX YES	<input checked="" type="checkbox"/>
Sec. II	Basis for Submission NDA# : 13-217 Ref Listed Drug: SKELAXIN Firm: JONES PHARMA INC. ANDA suitability petition required? NO - NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	<input checked="" type="checkbox"/>
Sec. III	Patent Certification 1. Paragraph: IV 2. Expiration of Patent: 12-03-2021 A. Pediatric Exclusivity Submitted? N/A B. Pediatric Exclusivity Tracking System checked? Exclusivity Statement: YES	<input checked="" type="checkbox"/>
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use OK 2. Active ingredients OK 3. Route of administration OK 4. Dosage Form OK 5. Strength OK	<input checked="" type="checkbox"/>
Sec. V	Labeling (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y (800mg strength only) 2. 1 RLD label and 1 RLD container label see previous application for 400mg only 3. 1 side by side labeling comparison with all differences annotated and explained Previously submitted 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	<input checked="" type="checkbox"/>
Sec. VI	Bioavailability/Bioequivalence 1. Financial Certification (Form FDA 3454) and Disclosure Statement (Form 3455) YES 2. Request for Waiver of In-Vivo Study(ies): YES ON 400 MG 3. Formulation data same? (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) (b) (4) 4. Lot Numbers of Products used in BE Study(ies): RDW00469 (400mg) RDW00470 (800mg) 5. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	<input checked="" type="checkbox"/>
Study Type	IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) FASTING AND FED ON 800 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) Fast Fed b. EDR Email: Data Files Submitted: YES SENT TO EDR AUC _t 91.23 – 103.45 96.52 – 109.09 c. In-Vitro Dissolution: YES Pg. 25-32 AUC _∞ 91.02 – 103.16 94.23 – 105.31 Cmax 84.1 – 102.64 81.44 – 105.38	<input checked="" type="checkbox"/>

Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	<input type="checkbox"/>
Study Type	TRANSDERMAL DELIVERY SYSTEMS NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	<input type="checkbox"/>
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	<input type="checkbox"/>
Study Type	TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	<input type="checkbox"/>
Sec. VII	Components and Composition Statements 1. Unit composition and batch formulation Pg. 39 2. Inactive ingredients as appropriate Excipients are acceptable per IIG	<input checked="" type="checkbox"/>

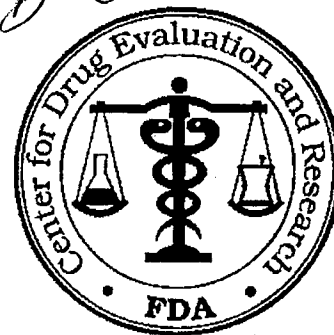
Sec. VIII	Raw Materials Controls 1. Active Ingredients a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfr(s) Y d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. Inactive Ingredients a. Source of inactive ingredients identified Pg. 128A b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	<input checked="" type="checkbox"/>
Sec. IX	Description of Manufacturing Facility 1. Full Address(es) of the Facility(ies) Pg. 199 2. CGMP Certification: YES 3. CFN numbers	<input checked="" type="checkbox"/>
Sec. X	Outside Firms Including Contract Testing Laboratories 1. Full Address Pg. 201 2. Functions Y 3. CGMP Certification/GLP Y 4. CFN numbers	<input checked="" type="checkbox"/>
Sec. XI	Manufacturing and Processing Instructions 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 400mg – (b) (4) 800mg – (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Filter validation (if aseptic fill) N/A 5. Reprocessing Statement Pg. 292	<input checked="" type="checkbox"/>
Sec. XII	In-Process Controls 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. In-process Controls - Specifications and data Y 400mg 800mg Ty: (b) (4) Ay: (b) (4) 100: (b) (4) 1000: (b) (4) Bulk: (b) (4)	<input checked="" type="checkbox"/>

Sec. XIII	Container 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes 100, (b) (4), 1000, Bulk 4. Container/Closure Testing Y 5. Source of supply and suppliers address Pg. 510	<input checked="" type="checkbox"/>
Sec. XIV	Controls for the Finished Dosage Form 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y	<input checked="" type="checkbox"/>
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted Y 2. Post Approval Commitments Y 3. Expiration Dating Period 2 Years 4. Stability Data Submitted a. 3 month accelerated stability data Y RDW00469 b. Batch numbers on stability records the same as the test batch Y RDW00470	<input checked="" type="checkbox"/>
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance Y 2. Finished Dosage Form Y 3. Same lot numbers Y	<input checked="" type="checkbox"/>
Sec. XVII	Environmental Impact Analysis Statement Pg. 920	<input checked="" type="checkbox"/>
Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) N/A 4. Field Copy Certification (original signature) YES	<input checked="" type="checkbox"/>

BIOEQUIVALENCY AMENDMENT

ANDA 40-445

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APPLICANT: Eon Labs, Inc.

TEL: 252-234-2212

ATTN: Dietrich Bartel

FAX: 252-234-2323

MAY 09 2005

FROM: Keri Suh *KS*

PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on November 1, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 400 mg and 800 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 40-445

APPLICANT: Eon Labs Inc.

DRUG PRODUCT: Metaxalone tablets; 400 mg and 800 mg

MAY 09 2005

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

(b) (4)



Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

July 21, 2005

Gary J. Buehler, RPh.
Director, HFD-600
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NHS

**- GENERAL CORRESPONDENCE -
CHANGE IN OWNERSHIP OF EON LABS, INC.**

**Re: Metaxalone Tablets, 400 mg and 800 mg
ANDA 40-445**

Dear Mr. Buehler:

Eon Labs, Inc. (Eon Labs), the holder and owner of the above-referenced ANDA, was recently acquired by Sandoz Inc. (Sandoz), 506 Carnegie Center, Suite 400, Princeton, NJ, 08540 in a corporate merger that closed on July 20th, 2005. Effective immediately, Eon will adopt the Sandoz name on all official correspondence to the agency and will begin operating under the Sandoz business structure.

In accordance with **21 CFR 314.72 (a)**, we are notifying you of the **CHANGE IN OWNERSHIP** of the corporation and are advising you that all rights, title and interest with regards to our approved and pending applications will be transferred to Sandoz. The corporate headquarters for the new Sandoz will remain at the 506 Carnegie Center, Princeton, NJ address provided above.

In the new Sandoz organization, Regulatory Affairs will be coordinated from four separate locations. Each location will have a fully functional Regulatory Affairs Department headed by a Director (or equivalent) that will have responsibilities for filing ANDAs, annual reports, supplements, FPL labeling, deficiency letter responses, etc. Because of this organizational structure, there will be multiple points of interface between the new Sandoz and the agency. All four sites will report into the corporate Vice President Regulatory Affairs, Ms. Sadie M. Ciganek.

The Regulatory Affairs contact person for each site is provided below. This information will help facilitate future communication between the agency and the new Sandoz:

- 1) Sandoz (New York)
227-15 North Conduit Avenue,
Laurelton NY 11413

Ms. Enna Krivitsky
Ph: (718) 276-8607 x235
Fax: (718) 276-8635

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AUG 01 2005

OGD / ODER

2). Sandoz (North Carolina)
4700 Eon Labs Drive
Wilson, NC 27893

Mr. Dietrich Bartel
Ph: (252) 234-2212
Fax: (252) 234-2323

3). Sandoz (Colorado)
2555 W Midway Blvd
Broomfield, CO 80020

Ms. Beth Brannon
Ph: (303) 438-4237
fax: (303) 438-4600

4). Sandoz (New Jersey)
2400 Route 130 North
Dayton, NJ 08810

Ms. Carmelle Lucas
Ph: (732) 355-4083
Fax: (732) 355-4828

This is the next phase in the history of Eon Labs. We are looking forward to the coming challenges and intend to provide the agency with the same responsive interaction that was shared in the past. If you require additional information regarding the merger, feel free to call. I can be reached at (516) 478-9713.

Sincerely,
Sadie M. Ciganek

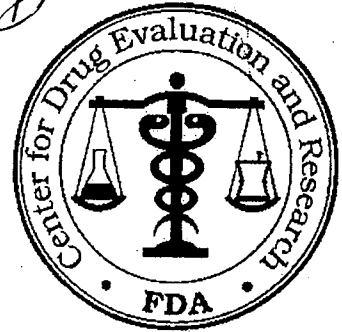
Sadie M. Ciganek for
Vice President Regulatory Affairs
Sandoz Inc.

MINOR AMENDMENT

ANDA 40-445

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

DEC 05 2005
DEC 05 2005



APPLICANT: Sandoz Inc.

TEL: 252-234-2212

ATTN: Dietrich Bartel

FAX: 252-234-2323

FROM: Thuyanh (Ann) Vu

PROJECT MANAGER: (301) 827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 400 and 800 mg.

Reference is also made to your amendments dated May 10, November 1, and December 15, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

See CMC comments enclosed.

RA 12/2/05

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-445 APPLICANT: Sandoz, Inc.





DRUG PRODUCT: Metaxalone Tablets, 400 mg and 800 mg

The deficiencies below represent MINOR deficiencies.

DEC 05 2005

A. Deficiencies:

DEC 05 2005

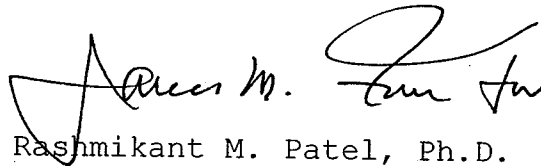
1. Please establish both the (b) (4)

Please provide an updated (b) (4)
2. (b) (4)
 Please reconcile these differences.
3. Please revise the (b) (4)

for the drug product.
4. (b) (4)

data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.
2. Your Labeling information is pending review. Deficiencies, if any, will be communicated to you separately.

3. Bioequivalence deficiencies were communicated to you via facsimile on May 9, 2005. You should address the issues in the May 9 communication prior to or concurrent with your response to this communication.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Rashmikant M. Patel". The signature is fluid and cursive, with a large initial 'R' and a stylized 'P'.

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research



old 400mg strength
only out of 40-445
request 21 CFR 314.65
SD

September 6, 2006

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

**WITHDRAWAL LETTER-
400 MG STRENGTH**

N/NC

**RE: ANDA 40-445
Metaxalone Tablets, 400 mg and 800 mg**

Dear Mr. Buehler:

Reference is made to our unapproved Abbreviated New Drug Application, ANDA 40-445, for Metaxalone Tablets, 400 mg and 800 mg, filed on August 31, 2001. We also refer to Amendments dated May 10, November 1 and December 15, 2004, and FDA's deficiency letters dated March 6, 2003 and May 10, 2005, which addressed the bioequivalence of the 400 mg formulation and (b) (4)

As a result of the FDA's determinations with regard to the 400 mg strength of the drug product only, we hereby request, under 21 CFR 314.65, that the 400 mg strength be withdrawn from the ANDA. This withdrawal is without prejudice to refilling.

We certify that an identical copy of this submission is also being filed to the FDA Atlanta District Office, 60 Eighth St. NE, Atlanta, GA 30309.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Sincerely,

Dietrich Bartel
Director, Regulatory Affairs,
Sandoz Inc.

RECEIVED

SEP 07 2006

OGD / ODER



DEPARTMENT OF HEALTH & HUMAN SERVICES

DW
Food and Drug Administration
Rockville, MD 20857

ANDA 40-445

Sandoz Inc.
Attention: Dietrich Bartel
4700 Sandoz Drive
Wilson, NC 27893

SEP 20 2006

Dear Sir:

We acknowledge the receipt of your communication dated September 6, 2006, requesting withdrawal of your abbreviated new drug application for Metaxalone Tablets, 400 mg.

In compliance with your request and in accordance with Section 314.65 of the regulations under the Federal Food, Drug and Cosmetic Act, the application is regarded as withdrawn. This withdrawal does not prejudice any future filing of the application. You may request that the information in this application be considered in connection with any resubmission.

Sincerely yours,

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-445
Division File
HFD-650/Bio PM
HFD-143
Field Copy
HFD-610/PRickman

Endorsements:

HFD-617/L.Matheny/
HFD-623/D.Gill/
HFD-617/T. Ames, Acting Chief, RSB/

Prepared By Susan E. Pellock

F/T by

V:\FIRMSNZ\Sandoz\LTRS&REV\40445.wd400mg.doc

Withdrawal of Unapproved Application!



October 19, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

Phone: 609.627.8728
Fax: 609.627.8673
Email: sadie.ciganek@sandoz.com

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

N/XP

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

Dear Mr. Buehler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED

OCT 20 2006
OGD / CDER

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
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Sadie Ciganek
Vice President, Regulatory Affairs

October 23, 2006

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

WXP

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

Dear Mr. Beuhler;

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Sincerely,

Sadie M. Ciganek

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

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OCT 24 2006
OGD / CDER

Sandoz

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October 24, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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N/XP

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

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OCT 25 2006
OGD / ODER

Sandoz

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October 25, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

N/XP

- PATENT AMENDMENT -

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
OCT 26 2006
OGD/ODER

Sandoz

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October 26, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

Phone: 609.627.8728
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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/KP

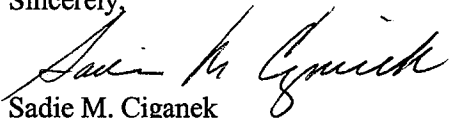
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ANDA 40-445**

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Sincerely,



Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
OCT 27 2006
OGD / CDER

Sandoz

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October 27, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
w/xp

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
OCT 30 2006
CGD / CDER

Sandoz

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Princeton, NJ 08540
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October 30, 2006

Sadie Ciganek
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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

- PATENT AMENDMENT -

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ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
OCT 31 2006
CGD / CDEF

Sandoz

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October 31, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Email: sadie.ciganek@sandoz.com

Mr. Gary Buchler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/xp

- PATENT AMENDMENT -

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ANDA 40-445

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 01 2006
OGD / CDER

Sandoz

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a Novartis company



November 1, 2006

Sadie Ciganek
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Mr. Gary Buehler, Director
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Metropark North II
7500 Standish Place
Rockville, MD 20855

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NOV 02 2006

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ORIG AMENDMENT

N/XP

- PATENT AMENDMENT -

Re: Metaxalone Tablets, 800 mg
ANDA 40-445

Dear Mr. Buehler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

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Sadie Ciganek
Vice President, Regulatory Affairs

November 2, 2006

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ORIG AMENDMENT
n/xp

Mr. Gary Buchler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
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Rockville, MD 20855

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NOV 08 2006
CDER/OTIA

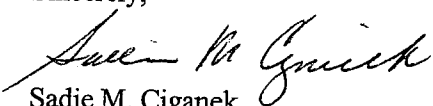
- PATENT AMENDMENT -

Re: **Metaxalone Tablets, 800 mg**
ANDA 40-445

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Sincerely,


Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

Sandoz

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Princeton, NJ 08540
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November 3, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

N/MC

- PATENT AMENDMENT -

Re: Metaxalone Tablets, 800 mg
ANDA 40-445

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NOV 06 2006

0207/06/06

Dear Mr. Beuhler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

Sandoz

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November 6, 2006

Sadie Ciganek
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Email: sadie.ciganek@sandoz.com

ORIG AMENDMENT

N/XP

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

RECEIVED

NOV 07 2006

003 / 0118

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

Dear Mr. Beuhler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

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November 7, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

- PATENT AMENDMENT -

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ANDA 40-445**

Dear Mr. Beuhler;

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED

NOV 08 2006

OGD / CDER

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November 8, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

- PATENT AMENDMENT -

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ANDA 40-445**

Dear Mr. Beuhler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

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NOV 09 2006

OGD / CDER

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
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November 9, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/XP

- PATENT AMENDMENT -

Re: Metaxalone Tablets, 800 mg
ANDA 40-445

Dear Mr. Beuhler;

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED

NOV 13 2006

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Sandoz

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November 13, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

n/xp

- PATENT AMENDMENT -

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ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 14 2006
OGD / CDER

Sandoz

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Princeton, NJ 08540
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November 14, 2006

ORIGINAL

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDME

N/RP

- PATENT AMENDMENT -

Re: Metaxalone Tablets, 800 mg
ANDA 40-445

Dear Mr. Beuhler;

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 15 2006
OGD / CDER

Sandoz

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November 15, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

- PATENT AMENDMENT -

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ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

Sandoz

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www.us.sandoz.com

RECEIVED
NOV 16 2006
OGD / CDER



Sadie Ciganek
Vice President, Regulatory Affairs

November 16, 2006

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ORIGINAL

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/XP

- PATENT AMENDMENT -

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ANDA 40-445

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Sincerely,

Sadie M. Ciganek
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Sandoz, Inc.

Sandoz

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www.us.sandoz.com

RECEIVED
NOV 17 2006
OGD / CDER

a Novartis company



November 17, 2006

ORIGINAL

Sadie Ciganek
Vice President, Regulatory Affairs

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Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
n/xp

- PATENT AMENDMENT -

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ANDA 40-445**

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 20 2006
OGD / CDER

Sandoz

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SANDOZ

November 20, 2006

ORIGINAL

Sadie Ciganek

Vice President, Regulatory Affairs

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Email: sadie.ciganek@sandoz.com

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

W/xp

- PATENT AMENDMENT -

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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

**RECEIVED
NOV 21 2006
OGD / CDER**

Sandoz

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www.us.sandoz.com



November 21, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

Phone: 609.627.8728
Fax: 609.627.8673
Email: sadie.ciganek@sandoz.com

Mr. Gary Buehler, Director
The Food and Drug Administration
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Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 22 2006
OGD / CDER

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
www.us.sandoz.com



November 22, 2006

Sadie Ciganek
Vice President, Regulatory Affairs

Phone: 609.627.8728
Fax: 609.627.8673
Email: sadie.ciganek@sandoz.com

Mr. Gary Buehler, Director
The Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
Metropark North II
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT

N/XP

- PATENT AMENDMENT -

**Re: Metaxalone Tablets, 800 mg
ANDA 40-445**

Dear Mr. Beuhler;

Submitted herein is a Patent Amendment for Metaxalone Tablets, 800 mg, **ANDA 40-445**. This amendment provides for certification to a newly listed patent for the base molecule.

Sincerely,

Sadie M. Ciganek
Vice President Regulatory Affairs
Sandoz, Inc.

RECEIVED
NOV 24 2006
OGD / CDER

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
www.us.sandoz.com



February 2, 2007

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

MINOR AMENDMENT

ORIG AMENDMENT

N/A

**RE: MINOR AMENDMENT - ANDA 40-445
Metaxalone Tablets, 800 mg**

Dear Mr. Buehler:

In accordance with 21 CFR 314.120, this submission constitutes a Minor Amendment to ANDA 40-445, Metaxalone Tablets, 800 mg. It is being filed in response to a deficiency letter from Rashmikan M. Patel, Ph. D. of the Division of Chemistry I, OGD, to Sandoz Inc. on December 5, 2005 and contains our responses to the deficiencies outlined in that letter.

Please note that, in accordance with 21 CFR 314.65, Sandoz submitted a withdrawal letter to the Agency on September 6, 2006, withdrawing the 400 mg strength of the drug product. Our responses to the OGD's deficiency comments therefore only address the 800 mg strength.

In the following pages, each of the deficiencies is reiterated, in bold type, followed by our response.

A. Deficiencies:

- ✓ 1. **Please establish both the**

(b) (4)

an updated

Please provide

(b) (4)

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FEB 05 2007

Sandoz Inc.

4700 Sandoz Drive OGD / CDER Wilson, NC 27893

Following this page, 2 pages withheld in full - (b)(4)

ANDA # 40-445
Metaxalone Tablets, 800 mg

- a dissolution profile report comparing the new batch, (L)RDW00891, to the original 800 mg bio-batch, (L)RDW00470 (previously submitted).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.

Response:

The following stability data is being provided on the new test batch in each of the smallest and largest bottle sizes:

- accelerated stability test data to three months.
- controlled room temperature stability test data to six months.

See Attachment #5.

2. Your labeling information is pending review. Deficiencies, if any, will be communicated to you separately.

Response:

We acknowledge that the labeling is still under review and that we will be notified under separate cover of any deficiencies.

3. Bioequivalence deficiencies were communicated to you via facsimile on May 9, 2005. You should address the issues in the May 9 communication prior to or concurrent with your response to this communication.

Response:

We note and acknowledge that bioequivalence deficiencies were communicated via facsimile on May 9, 2005. However, the deficiencies in the letter pertained to the 400 mg strength of the drug product, which has now been withdrawn (reference the withdrawal letter dated Sept. 6, 2006). We consider the deficiency letter moot but will concurrently file a formal Bioequivalence Amendment to close the file.

ANDA # 40-445
Metaxalone Tablets, 400 mg and 800 mg

We certify that an identical copy of this MINOR AMENDMENT is also being filed to the FDA Atlanta District Office, 60 Eighth St. NE, Atlanta, GA 30309.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Sincerely,

A handwritten signature in cursive script, appearing to read "Dietrich Bartel".

Dietrich Bartel
Director, Regulatory Affairs
Sandoz Inc.



December 10, 2007

Mr. Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD. 20855-2793

**ANDA CORRESPONDENCE –
REQUEST FOR MEETING**

N/MC

Re: ANDA 40-445: Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

We are writing with regard to our pending ANDA 40-445 for Metaxalone Tablets, 800 mg. For the reasons discussed below, we request a meeting with you and other appropriate Agency staff to discuss the status of this long pending application.

By way of brief background, Sandoz Inc. (then known in relevant part as Eon Labs, Inc.) submitted its ANDA for Metaxalone Tablets, 400 mg on August 31, 2001. The FDA notified Sandoz on November 30, 2001 that the ANDA had been accepted for review. On November 1, 2004, Sandoz amended the ANDA to include an 800 mg strength, including a new bioequivalence study to support approval of this strength. On September 6, 2006, Sandoz amended the ANDA to withdraw the 400 mg strength.

In a recent telephone discussion with your staff, Sandoz was informed that the Agency will not review Sandoz Inc.'s bioequivalency study until after a decision is made on several pending citizen petitions. To the best of our knowledge, the pending petitions include the following:

- Citizen petition submitted on behalf of Sandoz, January 28, 2003, Docket No. 03P-0027
- Citizen petition and accompanying petition for stay of action submitted on behalf of King Pharmaceuticals, Inc., the sponsor of the RLD, Skelaxin®, March 18, 2004, Docket No. 2004P-0140
- Citizen petition submitted on behalf of Mutual Pharmaceutical Co., July 27, 2007, Docket No. 2007P-0296

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DEC 11 2007

Metaxalone Tablets, 800 mg
ANDA # 40-445

In one way or another, these petitions are all related to the food effect of administration of Metaxalone Tablets.

Sandoz believes that the Agency's apparent refusal to proceed with review of our bioequivalency study until after a decision is made on these pending citizen petitions violates both the spirit and the letter of new Section 505(q) of the FDC Act, as added by the Food and Drug Administration Amendments Act of 2007. Section 505(q) prohibits FDA from delaying the approval of a pending ANDA because of a citizen petition unless FDA concludes that a delay is "necessary to protect the public health." If FDA determines that a delay in ANDA approval is necessary, FDA is required to notify the applicant within 30 days and provide, among other information, a brief summary of the specific substantive issues raised in the petition that form the basis of the Agency's determination. There was no effective date or transitional provision for new Section 505(q) of the FDC Act; therefore, our lawyers have advised us that the new requirements are already in effect and apply to all pending petitions, such as the three pending Metaxalone petitions.

Sandoz seeks a meeting with you and other appropriate Agency representatives to discuss this important matter. We will contact your office in the near future to schedule a meeting at a mutually convenient time.

We appreciate your attention to this important matter. If the Agency has questions about this matter, please contact me at the office at (609) 627-8882 or on my mobile phone at (516) 304-8780.

Respectfully submitted,



for Kalpana Rao Vanam
Vice President, Regulatory Affairs



January 26, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

N/AF

LABELING AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, this submission constitutes a labeling amendment to ANDA 40-445, Metaxalone Tablets, 800 mg. It is being filed in response to a telephone conversation between Rita Hassal of the OGD, CDER and Sandoz Inc. on January 17, 2008. As requested Sandoz labeling is being updated to the current reference listed drug (SKELAXIN, dated Aug. 2006) posted on the CDER website Drugs@FDA.

All labeling was originally submitted in the Eon Labs format. The labeling (package outsert and bottle labels) is being resubmitted in the current Sandoz (formerly Eon Labs) format.

Please note that, in accordance with 21 CFR 314.65, Sandoz submitted a withdrawal letter to the Agency on September 6, 2006, withdrawing the 400 mg strength of the drug product. The labeling submitted only address the 800 mg strength.

Per the *Guidance for Industry: Providing Regulatory Submission in Electronic Format*; the draft labeling and annotated changes are being submitted in Adobe Acrobat (*.pdf) format on the enclosed CD. In addition, the labeling content is provided in MS Word (.doc), as well as SPL (.xml), formats.

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JAN 29 2008

Metaxalone Tablets, 800 mg
ANDA #40-445

Side-by-Side comparisons, annotations, and DeltaView (DV) comparisons are also provided. The CD contains the following folders and files:

Folder: Package Outsert

Files: - Comparison.pdf
- OS7750 Issued 01-08 Content.doc
- OS7750 Issued 01-08 Mac Draft.pdf

Folder: spl

Files: metaxalone-metaxaloneos7750Issued01-08.xml
metaxalone-01.jpg
metaxalone-02.jpg

Folder: Container Labels

Files: - Container Label Annotations.pdf
- Container Label SbS.pdf
- L8917 Iss. 01-08 800 mg x 100.ai.pdf
- L8931 Iss. 01-08 800 mg x 1000.ai.pdf

A Letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212 or by facsimile at (252) 234-2323.

Sincerely,

Sandoz Inc.



E. Jean Herald
Regulatory Affairs Associate

JONES DAY

222 EAST 41ST STREET • NEW YORK, NEW YORK 10017-6702

TELEPHONE: 212-326-3939 • FACSIMILE: 212-755-7306

Direct Number: (212) 326-3413
fdcerrito@jonesday.com

February 27, 2008

N-000-XP

Gary J. Buehler, RPh.
Office of Generic Drugs (HFD-600)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Abbreviated New Drug Application No. 40-445 for 800 mg Metaxalone Tablets

Dear Sir or Madam:

We write on behalf of King Pharmaceuticals, Inc. and King Pharmaceuticals Research and Development, Inc. (collectively, "King"). We write to inform the FDA that the 30-month stay of FDA approval of the above-identified ANDA 40-455 expires on August 23, 2009.

Eon Labs, Inc. ("Eon") is the holder of ANDA 40-455. That ANDA seeks approval for a generic version of King's 800 mg SKELAXIN® tablets prior to the expiration of two patents listed in the Orange Book for SKELAXIN®. On November 3, 2004, Eon provided King with notification of its Paragraph IV Certification. On December 17, 2004, King brought suit in the United States District Court for the Eastern District of New York, Case No. 04-CV-5540. Pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), the filing of that Complaint triggered a 30-month stay of FDA approval of Eon's supplemental ANDA.

At Eon's request, the parties agreed to stay the above-referenced Civil Action Case No. 04-CV-5540 and toll the 30-month stay. On January 10, 2005, the Court entered an order staying the action and tolling the 30-month stay. *See* January 10, 2005 Order, attached hereto as Exhibit 1. The stay of the action and the tolling of the 30-month stay was subsequently lifted as of April 30, 2007. *See* May 2, 2007 Order, attached hereto as Exhibit 2. Thus, the 30-month stay of approval of Eon's ANDA No. 40-455 was tolled for 27 month and 20 days.

Under 21 U.S.C. § 355(j)(4)(B)(iii) and 21 C.F.R. § 314.107(b)(3), based on the filing of this action, Eon's ANDA No. 40-445 may not be made effective until at least August 23, 2009

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FEB 28 2008

OGD

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ATLANTA • BEIJING • BRUSSELS • CHICAGO • CLEVELAND • COLUMBUS • DALLAS • FRANKFURT • HONG KONG • HOUSTON
IRVINE • LONDON • LOS ANGELES • MADRID • MILAN • MOSCOW • MUNICH • NEW DELHI • NEW YORK • PARIS • PITTSBURGH
SAN DIEGO • SAN FRANCISCO • SHANGHAI • SILICON VALLEY • SINGAPORE • SYDNEY • TAIPEI • TOKYO • WASHINGTON

Office of Generic Drugs (HFD-600)
February 27, 2008
Page 2

(i.e., 30 months from November 3, 2004, taking into account the tolled period of January 10, 2005 to April 30, 2007.)

Very truly yours,

A handwritten signature in black ink, appearing to read 'F. Cerrito', is written over a horizontal line.

F. Dominic Cerrito
JONES DAY
Counsel for King Pharmaceuticals, Inc. and
King Pharmaceuticals Research &
Development, Inc.

Enclosures

Record of t-con between Sandoz and FDA
Office of Generic Drugs
Division of Chemistry 1
Team 3

FROM: Liang-Lii Huang, Ph.D.

DATE: June 27, 2008

ANDA: 40-445

NAME/TITLE OF INDIVIDUAL from FDA: Liang-Lii Huang, Ph.D.
Review Chemist

FIRM: Sandoz

NAME/TITLE OF INDIVIDUAL from the firm: Griha Mangru, Reg. Affair

PRODUCT NAME:

ANDA: 40-445

Mataxalone tablets 800 mg

TEL #: 252-234-2206

Record of t-con of 6/27/08

FDA initiated this t-con

Effective 7/1/08, all ANDAs applicants have to demonstrate that their drug products are in compliance with USP<467> residual solvents for the drug products.

- (1) I called Sandoz to tell them that if their ANDAs are not approved prior to July 1, 2008, they will need to submit a telephone amendment to address the new USP <467> issue.
- (2) I told them that their DP release specifications should be revised to include "Residual Solvents" with an acceptance criterion as "Complies with USP <467>". I also told Sandoz that information and test data are necessary to fulfill this requirement.
- (3) I told Sandoz that they may refer to OGD website at

[http://www.fda.gov/cder/ogd/Residual Solvents.pdf](http://www.fda.gov/cder/ogd/ResidualSolvents.pdf).

Also, I told Sandoz that if their ANDAs are approved prior to July 1, 2008, they may provide this information in their first Annual Report(s).

SIGNATURE OF OGD REPRESENTATIVES:
Liang-Lii Huang, Ph.D., Review chemist

Location of Electronic Copy:

V:\Chemistry Division I\Team 3\T-CONS\40-445 6-27-08 TCON.doc

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

/s/

Liang Lii Huang
7/17/2008 04:08:35 PM
CHEMIST



August 29, 2008

ORIG AMENDMENT

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N-~~000~~-AA

TELEPHONE AMENDMENT

Re: ANDA 40-445

Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.120, this submission constitutes a Telephone Amendment to our Abbreviated New Drug Application 40-445, Metaxalone Tablets, 800 mg. It is being filed in response to a telephone communication from Dr. Liang-Lii Huang, OGD, CDER, FDA to Sandoz Inc. on June 27, 2008. The communication provided deficiency comments and specified that the response should be categorized as a Telephone Amendment.

The deficiency comments are reiterated below (**in bold type**), followed by our response.

Deficiency:

Please submit the residual solvents data for Metaxalone Tablets, 800 mg in accordance with the revised USP General Chapter <467>, which becomes official on July 1, 2008. We request that you demonstrate that the levels of residual solvents in your drug product are within the safety recommendations of this USP General Chapter.

Response:

To ensure the compliance of Metaxalone Tablets, 800 mg, to the guidelines set forth in the USP General Chapter <467>, the product was evaluated to meet the criteria stated in the FDA announcement, which are reiterated below:

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SEP 02 2008

ANDA # 40-445
Metaxalone Tablets, 800 mg

- Ensure that all drug substance and excipient components of the drug product, have residual solvent acceptance limits that fall within the ICH Q3C (option 1) limit (this approach requires that the total daily dose of the drug product be less than 10 g/day), or
- Ensure that all drug substance and excipient components of the drug product, weighted by their amount in the drug product, results in a cumulative daily exposure for residual solvents that falls within the ICH Q3C (option 2) limit, or
- Ensure via direct testing of the drug product, that the total daily exposure for the residual solvents falls with the ICH Q3C (option 2) limit (direct testing for residual solvents in the drug product (or via applicable in-process tests) should be employed for those solvents used in the manufacturing process of the drug product).

The evaluation of Metaxalone Tablets, 800 mg, for residual solvents content concludes that the product is within the safety recommendations and meets the criteria for compliance. This conclusion was derived from both the information gathered from each of the excipient suppliers, and the knowledge that the drug product (b) (4)

Based on the information obtained from each of the excipient suppliers, (b) (4)

Additionally, the statement received from the manufacturer (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

Following this page, 1 page withheld in full - (b)(4)

ANDA # 40-445
Metaxalone Tablets, 800 mg

USP acceptance criteria, [REDACTED]

(b) (4)

(D) (4)

published in USP.

(b) (4)

specification sheet has been included in **ATTACHMENT-C**.

ATTACHMENT-C:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.

(b) (4)

Furthermore, Sandoz makes the commitment to re-assess this product's compliance with USP <467> if there is a change to ingredient suppliers for the products in the post approval period, including revision controls, if appropriate.

A Letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Best Regards,



Ellen Camos
Regulatory Affairs Associate III
Sandoz, Inc.



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 5, 2008

ORIG AMENDMENT
w/xp

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 800 mg; ANDA 40-445

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent certification. We are revising our Patent Certification to include a Paragraph IV Certification for U.S. Patent Numbers 6,407,128, 6,683,102, 7,122,566 and 7,378,434. In support of this revision, a revised signed Patent Certification is provided in **Attachment 1**.

In accordance with 21 CFR 314.95(b), we certify that we have provided Patent Certification Notice to the patent holder and to the holder of the approved NDA application (as defined in 21 CFR 314.95(a)), for the reference listed drug, SKELAXIN® Tablets, and that the notice has met the content requirements under 21 CFR 314.95(c). A copy of the notice is provided in **Attachment 2**.

RECEIVED

NOV 05 2008

OGD

ANDA 40-445
Metaxalone Tablets, 800 mg

The notice has been sent to the following 6 recipients:

Brian Markison, President & CEO King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124
Chief Legal Officer King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer UBS AG, Stamford Branch 677 Washington Blvd Stamford, CT 06901
Richard Roberts, MD, Ph.D. Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124	Chief Legal Officer UBS AG, Stamford Branch c/o Latham & Watkins LLP 650 Town Center Dr., 20th Floor Costa Mesa, CA 92626

This submission is submitted for your review and approval.

A letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.



Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 6, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

w/xp

PATENT AMENDMENT

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OGD

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Metaxalone Tablets, 800 mg

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Yours truly,

Sandoz Inc.

Dietrich Bartel BSS

Dietrich Bartel,
Director, Regulatory Affairs



November 07, 2008

NXP

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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Metaxalone Tablets, 800 mg

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RECEIVED

NOV 07 2008

OGD

ANDA 40-445
Metaxalone Tablets, 800 mg

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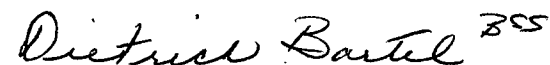
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Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 10, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

n/xp

PATENT AMENDMENT

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NOV 10 2008

ANDA 40-445
Metaxalone Tablets, 800 mg

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If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 12, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/xp

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 800 mg; ANDA 40-445

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent certification. We are revising our Patent Certification to include a Paragraph IV Certification for U.S. Patent Numbers 6,407,128, 6,683,102, 7,122,566 and 7,378,434. In support of this revision, a revised signed Patent Certification is provided in **Attachment 1**.

In accordance with 21 CFR 314.95(b), we certify that we have provided Patent Certification Notice to the patent holder and to the holder of the approved NDA application (as defined in 21 CFR 314.95(a)), for the reference listed drug, SKELAXIN® Tablets, and that the notice has met the content requirements under 21 CFR 314.95(c). A copy of the notice is provided in **Attachment 2**.

ANDA 40-445
Metaxalone Tablets, 800 mg

The notice has been sent to the following 6 recipients:

Brian Markison, President & CEO King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124
Chief Legal Officer King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer UBS AG, Stamford Branch 677 Washington Blvd Stamford, CT 06901
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Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 13, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N-000-XP

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RECEIVED

NOV 13 2008

OGD

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Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton

12/1/08

November 14, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

w/xp

PATENT AMENDMENT

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RECEIVED

NOV 14 2008

OGD

ANDA 40-445
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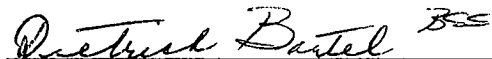
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Sandoz Inc.



Dietrich Bartel,
Director, Regulatory Affairs



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Patents '566 and '434 are not listed in the
OB or dockets S. Middleton 11/20/08

November 17, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

al/xp

PATENT AMENDMENT

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RECEIVED

NOV 17 2008

OGD

ANDA 40-445
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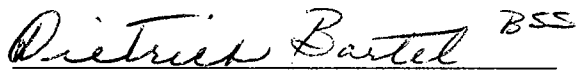
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Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs

Multiple PIV certs to 102, 1566 + 1434.

RGrange
12/12/08



November 18, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

W/XP

PATENT AMENDMENT

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RECEIVED

NOV 18 2008

DED

ANDA 40-445
Metaxalone Tablets, 800 mg

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Yours truly,

Sandoz Inc.

 ^{BSS}

Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patents '566 and '434 are not listed in the
OB or dockets S. Middleton

24.1
12/1/08

November 19, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

N/XP

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REC'D

NOV 19 2008

000

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Dietrich Bartel,
Director, Regulatory Affairs



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OB or dockets S. Middleton

12/1/08

November 20, 2008

XP

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT AMENDMENT

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NOV 20 2008

ODD

ANDA 40-445
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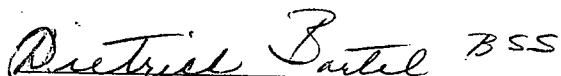
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Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



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OB or dockets S. Middleton

12/1/08

November 21, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

XP

RECEIVED

NOV 21 2008

OGD

PATENT AMENDMENT

RE: ANDA 40-445
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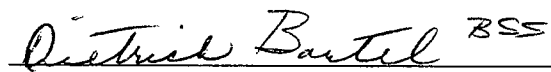
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Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton

12/3/08

November 24, 2008

JP

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

OGD

NOV 24 2008

RECEIVED

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

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Yours truly,

Sandoz Inc.

Dietrich Bartel BSS
Dietrich Bartel,
Director, Regulatory Affairs

RECEIVED

NOV 24 2008

OGD



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton 12/8/08

November 25, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

RECEIVED

NOV 25 2008

OGD

NXP

PATENT AMENDMENT

RE: **ANDA 40-445**
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

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Sandoz Inc.

Dietrich Bartel BSS
Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton

12/8/08

November 26, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

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Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 800 mg; ANDA 40-445

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent certification. We are revising our Patent Certification to include a Paragraph IV Certification for U.S. Patent Numbers 6,407,128, 6,683,102, 7,122,566 and 7,378,434. In support of this revision, a revised signed Patent Certification is provided in **Attachment 1**.

In accordance with 21 CFR 314.95(b), we certify that we have provided Patent Certification Notice to the patent holder and to the holder of the approved NDA application (as defined in 21 CFR 314.95(a)), for the reference listed drug, SKELAXIN® Tablets, and that the notice has met the content requirements under 21 CFR 314.95(c). A copy of the notice is provided in **Attachment 2**.

RECEIVED

NOV 26 2008

OGD

ANDA 40-445
Metaxalone Tablets, 800 mg

The notice has been sent to the following 6 recipients:

Brian Markison, President & CEO King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124
Chief Legal Officer King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer UBS AG, Stamford Branch 677 Washington Blvd Stamford, CT 06901
Richard Roberts, MD, Ph.D. Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124	Chief Legal Officer UBS AG, Stamford Branch c/o Latham & Watkins LLP 650 Town Center Dr., 20th Floor Costa Mesa, CA 92626

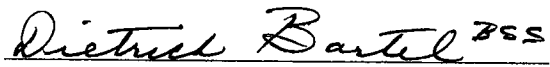
This submission is submitted for your review and approval.

A letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton

12/8/08

November 28, 2008

N-000-XP

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED

NOV 28 2008

OGD

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

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Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton 12/15/08

ORIG AMENDMENT

December 1, 2008

N-000-XP

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED

DEC 01 2008

OGD

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

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ANDA 40-445
Metaxalone Tablets, 800 mg

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If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton 12/15/08

December 2, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

W/XP

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

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RECEIVED

DEC 02 2008

OGD

ANDA 40-445
Metaxalone Tablets, 800 mg

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Brian Markison, President & CEO King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124
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This submission is submitted for your review and approval.

A letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton 12/15/08

December 3, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT

N/XP

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

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RECEIVED

DEC 03 2008

OGD

ANDA 40-445
Metaxalone Tablets, 800 mg

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Brian Markison, President & CEO King Pharmaceuticals, Inc. 501 Fifth St. Bristol, TN 37620	Chief Legal Officer Mutual Pharmaceutical Company, Inc. 1100 Orthodox St. Philadelphia, PA 19124
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This submission is submitted for your review and approval.

A letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.

 ^{BSS}
Dietrich Bartel,
Director, Regulatory Affairs



NAI PIV to '102, '128, '566 and '434.
Patent '434 is not listed in the OB or
dockets S. Middleton 12/15/08

December 4, 2008

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
R/XP

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 800 mg; ANDA 40-445

In accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act, Sandoz wishes to amend its application by providing a revised Patent certification. We are revising our Patent Certification to include a Paragraph IV Certification for U.S. Patent Numbers 6,407,128, 6,683,102, 7,122,566 and 7,378,434. In support of this revision, a revised signed Patent Certification is provided in **Attachment 1**.

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RECEIVED

DEC 04 2008

OGD

ANDA 40-445
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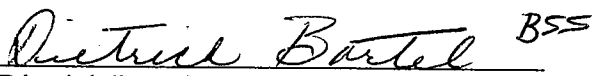
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If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.


Dietrich Bartel,
Director, Regulatory Affairs



June 26, 2009

Notice of dismissal on
CA# 04-5440 finding '128 +
'102 patents are invalid.

[Signature]

ORIG AMENDMENT

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

N/XP

PATENT AMENDMENT

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Metaxalone Tablets, 800 mg; ANDA 40-445.

With regard to our ANDA No. 40-445 ("Sandoz ANDA") for an 800 mg strength generic Metaxalone Tablets, please be advised that on June 4, 2009, final judgment was entered in our favor that all claims of Orange Book-listed U.S. Patents Nos. 6,407,128 and 6,683,102 ("the patents") are invalid. As such, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii)(I)(aa) and 21 C.F.R. § 314.107(b)(3)(B)(ii), there is no longer an automatic (30-month) stay of approval as to Sandoz's ANDA.

More specifically, on November 3, 2004, Sandoz's predecessor-in-interest in the Sandoz ANDA, Eon Labs, Inc. ("Eon"),* sent Paragraph IV certification notices to the required recipients concerning the patents. The notice was received by the last entity to receive same on November 9, 2004. 21 U.S.C. § 355(j)(2)(B). Copies of the certified mail return receipts confirming receipt of the notices by the required recipients are **Attachment A**.

RECEIVED

JUN 29 2009

* The subject ANDA was previously owned by Eon Labs, Inc. A July 21, 2005 letter to FDA confirmed change in ownership from Eon Labs, Inc. to Sandoz Inc.

ANDA 40-445
Metaxalone Tablets, 800 mg

The owner of the patents sued Eon for infringement of the patents on December 17, 2004, *i.e.*, within 45 days of November 9, 2004. A copy of the complaint filed against Eon, without exhibits, is **Attachment B**. 21 U.S.C. § 355(j)(5)(B)(iii).

On January 20, 2009, the Court held that all of the claims of the patents are invalid, *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 593 F. Supp.2d 501, 515 (E.D.N.Y. 2009) (**Attachment C**) and on June 4, 2009 the Court entered judgment on the above holding (**Attachment D**).

Therefore, as mentioned above, there is no longer an automatic stay of approval as to our ANDA. As previously advised, there is a second case pending against Sandoz regarding this product, which was filed on December 5, 2008 in the District of New Jersey (docket no. 08-5974), asserting U.S. Patent No. 7,122,566 in response to Sandoz's Paragraph IV notice letter. As this patent issued and became Orange Book-listed well after Sandoz's ANDA had been filed, this case does not impinge on the automatic stay.

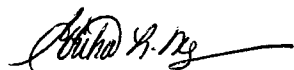
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If there are any questions concerning this amendment, please contact Mr. Dietrich Bartel, B.S., Director, Regulatory Affairs, by telephone at (252) 234-2212.

Yours truly,

Sandoz Inc.



Griha L. Mangru, M.S.
Manager, Regulatory Affairs



Joseph Carrado
Vice President
Regulatory Affairs

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893

Phone: (252) 234-2222

Fax: (252) 234-2323

ORIG-1
SD-70

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**AMENDMENT - Labeling
REQUEST FOR FINAL APPROVAL**

November 23, 2009

**RE: ANDA 40-445 Metaxolone Tablets, 800 mg
Labeling Amendment and Request for Final Approval**

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application dated August 31, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Metaxalone Tablets, 800 mg, ANDA 40-445. This letter is a follow-up to several telephone discussions between Sandoz representatives and your staff.

LABELING AMENDMENT

In an October 10, 2009 discussion, Sandoz informed Mr. Robert West that the pending ANDA is not based on a proposed labeling "carve out," and that Sandoz would be submitting revised proposed labeling and a request for final approval. This letter provides that information.

We enclose an amendment to our pending ANDA that includes revised proposed labeling that is identical in all substantive respects to the labeling of the Reference Listed Drug, Skelaxin®. Sandoz proposed labeling includes all indications and conditions of use set forth in the RLD labeling, and does not propose a "carve out" of any information in Skelaxin®'s labeling that is protected by one or more patents.

The Sandoz pending ANDA includes Paragraph IV certifications to all three patents currently listed in the Orange Book in connection with Skelaxin®, namely, U.S. Patent Nos. 6,407,128 (the '128 patent), 6,683,102 (the '102 patent), and 7,122,566 (the '566 patent). Sandoz's ANDA does not include any "(viii) statements" that seek to omit patent-protected labeling information in the labeling of the RLD.

RECEIVED

NOV 24 2009

OGD

REQUEST FOR FINAL ANDA APPROVAL

To the best of Sandoz knowledge, there are no outstanding bioequivalency or CMC issues with its pending ANDA. Sandoz will manufacture Metaxalone tablets at its Wilson, North Carolina facility. That facility was just inspected in August 2009. Based on that inspection, Sandoz understands that the facility generally, and pending ANDA 40-445 in particular, are regarded as having an acceptable compliance status.

Final approval of the Sandoz ANDA is not delayed by any non-patent exclusivity periods or by the 180-day exclusivity rights of a generic competitor. Final ANDA approval is also not delayed by any litigation stays resulting from lawsuits pursuant to receipt of notices of Sandoz Paragraph IV certifications. With regard to the '128 and '102 patents, the 30-month litigation delays of final ANDA have long expired. As stated and documented in the Sandoz Patent Amendment dated June 26, 2009, the last notice of Paragraph IV certification was received on November 9, 2004. Moreover, as also stated and documented in that Patent Amendment, the federal district court held, on January 20, 2009, that all claims of both patents are invalid.

The '566 patent did not issue until October 17, 2006, long after the Sandoz ANDA was submitted to FDA and accepted for substantive review.¹ Thus, no litigation stay is available with regard to the '566 patent. See 21 U.S.C. § 355(j)(5)(B)(iii) (as amended by MMA § 1101(a)(2)(A)(ii)(I), applicable to patent information submitted to FDA for Orange Book listing on or after August 18, 2003, see MMA § 1101(c)(3)).

Sandoz understands, based on several informal discussions with your staff that the FDA is in the process of ascertaining whether to permit ANDA sponsors to "carve out" labeling information protected by the '128, '102, and/or '566 patents. Sandoz further understands that such a decision is related to a pending March 18, 2004 citizen petition (Docket No. FDA-2004-P-0426 (old 2004P-0140)) that asks the agency to rescind a March 1, 2004 "Dear Applicant" letter regarding Metaxalone labeling. As a result of these pending matters, Sandoz understands that your office has generally advised ANDA applicants not to submit proposed Metaxalone labeling until these issues have been resolved and (if appropriate) until a "carved out" labeling "template" has been developed by the agency. Sandoz appreciates that complex and difficult scientific, medical, legal, and policy questions are involved in deciding whether to allow a labeling "carve out." Sandoz also appreciates that the submission of proposed "carved out" labeling by those ANDA sponsors that have chosen to proceed by means of "(viii) statements" on some or all of the three Orange Book patents before an agency decision on these matters would serve no useful purpose whatsoever. Importantly, however, the informal advice that Metaxalone ANDA applicants should not submit proposed labeling at this time has no application to Sandoz, which does not seek approval based on "carved out" labeling.

In addition to the pending March 18, 2004 citizen petition discussed above, a May 13, 2009 citizen petition submitted by Mutual Pharmaceutical Co. (Docket No. FDA-2009-P-0223) is also pending. On its face, Mutual's 2009 petition asks for, among other relief, certain changes in the labeling of Skelaxin® to reflect a delayed relief product, revision of the dissolution method for

¹ Sandoz's ANDA was initially filed on August 31, 2001. It was amended to include the 800mg strength for which Sandoz currently seeks approval on November 1, 2004. Both dates well predate the issuance and Orange Book listing of the '566 patent.

Skelaxin®, and application of the SUPAC-MR guidance for scale-up and post approval changes to Skelaxin® and to ANDAs relying upon Skelaxin® as the RLD. Mutual's petition does not seek to block or delay the approval of any ANDAs or 505(b)(2) NDAs. Therefore, Mutual's petition is not within the scope of the 180-day decision timeframe in section 505(q) of the FDC Act for petitions that seek to block or delay ANDA or 505(b)(2) NDA approvals. Based on Sandoz's informal discussions with Ms. Cecelia Parise of your staff on November 13, 2009, we understand that the agency agrees that Mutual's new petition is outside the scope of section 505(q) of the FDC Act. Since both the plain language of the petition itself and the agency's initial review of the petition lead to the conclusion that the petition does not seek to block or delay the approval of any ANDAs for generic versions of Skelaxin®, the agency's consideration of the petition should have no effect on final approval of the Sandoz pending ANDA for Metaxalone Tablets, 800 mg.²

Based on our informal discussion with Ms. Parise on November 13, 2009, we also understand that the agency is attempting to determine whether 180-day exclusivity rights for Metaxalone Tablets, 800 mg, are governed by pre- or post-MMA law. (Sandoz assumes the pre- versus post-MMA law question is relevant because Sandoz was the first ANDA sponsor to submit a Paragraph IV ANDA for Metaxalone Tablets, 800 mg, and because the Sandoz ANDA was initially submitted before enactment of the MMA but was amended after the MMA's effective date to include the 800 mg strength.) Sandoz respectfully submits that it is not necessary for the agency to make that determination at this time.

FDA has repeatedly stated that it will not make 180-day exclusivity decisions until necessary, namely, until a "subsequent" Paragraph IV ANDA sponsor is eligible for final approval, but possibly for the existence of 180-day exclusivity. Here, as stated above, Sandoz is currently eligible for, and requests, final ANDA approval. To the best of Sandoz knowledge, Sandoz was the first ANDA sponsor to submit a Paragraph IV ANDA for Metaxalone Tablets, 800 mg. As noted above, FDA's apparent interest in the pre- versus post-MMA law question appears to corroborate the view of Sandoz. Based on a careful search of publicly available documents, Sandoz is not aware of any other ANDA sponsor that has a pending ANDA for Metaxalone Tablets, 800 mg, much less a Paragraph IV ANDA for that drug product.³ There does not appear to be any ANDA sponsor that will be affected by 180-day exclusivity rights of Sandoz.

² It seems that the relief requested by Mutual could, if granted, have some effect on ANDAs for generic versions of Skelaxin®. Any future changes that affect approved ANDAs should be handled, in the regular course of business, as post approval changes.

³ See SEC Form 10-Q for the quarter ending September 30, 2009, King Pharmaceuticals, Inc. at page 21 (discussing in detail matters involving Skelaxin® and in particular the Eon Labs/ Sandoz ANDA for the 800 mg strength, but no other ANDAs for that strength), available at <http://www.sec.gov/Archives/edgar/data/1047699/000095012309058535/g20793e10vq.htm>.

**CONCLUSION**

For these reasons, Sandoz respectfully requests that the enclosed Labeling Amendment be reviewed, and that this Sandoz ANDA receive final approval, as expeditiously as possible.

In support of these changes, the following documents are provided on the enclosed CD:

- Final Printed Labeling – Patient Insert (PDF and Word)
- Side-by-Side Comparison of the Patient Insert (Sandoz vs. RLD)
- SPL

This submission is in electronic format. One CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	Filename
356h Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Supportive Labeling Documents	Labeling folder: Side-by-side.pdf OS7750 Issued 10-09 Content.doc OS7750 Issued 10-09 Mac Final.pdf SPL Folder

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sandoz appreciates the agency's attention to this important matter. If there are any questions concerning this Labeling Amendment or request for final approval, please contact Marcy Macdonald at 303-438-4599.

Respectfully submitted,

SANDOZ, INC.

Joseph Carrado, M.Sc., R.Ph.
Vice President, Regulatory Affairs

Enclosure (Labeling Amendment)

cc: Mr. Robert L. West
Mr. Wm. Peter Rickman
Ms. Cecelia Parise



December 8, 2009

Dr. Burhan Nour
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

orig-1
SD#71

REVISED SPL

RE: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Dr. Nour:

Per your request, I have corrected the Metaxalone Tablets, 800 mg SPL file to reflect "milligrams" in the product data.

The CD contains the following folders and files:

Folder: spl

Files: 1cf511f7-f6fc-409c-8acf-a6d7ab6d523f.xml
1cf511f7-f6fc-409c-8acf-a6d7ab6d523f-01.jpg
1cf511f7-f6fc-409c-8acf-a6d7ab6d523f-02.jpg
1cf511f7-f6fc-409c-8acf-a6d7ab6d523f-03.jpg
1cf511f7-f6fc-409c-8acf-a6d7ab6d523f-04.jpg

If there are any questions concerning these files, please contact me at (252) 234-2207.

Sincerely,
Sandoz Inc.

Deborah Y. Goff, B.S., R.A.C.
Regulatory Affairs Associate III
deborah.goff@sandoz.com

RECEIVED

DEC 09 2009

OGD



Marcy Macdonald, Director
Regulatory Affairs

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893

Tel +1 303 438-4599
Fax +1 252-234-2323
Email:
marcy.macdonald@sandoz.com

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DEC 11 2009

0216-1 / SD- 72

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

OGD

PATENT AMENDMENT

(Electronic Submission)

December 10, 2009

**RE: ANDA 40-445 Metaxalone Tablets 800 mg
Patent Amendment – Certified Mail Receipts and Notification of Litigation
(US Patent 7,122,566)**

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a patent amendment to pending Abbreviated New Drug Application 40-445 for Metaxalone Tablets 800 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

In accordance with 21 CFR 314.95(e), Sandoz also wishes to inform FDA that the Notice to the Patent Owner and to the NDA Holder was received on November 26, 2008 which corresponds to the date by which the Agency received U.S. Patent No. 7,122,566 according to Mary Ann Holovac of FDA. Enclosed as Ex. A please find receipt documentation in the form of certified mail receipts for each address notified.

Sandoz also wishes to inform FDA that the Notice to the Patent Owner and to the NDA Holder were sent on a rolling basis. Thus multiple return receipt cards were obtained. Accordingly, enclosed as Ex. B please find receipt documentation in the form of certified mail receipts for each address notified for the additional days as well.

Sandoz Inc. is also providing notice that King Pharmaceuticals, Inc. filed Civil Action 3:08-cv-05974-GEB-JJH in New Jersey on December 5, 2008. This suit is with respect to U.S. Patent No. 7,122,566. In accord with 21 U.S.C. § 355(j)(5)(B)(iii), this suit does not give rise to any additional 30-month stay and so does not affect approval of Sandoz's ANDA. In addition, any stay associated with Sandoz's certifications against U.S. Patent Nos. 6,407,128 and/or 6,683,102 have since expired and in any event terminated pursuant to the June 4, 2009 Judgment in Civil Action No. 04-5540, Eastern District of New York, holding all claims of U.S. Patent Nos. 6,407,128 and/or 6,683,102 invalid.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

**SANDOZ**

Document	ANDA 40-445
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
patent amendment- certified mail receipts (Attachment-A) Notice of Litigation (Attachment-B)	admin folder patent amendment.pdf (bookmarked)

This information is submitted for your review and approval.

Sincerely,

Sandoz Inc.

Marcy Macdonald

Marcy Macdonald, Director
Regulatory Affairs
Enclosures

MM/ags



Marcy Macdonald, Director
Regulatory Affairs

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893

Tel +1 303 438-4599
Fax +1 252-234-2323
Email:
marcy.macdonald@sandoz.com

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**TELEPHONE AMENDMENT
CMC
(Electronic Submission)**

DEC 23 2009

orig-1
SD#73

**RE: ANDA 40-445 Metaxalone Tablets 800 mg
Telephone Amendment – Response to 12/10/09 CMC Request**

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a telephone amendment to pending Abbreviated New Drug Application 40-445 for Metaxalone Tablets 800 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the discussion between FDA and Sandoz on December 10, 2009 with respect to the Sandoz CMC amendment dated August 29, 2008.

Provided is a complete response to all deficiencies.

- 1) **FDA Comment:** With Revise Drug Product specification sheet to include a compliance statement for USP <467>.

Sandoz Response: This item was resolved on the phone with FDA.

- 2) **FDA Comment:** Clarify the FMR pages submitted. Please explain why the (b) (4) (b) (4) Please submit all changes to the manufacturing process and with explanations.

Sandoz Response: It is Sandoz practice to include a copy of the (b) (4) from the manufacturing record in our USP <467> compliance statements for ease of internal review.

Enclosed please find a copy of the current proposed commercial manufacturing record.

The current manufacturing record contains (b) (4) as well as additional minor clarifications and changes. A complete summary, rationale and supportive data for these changes is included.

RECEIVED

DEC 24 2009

OGD



As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 40-445
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Telephone amendment- Deficiency Response	cmc folder telephone amendment.pdf (bookmarked)

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Sandoz Inc.

Marcy Macdonald, Director
Regulatory Affairs
Enclosures

MM/ags



SANDOZ

Marcy Macdonald, Director
Regulatory Affairs

Sandoz Inc.
4700 Sandoz Drive
Wilson, NC 27893

Tel +1 303 438-4599
Fax +1 252-234-2323
Email:
marcy.macdonald@sandoz.com

OVERNIGHT DELIVERY

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**TELEPHONE AMENDMENT
CMC**

(Electronic Submission)

*orig-1
SD# 74*

January 14, 2010

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JAN 15 2010

RE: ANDA 040445 Metaxalone Tablets 800 mg

Telephone Amendment :

Follow up to Jan 13, 2010 T-Con: Clarification of Manufacturing Process

OGD

Dear Mr. Buehler:

Sandoz Inc. is hereby submitting a Telephone amendment to pending Abbreviated New Drug Application 040445 for Metaxalone Tablets 800 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to a teleconference discussion on January 13, 2010 with the following participants:

Sandoz: Alison Sherwood, [REDACTED]

(b) (6)

FDA: Dr. Liang Lii Huang, Dr. Paul Schwartz, Dr. James Fan, Trang Tran

Pursuant to this discussion Sandoz is providing written clarification of the [REDACTED]

(b) (4)

Prior to the December 23, 2009 amendment, the proposed [REDACTED]

(b) (4)

Overview of Submission History:

The previous filed [REDACTED] were submitted in our November 1, 2004 major amendment which included a bioequivalence study for the 800 mg

(b) (4)

strength. For ease of reference, the formula pages of these batch records are provided in **Attachment 1**. The batch size for the (b) (4) was (b) (4).

The previous filed (b) (4) was submitted in our February 2, 2007 amendment. For ease of review the formula pages of these batch records are provided in **Attachment 2**. The exhibit batch size for (b) (4) and the exhibit batch size for tablets was (b) (4) tablets. The proposed record was for (b) (4) Tablets and consisted of 3 Parts (A, B, C) with approx (b) (4) for each.

The current Metaxalone Tablets blank record submitted on December 23, 2009 is provided again as **Attachment 3**. (b) (4) is bookmarked for ease of review.

As this submission is in electronic format- one CD is provided which includes the content described below. Accordingly, Sandoz confirms that this CD is virus free and that a letter of non repudiation agreement was submitted by Sandoz Inc. on November 30, 2007.

Document	ANDA 040445
356(h) Form (scanned)	356h.pdf
Sandoz Cover Letter (scanned)	cover.pdf
Telephone amendment- Chemistry Deficiency	cmc folder amendment.pdf (bookmarked)

This information is submitted for your review and approval.

Sincerely,

Sandoz Inc.

Asherwood for
Marcy Macdonald, Director
Regulatory Affairs
Enclosures

MM/ags



January 27, 2010

DRIG-1

SD # 75

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

Re: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, this submission constitutes a Telephone Amendment to our Abbreviated New Drug Application 40-445, Metaxalone Tablets, 800 mg. Sandoz Inc. would like to request, the withdrawal of the following contract testing laboratory from our ANDA 40-445, Metaxalone Tablets, 800 mg:

(b) (4)

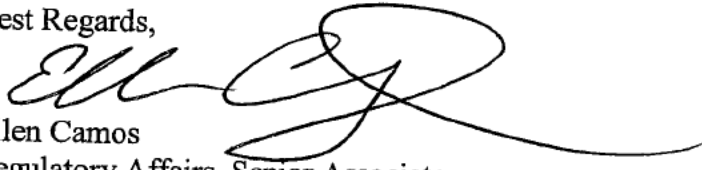
(b) (4)

was included as a contract testing laboratory in *Section 10* of the Major Amendment, filed on November 1, 2004. Reference is also made to the Telephone Amendment, filed on December 15, 2004 which included the cGMP statement for this laboratory. This laboratory was not used for any of the analytical procedures performed to support this application. The decision to withdraw this contract facility is without prejudice to re-filing.

A Letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on 11/30/07.

If there are any questions concerning this amendment, please contact me by telephone at (252) 234-2413, by fax at (252) 234-2323, or email at ellen.campos@sandoz.com.

Best Regards,


Ellen Campos
Regulatory Affairs, Senior Associate
Sandoz Inc.

RECEIVED

JAN 28 2010

OGD



March 9, 2010

ORIG-3
SON-77

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

TELEPHONE AMENDMENT

Re: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, this submission constitutes a Telephone Amendment to our Abbreviated New Drug Application 40-445, Metaxalone Tablets, 800 mg. It is being filed in response to a telephone communication from Dr. Liang-Lii Huang, OGD, CDER, FDA to Sandoz Inc. on February 25, 2010. Dr. Huang also indicated to submit the response as a Telephone Amendment.

The deficiency comment is reiterated below (**in bold type**), followed by our response.

Deficiency:

Please provide information for the

(b) (4)

(b) (4)

Please indicate whether the

(b) (4)

Response:

There are

(b) (4)

and

are the following:

- 1)
- 2)
- 3)

(b) (4)

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MAR 10 2010

OGD

ANDA # 40-445
Metaxalone Tablets, 800 mg

Drug Product (Metaxalone Tablets, 800 mg):

(b) (4)

Please refer to **ATTACHMENT-B** for copies of the updated, revised

(b) (4)

reflecting the updated specifications can also be found in **ATTACHMENT-B**.


ATTACHMENT-B:

(b) (4)

A Letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on November 30, 2007.

If there are any questions concerning this amendment, please contact me by telephone at (252) 234-2413, by fax at (252) 234-2323, or email at ellen.camos@sandoz.com.

Best Regards,


Ellen Camos
Regulatory Affairs, Senior Associate
Sandoz Inc.



MEMORANDUM

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

DATE: March 29, 2010

FROM: Martin Shimer
Branch Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-600)

TO: ANDA 040445

SUBJECT: Background for Sandoz' Metaxalone Tablets, 800 mg; Decision regarding non-forfeiture of 180-day exclusivity

The purpose of this memorandum is to document the status of Sandoz's ANDA 040445 for Metaxalone Tablets, 800 mg, as of the date of approval, and to document the agency's decision regarding whether Sandoz forfeited its 180-day generic drug exclusivity because it did not obtain tentative approval within 30 months. Sandoz' new strength amendment for the 800 mg strength was submitted on November 4, 2004, and contained paragraph IV certifications to the '128 and '102 patents. The paragraph IV certifications made Sandoz eligible for 180-day generic drug exclusivity. However, Sandoz did not receive tentative approval within 30 months.

I. FACTUAL BACKGROUND

The following is a timeline of ANDA 040445:

9/05/01	ANDA submitted
10/17/01	Refuse to receive
11/07/01	Amendment; this is the receipt date of the ANDA
11/30/01	Amendment
4/03/02	Chemistry review #1 (deficient), chemistry deficiencies faxed
6/20/02	Bioequivalence amendment
6/24/02	Chemistry amendment
7/19/02	Bioequivalence amendment
10/25/02	Chemistry amendment
11/18/02	Chemistry amendment
12/06/02	Chemistry amendment
1/08/03	Labeling amendment
3/06/03	Chemistry review #2 (deficient – major), chemistry deficiencies faxed
4/15/03	Correspondence

4/15/03	Correspondence
2/10/04	Patent amendment
5/13/04	Amendment (chemistry)
11/04/04	Amendment adding 800 mg strength; included PIV certifications to the '128 and '102 patents
12/16/04	Telephone amendment (chemistry)
5/09/05	Bioequivalence review (deficient), bioequivalence deficiencies faxed
12/05/05	Chemistry review #3 (deficient), chemistry deficiencies faxed
9/06/06	Firm withdrew 400 mg strength
9/07/06	Bioequivalence (amendment)
10/20/06-	Serial patent amendments to the '566 patent (but this patent was
11/22/06	not listed until 11/26/08)
11/24/06	Patent amendment
2/05/07	Chemistry amendment
5/04/07	11/04/04 plus 30 months
11/09/07	Bioequivalence review (acceptable)
12/11/07	Correspondence
1/29/08	Labeling amendment
2/28/08	Patent amendment
7/17/08	Telecon (chemistry)
9/02/08	Telephone amendment (chemistry)
10/01/08	Labeling review (acceptable)
11/05/08-	Serial patent amendments to the '566 patent, which was listed on
12/05/08	11/26/08
6/29/09	Patent amendment
11/24/09	Labeling amendment
12/08/09	Labeling review (acceptable)
12/09/09	Labeling amendment
12/11/09	Patent amendment
12/24/09	Telephone amendment (chemistry)
1/15/10	Telephone amendment (chemistry)
1/28/10	Telephone amendment (chemistry)

The following chart lists the many citizen petitions that have been submitted regarding metaxalone:

Citizen Petition Number	Date Submitted	Action Requested	Action Taken
FDA-2001-P-0001 (formerly 01P-0117), submitted by Mutual	3/06/01	Reclassify metaxalone tablets as a drug product with potential or actual bioequivalence problems and make inclusion of an <i>in vivo</i> fasting bioequivalence study a condition of approval for an ANDA	Granted 1/30/02
01P-0481, submitted by Elan	10/17/01	That FDA require, as a condition for generic approval of solid oral dosage forms of metaxalone, an acceptable <i>in vivo</i> fasting and fed BE study.	Granted 3/21/02
FDA-2003-P-0081 (formerly 03P-0027), submitted by Eon (now Sandoz)	1/28/03	Restore the labeling for Skelaxin that was approved as of May 31, 2002; or in the alternative, determine that the May 31, 2002 labeling was not withdrawn for safety or effectiveness reasons.	Withdrawn 1/17/08
FDA-2004-P-0426 (formerly 04P-0140), CP1 and PSA1 submitted by RLD-holder King Pharmaceutical PSA2 submitted by Mutual	3/18/04 (CP1 & PSA1) 4/05/04 (PSA2)	CP1 & PSA1:: (1) Rescind the March 1, 2004, “Dear Applicant” letter regarding metaxalone labeling, (2) require applicants seeking approval to market generic metaxalone products that rely on Skelaxin to submit a patent certification, and (3) prohibit the removal from generic labeling of the pharmacokinetics information that appears in the Skelaxin labeling. PSA2: Stay any final approval of NDA 13-217/S-046 or any other labeling supplement for Skelaxin	Pending
FDA-2007-P-0017 (formerly 07P-0296), submitted by Mutual	7/27/07	Require potential drug-drug interaction (DDI)-related labeling changes for Skelaxin	Denied 7/18/08
FDA-2008-P-0052, submitted by Mutual	1/22/08	Refrain from approval of any ANDAs for metaxalone products until (1) certain <i>in vivo</i> DDI studies of Skelaxin are conducted and any relevant results are included in Skelaxin’s labeling, and (2) the Agency establishes statistical criteria related to T _{max} , if T _{max} is determined to be a relevant safety consideration, and requires all applicants seeking approval of a generic version of metaxalone to demonstrate equivalence either by satisfying the criteria or submitted the results of certain <i>in vivo</i> DDI studies.	Denied 7/18/08
FDA-2009-P-0223, submitted by Mutual	5/15/09	Declare that Skelaxin (metaxalone tablets 800 mg) is a delayed dosage form and take other related actions.	Pending

II. STATUTORY AND REGULATORY BACKGROUND

A question could be raised about whether exclusivity for the 800 mg product should be determined under the pre-Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) or post-MMA regime. This question arises because ANDA 040445 was submitted pre-MMA (for the 400 mg strength), but the amendment for the 800 mg strength was submitted post-MMA. This latter fact, coupled with the fact that, for purposes of exclusivity, each strength of each dosage form is regarded as a separate product, seems to point toward a post-MMA analysis as the appropriate regime, and this memorandum is based on that assumption.¹ However, it is acknowledged that because of the submission date of the original ANDA 040445, using a pre-MMA regime is not out of the question.

This memorandum does not closely examine the pre- versus post-MMA question because this memorandum is limited to the situation at the time of approval of ANDA 040445, and we reach the same conclusion regardless of whether a pre- or post-MMA analysis is used: under a pre-MMA analysis, Sandoz is entitled to exclusivity (there is no forfeiture pre-MMA), and as discussed below, under the post-MMA regime we have determined that metaxalone falls under the “change in or a review of the requirements for approval” exception to the forfeiture provision at section 505(j)(5)(D)(i)(IV). Because under either analysis it is determined that Sandoz is eligible for 180-day exclusivity, it is not necessary at this time to firmly establish which regime should apply.

The MMA describes, among other things, certain events which can result in the forfeiture of a first applicant’s 180-day generic drug exclusivity as described in section 505(j)(5)(B)(iv). The forfeiture provisions of the MMA now appear at section 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act). Included among these is section 505(j)(5)(D)(i)(IV), which states the following:

FAILURE TO OBTAIN TENTATIVE APPROVAL.--The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

A “first applicant” is eligible for 180-day exclusivity by virtue of submitting a substantially complete ANDA with a paragraph IV certification on the first day on which such an ANDA is submitted. Section 505(j)(5)(B)(iv)(II)(bb). If only one such ANDA is submitted on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, first applicant status is shared.

¹

“Tentative approval” means, generally, that an ANDA otherwise meets the requirements for approval under the Act, but cannot be fully approved for marketing because of patent or exclusivity protections. Section 505(j)(5)(B)(iv)(II)(dd). The “failure to obtain tentative approval” forfeiture provision establishes a bright line standard: If within 30 months an ANDA has been determined by the agency to meet the statutory standards for approval and it is only patent and/or exclusivity protection that prevents full approval, then an applicant maintains eligibility for 180-day exclusivity. If this standard is not met in 30 months, eligibility for 180-day exclusivity is forfeited. It should be noted that the 30-month timeframe generally is without regard to the length of time the ANDA was under review by the Agency. One exception to this general rule, described in section 505(j)(5)(D)(i)(IV), states that forfeiture will not occur if “the failure [to obtain a tentative approval] is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed”.

A second exception is found in new section 505(q)(1)(G) of the Act, enacted as part of the Food and Drug Administration Amendments Act of 2007 (Pub. Law 110-85)(FDAAA).² This section, however, is not relevant here because the still-pending petitions regarding metaxalone are not 505(q) petitions.³ Therefore, only the first exception described above might provide a basis for finding that Sandoz has not forfeited its 180-day exclusivity. It was FDA’s policy, prior to passage of the FDAAA, generally to regard a citizen petition that seeks to impose conditions on the approval of ANDAs (such as the citizen petition submitted by King) as creating a “review of the requirements for approval.”

II. DISCUSSION

Sandoz’ new strength amendment for the 800 mg strength was submitted on November 4, 2004, and was never tentatively approved. The date of submission of the new strength amendment plus 30 months was May 4, 2007; therefore, Sandoz’ ANDA was not tentatively approved within 30 months.

² This provides that

If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a [505(q)] petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

Pursuant to this provision, therefore, the 30-month period will be extended for the prescribed period during the review of a related petition subject to section 505(q).

³ The petition and petition for stay of action in FDA-2004-P-0426 were submitted well before passage of the FDAAA, and the petition in FDA-2009-P-0223 does not contain a request to take any form of action relating to a pending 505(b)(2) or 505(j) application.

The following patents are listed for Skelaxin, 800 mg:

<u>Patent Number</u>	<u>Expiration Date</u>	<u>Listed in OB</u>
6,407,128 ('128)	December 3, 2021	June 2002
6,683,102 ('102)	December 3, 2021	September 2004
7,122,566 ('566)	February 6, 2026	November 2008

All three of these patents are method of use patents. Sandoz filed PIV certifications for all three patents. (b) (4)

(b) (4)

(b) (4)

(b) (4)

So the question of whether Sandoz forfeits its exclusivity is almost entirely academic. (b) (4)

(b) (4)

To date, seven dockets have been opened for petitions regarding metaxalone. Five of these dockets have been closed. Currently, docket numbers FDA- 2004-P-0426 and FDA-2009-P-0223 remain open. The only pending petition that seeks to impose conditions on the approval of ANDAs is that of King (Docket No. 2004-P-0426/CP1 and PSA1). That petition is moot with respect to ANDA 040445: Sandoz certified to the listed patents and its labeling is identical to that of Skelaxin.

The '128 and '102 patents -- which have as their Use Code "Enhancement of the bioavailability of the drug substance," and were the basis of the pharmacokinetic data in Skelaxin's labeling that was at issue in the King petition -- were determined in a 2009 decision to be invalid in an infringement case brought by King against Sandoz. The patents and the labeling of the reference listed drug Skelaxin pertaining to the use of metaxalone under fed and fasted conditions created a dilemma for both the agency and ANDA applicants. Namely, it was questionable whether certain labeling could be carved out. That a carve-out was not permissible was the central argument of King's 2004 citizen petition. The dilemma was deepened when, 24 months after the submission of Sandoz' amendment for the 800 mg strength, the agency approved, on November

24, 2006, labeling changes for Skelaxin that included, among other changes, the following information in the Precautions section:

Taking SKELAXIN with food may enhance general CNS [depression](#); elderly patients may be especially susceptible to this CNS effect.

Skelaxin has only one indication (as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions), so everything in the Precautions section applies to that one use. Carving out patent-protected language from the Precautions section of a label that pertains to a labeled use would generally not be permitted.

When an ANDA is tentatively approved, the proposed labeling must be acceptable to the agency. It was not possible, therefore, because of the patent-protected language, to tentatively approve Sandoz' 800 mg product prior to the resolution of the patent case involving these patents. Sandoz submitted its amendment for the 800 mg strength on November 4, 2004, and 30 months from that date is May 4, 2007. During that entire time the agency had pending before it King's citizen petition that prompted a review of a requirement for approval of a generic drug application, namely, what the appropriate labeling should be. The court's finding that the two patents are invalid essentially renders the matter moot, for it permitted Sandoz to amend its proposed labeling so that it is identical to that of Skelaxin.

III. CONCLUSION

Sandoz was the first ANDA applicant to submit a substantially complete ANDA for Metaxalone Tablets, 800 mg, with a paragraph IV certification to the '128 and '102 patents. Therefore, Sandoz is eligible for 180 days of generic drug exclusivity for Metaxalone Tablets, 800 mg. Although Sandoz failed to obtain tentative approval of their ANDA within 30 months after the date on which the supplement for the 800 mg strength was filed, we have determined that this was caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application was filed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
-----	-----	-----	-----
ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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

/s/

MARTIN H Shimer
03/29/2010

From: West, Robert L
Sent: Sunday, March 28, 2010 10:54 AM
To: CDER EESQUESTIONS
Cc: Tran, Trang; Ames, Timothy W; Rickman, William P; Read, David T
Subject: FW: SANDOZ'S ANDA 40-445 FOR METAXALONE TABLETS - FIRST GENERIC APPROVAL - STATUS OF (b) (4) INSPECTION

Dear EES:

Please refer to the email sent to CDER EESQUESTIONS on February 1, 2010 (copy below) regarding OGD's planned approval of Sandoz's ANDA 40-445 for Metaxalone Tablets.

At this time, there does not appear to be any indication in EES that an inspection of the (b) (4) facility in (b) (4) has been scheduled or initiated.

In the absence of information from the Office of Compliance documenting safety issues associated with the (b) (4) at the (b) (4) facility, OGD plans to grant approval to Sandoz's ANDA 40-445 for Metaxalone Tablets 800 mg by noon on Wednesday, March 31, 2010. As noted below, this site appears to have an acceptable inspectional history and there are no "OAI" alerts indicated. All other sites associated with the manufacture of this drug product have "Acceptable" recommendations made since September 2009.

Thank you,

Bob

From: West, Robert L
Sent: Monday, February 01, 2010 12:09 PM
To: CDER EESQUESTIONS
Cc: Rosa, Carmelo R; Stock, Marisa; Ames, Timothy W; Tran, Trang
Subject: SANDOZ'S ANDA 40-445 FOR METAXALONE TABLETS - FIRST GENERIC APPROVAL - STATUS OF (b) (4) INSPECTION

Dear EES:

Later this month OGD anticipates having a first-generic approval package ready for Sandoz's ANDA 40-445 for Metaxalone Tablets, 800 mg. This represents a first-generic approval for a product that has been without generic competition for more than 40 years! The NDA holder has up until now been successful in delaying generic competition through a series of labeling changes and Citizen Petitions.

Currently, all facilities in EES are "acceptable", with the exception of the (b) (4). Acceptable recommendations have been provided twice in the past for this facility under this ANDA. However, due to the length of time this ANDA is been with us, another update was requested in September 2009. It now appears that a reinspection has been proposed for this facility.

Please advise as to whether this inspection has been scheduled.

Thank you,

Bob

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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

/s/

TRANG Q TRAN
03/31/2010

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-445 Applicant Sandoz, Inc.
Drug Metaxalone Tablets Strength(s) 800 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer Chief, Reg. Support Branch	Date <u>3 February 2010</u> Initials <u>MHS</u>	Date <u>3/30/10</u> Initials <u>rlw</u>
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Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes ☒ No ☐ RLD = Skelaxin NDA# 13-217

If Para. IV Certification- did applicant Date Checked N/A

Notify patent holder/NDA holder Yes ☒ No ☐ Nothing Submitted ☐

Was applicant sued w/in 45 days: Yes ☒ No ☐ Written request issued ☐

Has case been settled: Yes ☒ No ☒ Study Submitted ☐

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Date of latest Labeling Review/Approval Summary _____

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter: Full Approval.

Comments: 800 mg strength was submitted as a New Strength Amendment to ANDA 40-445 on 11/4/2004, BOS=Skelaxin NDA 13-217, PIV to '128 and '102. As this strength was submitted as an amendment there is no outgoing filing letter. There is both a filing review checklist indicating that the application is substantially complete and a DBE checklist which indicates that Fasting and Fed studies were conducted and are acceptable for the purpose of filing the ANDA. Applicant sent a letter w/d the 400 mg strength from this ANDA on 9/6/2006-this correspondence was formally acknowledged and the Agency's W/D Letter was issued on 9/20/2006. Firm submitted PIV certs to the '128 and '102 (from looking at this PIV cert it appears that Sandoz's intent was to provide a PIV to the '566 but their certification does not come out and state this. The same patent cert was provided again on 10/24, 10/25, 10/26, 10/27, 10/30, 11/13, 11/14, 11/15, 11/16, 11/17, 11/20, 11/21, 11/22. On June 26, 2009 the sponsor submitted a patent amendment which included-RR from Elan Pharmaceuticals signed and dated 11/8/2004, RR from Jones PHarma signed and dated 11/9/2004, RR from King signed and dated 11/8/2004, notice was sent on 11/3/2004, CA 04-5540 was filed in the Eastern D of NY on 12/17/2004 for infringement of the '128 and '102 patents, 30 month stay of approval will expire on 5/9/2007. The 6/26/2009 (in the EDR) amendment also included a copy of an Order signed by the DC for the Eastern District of NY on 6/3/2009 which found that the '128 and '102 patents are INVALID and the case was dismissed. Sandoz provided a PIV cert to the '566 patent on 11/5/2008, 11/6, 11/7, 11/10, 11/12, 11/13, 11/14, 11/17, 11/19, 11/20, 11/21, 11/24, 11/25, 11/26, 11/28, 12/1, 12/2, 12/3, 12/4, and 12/5/2008. Sandoz submitted a patent amendment on 12/11/2009-RR from UBS AG Stamford signed and dated 11/18/2008, RR from King Pharmaceuticals in Bristol TN signed and dated 11/10/2008, RR from UBS AG Stamford in Costa Mesa CA signed and dated 11/17/2008 again 11/18/2008...after reviewing this patent amendment it is clear that Sandoz sent notice to the appropriate parties on a daily basis as they submitted their serial certifications to the '566 patent. The 12/11/09 patent amendment contains multiple RRs from the same parties with dates on the RRs between 11/10/2008 and 12/8/2008. CA 08 CV 5974 was filed in the D of NJ on 12/5/2008 for infringement of the '566 patent.

Normally it would be necessary to ascertain the date upon which the '566 was listed in the OB in order to figure out which of the serial certifications was the first valid certification. However, because there can be no 30 month stay of approval related to the '566 patent and because there is no opportunity for 180 day exclusivity related to the '566 patent this information is unnecessary. Furthermore, we know that notice was adequately served to the appropriate parties as suit was brought in the D of NJ.

This application is subject to post-MMA (this amendment submitted by Sandoz was the first submitted for the 800 mg strength and was submitted after implementation of MMA) rules concerning 180 day exclusivity and eligibility for approval. Therefore, there is no 30 month stay of approval associated with the suit on the '566 patent, the '566 is not a barrier to approval at this time. The DC issued a ruling in favor of Sandoz with respect to the '128 and '102 patents so neither of these patents is a barrier to approval. Under MMA the first applicant is required to secure TA within 30 months of the submission date that qualifies that applicant for 180 day exclusivity. The NSA for the 800 mg product was submitted on 11/4/2004, became eligible for exclusivity as of this date but was not TA'd before 5/4/2007. Therefore at first pass it would appear that Sandoz has forfeited eligibility for 180 day exclusivity. The Agency will need to make a formal determination regarding whether either of the pending Citizen's Petitions for this drug product resulted in a tolling of the forfeiture period such that Sandoz would still be considered eligible for 180 day exclusivity.

Addendum: The agency has determined that Sandoz is eligible for 180-day generic drug exclusivity for Metaxalone Tablets, 800 mg. See Memorandum to the Record dated March 29, 2010 and entered into DARRTS./RLWest 3/30/10.

2.	Project Manager , <u>Nitin Patel</u> Team <u>3</u>	Review Support Branch	Date <u>12/11/2009</u> Initials <u>NP</u>	Date <u>3/31/10</u> Initials <u>TTforNP</u>
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Original Rec'd date <u>8/31/2001</u>	EER Status Pending <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> OAI <input type="checkbox"/>
Date Acceptable for Filing <u>11/7/2001</u>	Date of EER Status Please see Memo
Patent Certification (type) <u>IV</u>	Date of Office Bio Review <u>11/9/2007</u>
Date Patent/Exclus. expires <u>2/6/2026</u>	Date of Labeling Approv. Sum <u>12/8/2009</u>
Citizens' Petition/Legal Case Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Labeling Acceptable Email Rec'd Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
(If YES, attach email from PM to CP coord)	Labeling Acceptable Email filed Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
First Generic Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Date of Sterility Assur. App. <u>NA</u>
Priority Approval Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Methods Val. Samples Pending Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)	MV Commitment Rcd. from Firm Yes <input type="checkbox"/> No <input type="checkbox"/>
Acceptable Bio reviews tabbed Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Modified-release dosage form: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Bio Review Filed Electronically: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Interim Dissol. Specs in AP Ltr: Yes <input type="checkbox"/>
Suitability Petition/Pediatric Waiver Yes <input type="checkbox"/>	
Pediatric Waiver Request Accepted <input type="checkbox"/> Rejected <input type="checkbox"/> Pending <input type="checkbox"/>	
Previously reviewed and tentatively approved <input type="checkbox"/>	Date _____
Previously reviewed and CGMP def. /NA Minor issued <input type="checkbox"/>	Date _____
Comments: PM will put CP note here.	

3.	Labeling Endorsement	
Reviewer:	Labeling Team Leader:	
Date <u>3/18/10</u>	Date <u>3/22/10</u>	
Name/Initials <u>BN</u>	Name/Initials <u>JG</u>	
	Comments:	

From: Grace, John F
Sent: Monday, March 22, 2010 9:44 AM
To: Nour, Burhan; Tran, Trang; Hoppes, Charles V
Subject: RE: Request for labeling endorsement for ANDA-040445 Product Name: METAXALONE Dosage Form: TABLET Applicant: SANDOZ INC

concur.

From: Nour, Burhan
Sent: Thursday, March 18, 2010 4:53 PM
To: Tran, Trang; Hoppes, Charles V
Cc: Grace, John F
Subject: RE: Request for labeling endorsement for ANDA-040445 Product Name: METAXALONE Dosage Form: TABLET Applicant: SANDOZ INC

Charlie,

There are no changes or updates.

Burhan

From: Tran, Trang
Sent: Thursday, March 18, 2010 4:03 PM
To: Nour, Burhan; Grace, John F
Subject: Request for labeling endorsement for ANDA-040445 Product Name: METAXALONE Dosage Form: TABLET Applicant: SANDOZ INC

Hi Burhan and John,

Could you please send me the labeling endorsement for the above ANDA? Attached are the copies of the Labeling Approval Summary and the AP letter.

Thanks,

Trang

4. **David Read (PP IVs Only)** Pre-MMA Language included ☐ Date 3/30/10
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: Text of approval letter has been reviewed by D.Read.

5. **Div. Dir./Deputy Dir.** Date 3/12/10
Chemistry Div. I Initials PS

Comments: cmc ok.

6. **Frank Holcombe** First Generics Only Date 3/30/10
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. CorePharma's ANDA 40-486 was granted tentative approval on 6/11/03.

7. Vacant Initials _____ Date _____ Deputy Dir., DLPS
RLD = Skelaxin Tablets, 800 mg
King Pharmaceuticals, Inc. NDA 13-217

8. Peter Rickman Date 3/30/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐ Comments: Bioequivalence
studies (fasting and non-fasting) found acceptable.
In-vitro dissolution testing also found acceptable. Bio study sites have acceptable
DSI inspectional histories. Office-level bio endorsed 11/9/07.

Final-printed labeling (FPL) found acceptable for approval (Approval Summary #3)
12/8/09, as endorsed 3/22/10.

CMC found acceptable for approval (Chemistry Review #4).

OR

8. Robert L. West Date 3/31/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☒
Press Release Acceptable ☐
Comments: Refer to M.Shimer's discussion above regarding the '128, '102 and '566
patents and why they do not block approval of this ANDA. There are no additional
patents or exclusivity listed in the current "Orange Book" for this drug product.

EES deemed to be Acceptable. All facilities have a current "Acceptable"
recommendation in EES with the exception of (b) (4) in
(b) (4). This facility appears not to have been scheduled for
a reinspection. As documented in my email memorandum to OC dated February 1,
2010 and again on March 28, 2010, OGD will proceed to approved this ANDA in the
absence of information from OC. OC has not responded to the March 28, 2010
email. Copy of email filed in DARRTS for this ANDA.

This ANDA is recommended for approval.

9. Gary Buehler Date 3/31/10
Director, OGD Initials rlw/for
Comments: First-generic approval for this drug product.
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

Press Release Acceptable ☐

10. Project Manager, Nitin Patel Team 3

Date 3/31/10

Review Support Branch

Initials

 Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

3/31/10 Date notified of approval by phone

3/31/10 Date approval letter faxed

FDA Notification:

3/31/10 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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ANDA-40445	ORIG-1	SANDOZ INC	METAXALONE

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

/s/

TRANG Q TRAN
03/31/2010



April 1, 2010

Mr. Gary Buehler, Director,
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

orig-1
SD#78

NOTIFICATION OF COMMERCIAL MARKETING DATE
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Re: ANDA 40-445
Metaxalone Tablets, 800 mg

Dear Mr. Buehler:

This communication is in response to the *Approval Letter* received on March 31, 2010 for Sandoz, Inc.'s Abbreviated New Drug Application for Metaxalone Tablets, 800 mg; ANDA 40-445. The *Approval Letter* instructs Sandoz, Inc. that a communication should be submitted to the agency to inform of the date commercial marketing begins. Therefore, Sandoz, Inc. hereby notifies the Office of Generic Drugs, Center for Drug Evaluation and Research, the Food and Drug Administration that commercial marketing of ANDA 40-445, Metaxalone Tablets, 800 mg, began on March 31, 2010.

A Letter of Non-Repudiation Agreement was submitted by Sandoz Inc. to the FDA on November 30, 2007.

If there are any questions concerning this communication, please contact me by telephone at (252) 234-2413, by fax at (252) 234-2323, or email at ellen.camos@sandoz.com.

Best Regards,

Ellen Camos
Regulatory Affairs, Senior Associate
Sandoz Inc.

RECEIVED

APR 02 2010

OGD