CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-589

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-589	Submission Date(s):	December 30, 2002; June 3, 2003 June 19, 2003 August 18, 2003
	Date received:	January 10, 2003 September 29, 2003 June 10, 2003 September 2, 2003
Brand Name	—	
Generic Name	Baclofen Orally Disintegrating Tablets	
Reviewer	Carol Noory	
Team Leader	Ramana Uppoor	
OCPB Division	HFD-860	
OND division	Neuropharm HFD-120	
Sponsor	Schwarz Pharma Milwaukee, WI 53201-2038	
Submission Type; Code	Original NDA 505(b)(2)	
Formulation; Strength(s)	Orally Disintegrating Tablets, 10 and 20 mg	
Indication	Treat spasticity and improve mobility in patients with multiple sclerosis	

I. Executive Summary

Schwarz Pharma has developed a new, orally disintegrating tablet that provides a pharmaceutical alternative to Baclofen immediate-release conventional tablets. The rapidly disintegrating tablets are formulated to disintegrate once exposed to fluid, such as saliva. The tablets are then easily swallowed. The sponsor proposes to market the rapidly disintegrating tablets in strengths of 10 mg and 20-mg, which are formulated to be bioequivalent to the reference listed drug, Watson Baclofen Tablets (ANDA 73-093). The sponsor is relying on the Agency's findings of safety and efficacy for the conventional immediate-release Baclofen Tablets, USP, originally approved in 1977 as NDA 17851, Lioresal® Tablets, manufactured by Ciba Geigy (later transferred to Novartis).

This application includes no clinical trials, but does include one (1) single dose, replicate design in vivo study comparing the 20 mg Baclofen orally disintegrating tablet (ODT) to

the Reference Listed Drug (RLD), a 20-mg immediate release tablet manufactured by Watson both given with water and one (1) single dose, 2-way crossover bioequivalence study comparing the 20 mg Baclofen orally disintegrating tablet (ODT) administered without water to the 20-mg immediate release tablet manufactured by Watson Laboratories, Inc., administered with water. The firm tested the products in three media to develop a suitable dissolution method for both the 10 and 20-mg tablets and to evaluate dissolution profile similarity to obtain a biowaver for the 10 mg ODT. Since the product is titrated beginning at 5 mg, the half and whole 10 mg tablets were tested using the three media. A dissolution study comparing the 20 mg OD tablet to the RLD using the current USP method is also included. Literature articles were submitted to support the absorption, distribution, metabolism, and elimination portion of the pharmacokinetics portion of the label.

The clinical pharmacology and biopharmaceutics section is acceptable based on the following:

1. The firm demonstrated that the orally disintegrating 20 mg tablet was bioequivalent to the 20 mg IR product manufactured by Watson (Study SP692).
2. A waiver for the lower strength, 10 mg ODT, was requested and found acceptable.
   The firm requested a waiver for the lower strength tablet. Based on formulation proportionality and dissolution profile comparison to the biobatch in three media, the waiver for the 10 mg tablet is acceptable
3. A bioequivalence study was conducted comparing the 20 mg orally disintegrating tablet administered without water to the 20 mg Reference Listed Drug taken with water (Study SP741). Comparison of the two studies demonstrated that taking the 20 mg orally disintegrating tablet with water (Study SP692) or without water (Study SP741) had no effect on the bioavailability. Baclofen orally disintegrating tablets can be taken with or without water.
4. An appropriate dissolution study was conducted.
   The firm developed a dissolution method for the rapidly disintegrating tablets, which uses the paddle method 25-rpm and acetate buffer as the medium with pooled sample analysis. The method and specification are not appropriate and should be revised.
5. Half vs. whole tablets have similar release characteristics and the tablets can be divided.
   The firm showed that the 10-mg tablet could be successfully broken in half in an in vitro study comparing the dissolution profiles of half vs. whole 10-mg tablets in three media.
6. DSI inspection of study sites for study SP692 was acceptable.

Comments:

1. The dissolution profiles of the Baclofen orally disintegrating tablets (10 mg and 20 mg) were determined in three media using the USP method (Paddle apparatus, 25 rpm). The sponsor proposed a new dissolution method for the rapidly disintegrating tablets which uses the Paddle apparatus at 25 rpm with 500 mL (10 mg) or 1000 mL

(20 mg) of 50 mM acetate buffer pH 4.5 as the medium. The sponsor proposes to keep the USP tolerance specification for currently marketed conventional tablet, that is based on a pooled samples (Q= —in 30 minutes). After evaluation of all of the dissolution data submitted, it appears that the ODT can meet a more stringent tolerance than the firm proposes. The recommended procedure, based on the data submitted is Paddle, 25 rpm, 500 mL (10 mg) or 1000 mL (20 mg) of 50mM acetate buffer, pH 4.5 as the medium. The Q value should be — in 15 minutes based on individual (not pooled) tablet data.

Labeling Comments:
Based on the most recent sponsor proposed labeling dated 07/03, we have the following comments:

1. There is no information for possible gender effects. There were 13 women and 12 men who completed the study. The firm should try to determine if there was a gender effect and include this in the label.
2. Upon reviewing the literature on baclofen (Ali, Imran, Aboul-Enein, Hassan Y., "Optimization of the chiral resolution of baclofen by capillary electrophoresis using β-Cyclodextrin as the Chiral Selector." Electrophoresis 2003, 24, 2064-2069.), I found that baclofen is a racemic mixture. This should be discussed in either the Clinical Pharmacology section of the label or the Chemistry Section
3. Please incorporate OCPB's changes to the Clinical Pharmacology section of the label from pages 18 -20 into your final labeling for —

II. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-589 and finds the Clinical Pharmacology and Biopharmaceutics section acceptable if the dissolution comment and the above labeling comments are appropriately addressed. The sponsor's proposed dissolution method of USP Apparatus 2 (Paddle) at 25 rpm, 500 mL (10 mg) or 1000 mL (20 mg) of 50 mM acetate buffer pH 4.5 and Q value of — in 30 minutes for pooled sample is not acceptable. The dissolution method and specification based on **individual tablet** data should be:

USP Apparatus 2	Paddle Method
Rotation speed:	25 rpm
Volume:	500 mL (10 mg) or 1000 mL (20 mg)
Medium:	50mM acetate buffer, pH 4.5
Tolerance:	Q = — in 15 minutes (individual not pooled samples)

This recommendation and the labeling comments should be forwarded to the sponsor.

OCPB briefing was on September 17, 2003 and there were no major issues.

A. Carol Noory
Division of Pharmaceutical Evaluation I

RD:
FT: Initialed by Ramana Uppoor, Ph.D._____

cc list: NDA 21-589; HFD-860: (Noory, Uppoor, Sahajwalla, Mehta); CDER Central Document Room

APPEARS THIS WAY
ON ORIGINAL

III. Table of Contents

IV. Summary of CPB Findings

Baclofen is an oral skeletal muscle relaxant. Clinically, Baclofen is used to treat spasticity and improve mobility in patients with multiple sclerosis and other spinal cord lesions by decreasing the number and severity of spasms and relieving associated pain, clonus, and muscle rigidity. Baclofen also improves bowel and bladder function in some of these patients. The FDA approved Baclofen Tablets in November 1977.

Schwarz Pharma has developed a new, rapidly disintegrating dosage form that provides a pharmaceutical alternative to the traditional dosing of tablets with water. The orally disintegrating tablet dissolves rapidly when exposed to fluid, such as saliva, and can be easily swallowed. Schwarz Pharma proposes to market the orally disintegrating tablets in 10 and 20 mg strengths, which are formulated to be bioequivalent to the Reference Listed Drug, Baclofen Immediate Release Tablets manufactured by Watson. This Abbreviated New Drug Application (ANDA 073093) was approved January 28, 1994.

The current application includes no clinical trials, but does include a single (1) single-dose, fasting, two treatment, four period, replicate *in vivo* bioequivalence study

comparing the 20-mg orally disintegrating tablet to the RLD both given with water. The clinical efficacy and safety of the drug are based on the clinical information from the original NDA (NDA 17-851). A single dose, fasting 2-way crossover, bioequivalence study is included to compare the 20 mg orally disintegrating tablet given without water to the 20 mg immediate release tablet manufactured by Watson Laboratories, Inc. given with water. Dissolution studies comparing the 20-mg ODT to the 20-mg RLD and the 20-mg ODT to the 10-mg ODT are also included. An in vitro study comparing the dissolution profiles of half vs. whole tablets (10-mg) is included to illustrate that the tablets can be successfully broken in half at the score. There were also waiver requests, one for a waiver for the lower strength and one for a waiver for a food effect study.

1. Study No. SP692: *"A Pharmacokinetic Study to Compare the Bioavailability of a Unique New Formulation (Test), 20 mg Orally Disintegrating Tablet (ODT), of Baclofen to a Marketed Immediate-Release 20 mg Baclofen Tablet Formulation (Reference) Manufactured by Watson Laboratories, Inc."* demonstrated the bioequivalence of the Baclofen 20 mg orally disintegrating tablet to the Baclofen immediate release 20 mg tablet manufactured by Watson when both were taken with water. Confidence intervals computed using the ratios of the product means for ln-transformed data were within the acceptable range of 80-125% required for determining bioequivalence.

2. Study No. SP741: " *A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Baclofen 20 mg Given Without Water, Compared to a Marketed Immediate-Release Baclofen 20 mg Tablet Formulation (Reference), by Watson Laboratories, Inc Given With Water."* demonstrated the bioequivalence of the Baclofen 20 mg orally disintegrating tablet administered without water to the Baclofen immediate release 20 mg tablet manufactured by Watson administered with water. Confidence intervals computed using the ratios of the product means for ln-transformed data were within the acceptable range of 80-125% required for determining bioequivalence.

   Results from studies 1 and 2 above indicate that the baclofen ODT can be given with or without water.

3. A biowaiver was requested for the lower strength based on formulation proportionality and the in vitro dissolution profile f2 comparison, which were similar in all three media tested. This biowaiver is acceptable based on criteria stated in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations". This guidance states that "when the drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients, an *in vivo* BE study of one or more lower strengths can be waived based on dissolution tests and an *in vivo* study on the highest strength."

4. The firm requested a waiver for a "food effect study". This request was acceptable based on the solubility, rapid dissolution and bioequivalence between the ODT and

the RLD. Schwarz Pharma conducted a solubility study that illustrated that the highest labeled dose (20 mg) dissolved rapidly in 200 mL of aqueous media over the pH range of 1-7.5. The dissolution study on both strengths of the ODT also showed that this product is rapidly dissolving. This waiver is further supported by the current baclofen label which does not indicate that food affects the bioavailability of baclofen.

5. An in vitro dissolution study (R-A-2002-24) comparing the 20-mg orally disintegrating tablet to the 20-mg RLD showed that the dissolution profiles are not considered similar. This is not unexpected when comparing an orally disintegrating tablet to a conventional immediate release tablet. The dissolution method and specification can be changed to reflect the dissolution characteristics of the ODT.

6. The firm conducted an in vitro study (R-A-2003-118) comparing the 10-mg ODT to the 20-mg ODT in three media of pH 1.2, 4.5 and 6.8. The profiles are similar in all three media which supports the request for a waiver of the lower, 10-mg, strength.

7. Study # R-S-2003-119 compared the 10-mg ODT broken in half along the score to whole tablets. The results of this dissolution study show that the 10-mg tablets can be broken into half to initially titrate the patient using a 5 mg starting dose.

8. An acceptable dissolution study to develop an in vitro quality control method for the 20 mg ODT was submitted. The firm proposed a dissolution procedure using the paddle method, 25 rpm and 500 mL (for the 10 mg ODT) or 1000 mL (for the 20-mg ODT) of 50 mM acetate buffer pH 4.5, as the medium. The data indicate that this product can meet a higher tolerance criterion. The following procedure should be adopted by the firm:

Apparatus	2 (Paddle Method)
RPM:	25 rpm
Medium:	50 mM acetate buffer, pH 4.5
Volume:	500 mL (10-mg) or 1000 mL (20-mg)
Tolerance:	Q=NLT – at 15 minutes

The specification is based on individual tablet dissolution data, not pooled sampling. The USP has informed me that they are phasing out pooled dissolution sampling. .

Conclusion:
The firm has demonstrated bioequivalence of a new dosage form of Baclofen 20-mg orally disintegrating tablet taken with or without water, to the approved 20-mg immediate release Baclofen tablet manufactured by Watson under fasted conditions. A waiver for a bioavailability study demonstrating that the product can be taken with or without food is acceptable. A waiver for an in vivo study demonstrating the bioequivalence of the 10-mg ODT compared to the 20-mg ODT is acceptable. To support the absorption, distribution, metabolism and elimination portion of the labeling, the firm also submitted a literature

search which was reviewed for validity. The firm has tested the dissolution of the 20-mg ODT compared to the 20 mg approved IR tablet. Both strengths of the new dosage form, and half tablets vs. whole 10 mg orally disintegrating tablets have been tested in three media of different pH using the USP Paddle method at 25 rpm. The sponsor's proposed dissolution method of USP Apparatus 2 (Paddle) at 25 rpm, 500 mL (10 mg) or 1000 mL (20 mg) of 50 mM acetate buffer pH 4.5 and Q value of — in 30 minutes based on pooled sampling is not acceptable. The following dissolution method and specification based on individual tablet data should be adopted.

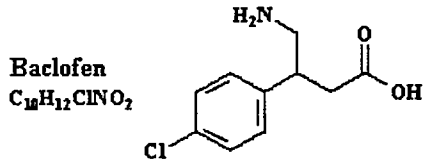
USP Apparatus 2	Paddle Method
Rotation speed:	25 rpm
Volume:	500 mL (10 mg) or 1000 mL (20 mg)
Medium:	50mM acetate buffer, pH 4.5
Tolerance:	Q = — in 15 minutes (individual sampling)

V. QBR

A. General Attributes

A.1. What are the chemical and physical-chemical properties of the drug substance and the formulation of the drug product?

Baclofen, USP is a racemic mixture, white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and insoluble in chloroform. The chemical name is 4-amino-3-(4-chlorophenyl)-butanoic acid. The molecular formula is $C_{10}H_{12}ClNO_2$.



The formulation of the Baclofen orally disintegrating tablets (Baclofen orally disintegrating tablets) is given in the following table (Table 1):

Table 1: Formulation of 10 and 20 mg Baclofen Orally Disintegrating Tablets

Component per tablet:	10 mg tablet		20 mg tablet	
	mg/tab	(%w/w)	mg/tab	(%w/w)
BACLOFEN —		—		

MANNITOL – JSP/EP/JP**				
Microcrystalline Cellulose, NF/EP/JP***				
CROSPOVIDONE, NF/EP/JP				
Aspartame – NF/EP				
Magnesium Stearate, NF/EP/JP				
NATURAL AND ARTIFICIAL ORANGE FLAVOR, –				
Colloidal Silicon Dioxide, NF/EP/JP				
Total	175.00	100.00	350.00	100.00

A.2. What is the proposed mechanism of drug action and the therapeutic indication?
Baclofen's mechanism of action is not fully understood. It is believed that the drug works mainly at the level of the spinal cord to block polysynaptic afferent pathways and, to a lesser extent, monosynaptic afferent pathways. Baclofen may inhibit the transmission of impulses through these pathways by acting as an inhibitory neurotransmitter itself or by hyperpolarizing the primary afferent nerve terminals, which inhibits the release of excitatory neurotransmitters such as glutamate and aspartic acids. Baclofen has been described as a gamma-aminobutyric acid (GABA) agonist; the drug stimulates the GABA-B receptor. This leads to a decreased release of the neurotransmitters aspartate and glutamate and decreased excitatory input into alpha-motor neurons. Approximately 15% of a baclofen dose is metabolized in the liver, mostly by deamination yielding the main metabolite, b-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

A.3. What is the solubility of Baclofen?
The firm determined the solubility of baclofen in 200 mL of pH 1.0, pH 2.9, pH 3.9 (the pKa of baclofen), pH 4.9 and pH 7.5. The study shows that baclofen is a highly soluble compound since the highest labeled dose (20 mg) dissolved rapidly in 200 mL of aqueous media over the pH range of 1-7.5.

PH	1.0	2.9	3.9	4.9	7.5
Buffer Solutions	0.05M HCl	0.05 M Phthalate	0.05 M Phthalate	0.05 M Acetate	0.05 M Phosphate
Baclofen USP Solubility Mg/1000 mL buffer solution % (mg/mL)					

Mean mg/1000 mL (mg/mL)	98.9 (0.0989)	99.7 (0.0997)	100.8 (0.1008)	99.7 (0.0997)	100.7 (0.1007)
pH Verification after adding baclofen USP	1.02	2.89	3.92	4.92	7.51
	1.01	2.90	3.91	4.93	7.50
	1.02	2.90	3.91	4.92	7.50

A.4. What is the proposed route of administration?
Baclofen orally disintegrating tablets are formulated to be placed on the tongue and sucked until completely dissolved precluding the need for taking it with water.

B. Clinical Pharmacology

B.1. What is the clinical pharmacology of baclofen?
The firm used the label of the reference listed drug, the Lioresal Intrathecal Label and available literature to determine the clinical pharmacology of baclofen. The sponsor also cited the following references to support the absorption, distribution, metabolism, excretion, food effect, and pharmacokinetics in the elderly which appear in the label. The following is a brief indication of the information and where it was located:

B.1.1. From the Reference Listed Drug Label (Watson Baclofen Tablets)

1. Baclofen is rapidly and extensively absorbed and eliminated.
2. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect.
3. Although Baclofen is an analog of the putative inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects.
4. Baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.
5. Absorption may be dose-dependent, being reduced with increasing doses.
6. Baclofen is excreted primarily by the kidneys in unchanged form and there is relatively large intersubject variation in absorption and/or elimination.
7. *Pregnancy*: Baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times the maximum dose recommended for human use, at a dose which cause significant reductions in food intake and weight gain in the dams. This abnormality was not seen in mice or rabbits. There was also an increased incidence of incomplete sternebral ossifications in fetuses of rats given approximately 13 times the maximum recommended human dose, and an increased incidence of unossified phalangeal nuclei of forelimbs and hind limbs in fetuses if rabbits given approximately 7 times the maximum recommended human dose. In mice, no teratogenic effects were observed, although reduction in mean fetal weight with consequent delays in skeletal ossification were present when dams were given 17 to 34 times human

daily dose. There are no studies in pregnant women. Baclofen should be used during pregnancy only if the benefit clearly justifies the potential risk to the fetus.

8. A dose related incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed in female rats treated chronically with Baclofen.
9. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with Baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

B.1.2. Lioresal® Intrathecal Label

CLINICAL PHARMACOLOGY

1. The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood.
2. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect.
3. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-amino-butyric acid (GABA), and may exert its effects by stimulation of the $GABA_B$ receptor subtype.
4. In people, as well as animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.
5. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No increase in tumors was seen in rats receiving Lioresal (Baclofen, USP) orally for two years at approximately 30-60 times on a mg/kg basis, or 10-20 times on a mg/m^2 basis, the maximum oral dose recommended for human use. Mutagenicity assays with Lioresal have not been performed.
6. *Pregnancy Category C:* Lioresal (baclofen USP) given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 13 times on a mg/kg basis, or 3 times on a mg/m^2 basis, the maximum oral dose recommended for human use; this dose also caused reductions in food intake and weight gain in the dams. This abnormality was not seen in mice or rabbits. There are no adequate and well-controlled studies in pregnant women. Lioresal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
7. *Nursing mothers:* In mothers treated with oral Lioresal (baclofen USP) in therapeutic doses, the active substance passes into the breast milk
8. A dose-related increase in incidence of ovarian cysts was observed in female rats treated chronically with oral Lioresal. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with oral Lioresal for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the oral drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

B.1.3. Journal Articles

1. Peterson GM, McLean S, Milligen KS. "Food Does Not Affect the Bioavailability of Baclofen." *Med J Aust* 142; 1985; (689-690). This study is a crossover design in 6 healthy subjects conducted by the University of Tasmania in Tasmania. The purpose of this study was to gather information on the influence of food on the rate and extent of gastrointestinal absorption of baclofen. Five subjects completed both legs of the study. The authors concluded that food does not significantly alter the rate or extent of gastrointestinal absorption of baclofen. They caution that the observed differences in the PK parameters between the treatments may have been statistically significant if a larger number of subjects had participated in the study. The authors recommended that the lack of a significant interaction indicates that there is no need to modify the current practice of administrating the drug with food to minimize the gastrointestinal side effects, although there does not appear to be a well-defined relationship between therapeutic responses and plasma levels of baclofen.

Comment: The information in this study [redacted]. The bioavailability of baclofen when administered with food is about 82% of the fasting BA. The time to maximum concentration is over 1.5 times longer than when administered in the fasting state. The rate of absorption is about half when administered with food compared to without food. The data does demonstrate that the food does have an effect on the PK of baclofen, however, this is not significant based on the limited data. There is no indication of a food effect in several conventional pharmaceutical reference books. In fact, the RLD label is silent regarding food effect. The labeling should reflect the labeling of the RLD and be silent on the effect of food on the bioavailability of oral baclofen.

2. Kochak GM, Rakhit A, Wagner WE, Honc F, Waldes L, and Kershaw RA. "The Pharmacokinetics of Baclofen Derived from Intestinal Infusion." *Clin Pharm Ther* 38; 1985 (251-257). This study was conducted by the Ohio State University in Columbus, Ohio. The objective of the study was to determine the PK disposition and dose proportionality at the absorption site by direct infusion of baclofen solution into the duodenum over a prolonged infusion interval. Evaluations of the assumption of near instantaneous absorption and appropriateness of treating the data with zero-order input were made. The four-way crossover study was conducted in 4 healthy non-smoking males between the ages of 21 and 26. Baclofen solution was delivered via a nasogastric tube directly to the duodenum at doses of approximately 12, 24 and 48 mgs over 8 hours infusion period. The actual dose was determined by weighing the loaded infusion pump before and after the treatment. The fourth treatment was an oral 24 mg bolus baclofen solution. Blood and urine were collected and analyzed. The data from all treatments were fitted to a PK model. The oral dose was fitted to a standard two compartment PK model with first-order input.

Comment: There seems to be a problem fitting all of the data to the model selected. It appears that this study may be adequate to suggest the volume of distribution cited in the sponsor labeling. The label statement that the volume of distribution is 59 liters can remain. The sponsor also takes the following statements from this article, "Total systemic clearance is 180 mL/min and the renal clearance is 103 mL/min." Data from a study with more subjects indicates that the renal clearance is 151 mL/min. The statement should say that, "Total systemic clearance is 180 mL/min and the renal clearance

3. Knutsson E, Lindblom U, Martensson A. "Plasma and Cerebrospinal Fluid levels of Baclofen (Lioresal®) at Optimal Therapeutic Responses in Spastic Paresis." *J Neuro Sci* 23; 1974 (473-484). The study was conducted by the Department of Clinical Neurophysiology in Stockholm, Sweden. The objective of the study was to elucidate how therapeutic responses and side effects may be related to the levels of the drug in the plasma and cerebrospinal fluid (CSF). Eleven patients with spastic paresis were evaluated. Doses were given three times a day from 30-90 mg total and plasma and CSF were evaluated at different times after dose administration.

   Comment: This study compared the therapeutic response in patients with spasticity (α or γ). Patients with γ –spasticity responded well at therapeutic levels. Three out of four patients with α –spasticity lacked functional improvement. The study assumes that only a fraction of baclofen passes into the brain from studies in dogs. This study shows that the concentrations in the CSF are less than in plasma. Based on the chemistry of baclofen, it can be expected that this drug does not readily pass the blood-brain barrier. The statement can remain.

4. Wuis EW, Dirks MJM, Termond EFS, Vree TB, Van der Kleyn E. "Plasma and Urinary Excretion Kinetics of Oral Baclofen in Healthy Subjects." *Eur J Clin Pharmacol* 37; 1989 (181-184). This study was conducted by the Department of Clinical Pharmacy at Sint Radboud University Hospital at the University of Nijmegen in The Netherlands. The pharmacokinetics of baclofen were evaluated in four healthy volunteers after receiving a single 40-mg dose. Both plasma and urine were collected, evaluated and compared to renal function. The study concluded that the mechanism of urinary excretion was more complicated than just glomerular filtration, but there was a high correlation between the apparent renal clearance of baclofen and the creatinine clearance.

Comment: The study did evaluate the protein binding of baclofen and found that the protein binding was 31%. The statement that "Plasma protein binding is approximately 30%." is acceptable. The average recovery of baclofen in the urine was 69%.

5. Faigle JW, Keberle H. "The Chemistry and Kinetics of Lioresal." Postgrad Med J 48 (Supp 5); 1972 (9-13). This study was conducted by the Department of Pharmacological Chemistry, Ciba Geigy Ltd. Basle. The study compared the PK in the dog, rat, mouse, and man. One female human subject was given a single radioactively labeled doses of 10, 20 and 40 mg. There were several findings based on this data. The group concluded that baclofen cannot penetrate the blood-brain barrier and other lipophilic membranes in the central nervous system (CNS) because it is strongly polar and hydrophilic. It was determined that 85% of the dose was excreted in the urine and feces and that the excretion was complete within 72 hours. The study also determined that the γ-hydroxymetabolite was formed from deamination. The study also concluded that blood levels increase with the three increasing doses, however, the increase in not quite proportional.

Comment: The information from this study can be used in the label

6. Wuis EW, Dirks MJM, Vree TB, Van der Kleyn E. "High Performance Liquid Chromatographic Analysis of Baclofen in Plasma and Urine of Man after Precolumn Extraction and Derivatization with o-phthaldialdehyde." *J Chromatogr* 337; 1985 (341-350). This study was also conducted by the Department of Clinical Pharmacy, Sint Radboud Hospital, at the University of Nijmegen. The Netherlands. The study evaluated urine and plasma from a single, female volunteer given a single oral dose of 20 mg of Lioresal 2 hours after breakfast. The study tested a new HPLC method and concluded that after 50 hours, 85% of the baclofen dose was recovered, unchanged in the urine. The article also states that commercially available Lioresal® is a racemic mixture.

Comment: This study supports the statement: "The γ-hydroxy metabolite, 3-(p-chlorophenyl)-4-hydroxybutyric acid, is formed after deamination of baclofen."

7. Wuis EW, Van Beijsterveldt LEC, Dirks RJM, Vree TB, Van der Kleyn E. " Rapid Simultaneous Determination of Baclofen and its γ-hydroxy metabolite in Urine by High-Performance Liquid Chromatography with Ultraviolet Detection." *J Chromatogr* 420; 1987 (212-216). This study was also conducted by the Department of Clinical Pharmacy, Sint Radboud Hospital, at the University of Nijmegen. A new HPLC method was evaluated using urine from a dog dosed with baclofen.

Comment: This information is not useful in the label.

8. Shellenberger MK, Groves L, Shah J. Novack GD. "A Controlled Pharmacokinetic Evaluation of Tizanidine and Baclofen at Steady State." *Drug Metab Dispos* 27; 1999 (201-204). This study was conducted by Athena Neurosciences, Inc. San Francisco, California. Fifteen healthy subjects were tested in a randomized, three period, multiple-dose, Latin Square design study consisting of (a) tizanidine HCL, 4 mg t.i.d. for 7 consecutive doses and (b)

baclofen, 10 mg t.i.d. and (c) both drugs dosed simultaneously for seven consecutive doses. Doses were administered every 8 hours three times a day. Blood and urine were evaluated throughout the study. The objective of the study was to investigate the potential drug-drug interaction between tizanidine and baclofen at steady-state conditions. The study concluded that the steady-state plasma concentration profiles for baclofen were very similar when administered alone and when coadministered with tizanidine. There was no clinically significant drug-drug interaction in the plasma pharmacokinetics of either tizanidine or baclofen when the two drugs were coadministered.

Comment: The study appears to be well designed and has more subjects. The renal clearance at steady-state was calculated to be 151 mL/min and the % of the dose recovered unchanged in the urine was 80.9%.

9. Hulme A, MacLennan WJ, Ritchie RT, John VA, Shotton PA. "Baclofen in the Elderly Stroke Patient: its Side-Effects and Pharmacokinetics." *Eur J Clin Pharmacol* 29; 1985; (467-469). This study was conducted by the Department of Geriatric Medicine, Dundee, U.K. Twelve elderly patients over the age of 65 years with muscle spasticity following a stroke were evaluated and compared to twelve healthy young subjects who had received a 10 mg oral dose in a separate study of identical design. Plasma concentrations in the elderly increased more slowly and reached significantly lower peak concentrations at later times compared to healthy subjects. These changes were suspected to be due to change in the GI tract as a result of aging. The AUC was almost identical between the two groups. The elimination half-life in elderly patients (2.78-6.60 hours) and healthy volunteers (2.49-5.46 hours) were similar, but the mean was greater by approximately 1 hour in the elderly and the difference was statistically significant ($p=<0.05$). This is consistent with a reduced renal function in the elderly.

Comment: The sponsor has included the data from this study. Even though the data were from two separate studies, this information can be included in the labeling.

B.2. What are the dose and dosing regimen and are there any unresolved dosing or administration issues?

Baclofen orally disintegrating tablets are designed to be bioequivalent to the conventional immediate-release Baclofen tablets of the same strength manufactured by Watson. Watson Baclofen tablets are the reference listed drug product in the Orange Book. Baclofen is initially titrated with a starting dose of 5 mg three times daily by mouth. The total daily dose is increased by 15 mg every fourth day. Doses of more than 80 to 100 mg daily are not generally recommended, although doses of up to 150 mg daily have been given to carefully supervised patients. The labeling for the ODT states that the optimal dosage regimen is individually titrated. Therapy is started at a low dosage and increased gradually until optimum effect is achieved (usually between 40-80 mg). The following dosage titration schedule is suggested:

5 mg t.i.d for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80-mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, the patient should be slowly withdrawn from the drug. The firm was asked to conduct an in vitro study on half vs. whole 10 mg tablets to determine if the scored tablet can be successfully broken in half. The orally disintegrating tablets are formulated to disintegrate in the oral cavity precluding the need for taking the tablet with water. The firm conducted two single dose, fasting bioequivalence studies which demonstrated that the tablets can be administered with or without water without a significant change in the bioavailability. There are no unresolved dosing or administration issues.

C. General Biopharmaceutics

C.1. Was bioequivalence demonstrated for the new orally disintegrating tablet when compared to the conventional dosage form, Baclofen Immediate-Release Tablets manufactured by Watson?

Yes, Study No. SP692, titled "*A Pharmacokinetic Study to Compare the Bioavailability of a Unique New Formulation (Test), 20 mg Orally Disintegrating Tablet (ODT), of Baclofen to a Marketed Immediate-Release 20 mg Baclofen Tablet Formulation (Reference) Manufactured by Watson Laboratories, Inc.*", conducted by the sponsor showed bioequivalence between the 20-mg orally disintegrating tablet and the 20-mg conventional immediate release tablet both administered with water.

C.2. Are the 10 and 20 mg orally disintegrating Baclofen tablets bioequivalent to each other?

Yes, a biowaiver was requested for the lower strength based on formulation proportionality and supported by the in vitro dissolution (f2 comparison), which were similar in three dissolution media tested. The biowaiver is acceptable and the 10 and 20 mg orally disintegrating tablets are deemed bioequivalent to each other as suggested in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations".

C.3. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The firm requested a waiver for a "food effect study" that is acceptable. The product rapidly disintegrates in the oral cavity. The dissolution study on both strengths of the ODT showed that this product is rapidly dissolving. The solubility study conducted by the firm indicates that the drug is highly soluble. The ODT is bioequivalent to the RLD and is both rapidly absorbed and eliminated as stated in the RLD product label. This

waiver is further supported by the current baclofen label which does not indicate that food affects the bioavailability of baclofen. This information suggests that there is little possibility that the food effect occurring with this product, if any, would be different from the RLD.

C.4. What is the effect of taking this dosage form with or without water on the bioavailability of the drug? What dosing recommendation should be made, if any, regarding administration of the product without water?

The sponsor conducted a single dose bioequivalence study (Study 741: "*A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Baclofen 20 mg Given Without Water, Compared to a Marketed Immediate-Release Baclofen 20 mg Tablet Formulation (Reference), by Watson Laboratories, Inc.*") in healthy subjects under fasting conditions that demonstrated that the orally disintegrating 20 mg tablet administered without water was bioequivalent to the 20 mg immediate release Reference product administered with water. The information from this study, together with the information from study SP692 show that the baclofen ODT can be given with or without water.

C.5. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The formulation to be marketed is identical to the formulation used in the pivotal in vivo trial.

C.6. Are the Sponsor's proposed dissolution method and specifications acceptable?

No. The sponsor's proposed dissolution method and tolerance uses the paddle method at 25 rpm with 50 mM acetate buffer, pH 4.5 and a tolerance specification for pooled samples of Q= — in 30 minutes. The dissolution data submitted indicates that the ODT can meet a more stringent requirement. The Q value should be — in 15 minutes based on individual, not pooled, data.

D. Analytical

D.1. Were the correct moieties identified and properly measured?

Baclofen is the only moiety measured. Known metabolites are inactive.

D.2. What bioanalytical methods are used to assess concentrations?

An LC-MS/MS method was developed and validated for the quantification of Baclofen in human EDTA plasma. The — was employed in this study. Positive ions were monitored in the — mode. Samples were spiked with the deuterated internal standard (d5-Baclofen) and centrifuged and then loaded into the — pipettor with the proper reagents and tips. The — would "run" and condition the plate with methanol followed by water, add the sample and push through the plate, then wash the sample with water and push through the plate and then elute the samples with ammonium hydroxide in methanol. The samples were evaporated to dryness under a stream of nitrogen gas and reconstituted with a mixture of acetonitrile and water.

Samples were injected onto the LC-MS/MS system. Samples were extracted (1962 samples) from July 18, 2002 through August 5, 2002.

The following parameters summarize the performance of the analytical method during the in vivo study.

Analytical Method Performance	
	Baclofen
Matrix	Plasma
Method	HPLC-MS/MS
Calibration curve range	2.00-500 ng/mL
Limit of Quantitation	2.00 ng/mL
Dates of analysis	July 18, 2002 - August 5, 2002.
Slope (n=30)	0.0178 (SD=0.0007)
Linearity	0.999440
Inter-day precision (%CV) n=59	3.91-5.93%
Inter-day accuracy (%RE) n=59	+1.17-+3.46
Two calibration curves and duplicate QC samples at four concentration levels were analyzed along with each batch of study samples.	

D.3. Was an Establishment Inspection requested for both the clinical and analytical sites?

Yes, an establishment inspection was requested for both sites.

D.4. Did the establishment inspection report reveal any deficiencies that may affect the outcome of the bioequivalence studies submitted by the firm?

Yes, the establishment inspection made (April 21-25, 2003) at the — — for Study #SP692, did reveal deficiencies that may affect the outcome of the bioequivalence study submitted by the firm. The firm adequately responded to these deficiencies in their letters dated May 9, 2003 and July 9, 2003, so there are no outstanding DSI issues.

VI. Clinical Pharmacology Labeling

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory neurotransmitter gamma-amino-butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

Pharmacokinetics

Absorption

Baclofen is rapidly and extensively absorbed. Absorption may be dose-dependent, being reduced with increasing doses. [redacted] given with or without water is bioequivalent to the baclofen conventional tablet. Thus [redacted] can be taken with water or placed on the tongue until dissolved and then swallowed. Following a single 20 mg oral dose of [redacted] the peak plasma concentration was reached about 1½ hours after administration.

Deleted

Distribution

The apparent volume of distribution is 59 liters. Baclofen does not readily cross the blood-brain barrier. Plasma protein binding is approximately 30%.

Metabolism

In a study using radiolabeled baclofen, approximately 85% of the dose was excreted unchanged in the urine and feces. About 15% of the dose was metabolized, primarily by deamination. The γ-hydroxy metabolite, 3-(p-chlorophenyl)-4-hydroxybutyric acid, is formed after deamination of baclofen.

Excretion

Baclofen is rapidly and extensively eliminated. There is a relatively large intersubject variation in elimination. Baclofen is excreted primarily by the kidney as unchanged drug; 70 - 80% of a dose appears in the urine as unchanged drug. The remainder is excreted as unchanged drug in the feces or as metabolites in the urine and feces. Excretion is complete within 72 hours after administration. The elimination half-life of [redacted] is approximately 5½ hours. Total systemic clearance is 180 mL/min and renal clearance is 103 mL/min.

Special Populations

Elderly

The pharmacokinetics of baclofen tablets were evaluated in elderly patients (69-81 years) and in healthy younger subjects (23-53 years) after a single 10 mg dose. The C_{max} was lower
(119 ng/mL vs. 178 ng/mL) and the T_{max} was longer (3 hours vs. 1 hour) in the elderly patients compared to the younger subjects. The AUCs were similar in the two groups. In

this study, the elimination half-life was slightly prolonged in the elderly patients compared to the younger subjects, 4.43 hours vs. 3.75 hours, respectively.

VII. Appendix

A. Individual Study Reviews

A.1. Study No. SP692

Title:
A Pharmacokinetic Study to Compare the Bioavailability of a Unique New Formulation (Test), 20 mg Orally Disintegrating Tablet (ODT), of Baclofen to a Marketed Immediate-Release 20 mg Baclofen Tablet Formulation (Reference) Manufactured by Watson Laboratories, Inc.

Investigator:

Objective:
The objective of the study was to assess the bioavailability of the test product, a 20 mg Baclofen ODT formulation, compared with the reference product, a 20 mg Baclofen tablet manufactured by Watson Laboratories, following a single dose in the fasted state.

Formulations:
Treatment A (Test Product) Baclofen 20 mg Orally Disintegrating Tablet, Manufactured by Cima Labs, Inc.; Lot 920094, Mfg. Date: May 2002, (— , tablet batch)

Treatment B (Reference Product) Baclofen 20 mg Immediate-Release tablet, Manufactured by Watson Laboratories, lot C1C0341 (exp. April 2003)

Study Dates:
Start Date: June 22, 2002
Ending Date: July 15, 2002

Study design:
This was a single-dose, randomized, open-label, 2-treatment, 4-period, replicate study. Twenty-eight subjects (14 males and 14 females) were enrolled in the study, and 25 subjects (12 males and 13 females) completed the study. The mean age of the subjects was 29 years (19-49 years), the mean height of the subjects was 68.2 inches (62.0-76.0 inches), and the mean weight of the subjects was 153.3 pounds (119.0-212.0 pounds). Subjects receiving the IR tablet (Reference) took the tablet with 240 mL of water. Subjects receiving the ODT (Test) tablet had the tablet placed on the tongue until

disintegrated and then were given 240 mL of water. Doses were administered after a 10 hour fast. There was a 7-day washout interval between the 4 dose administrations. The subjects were confined to the clinic during each study period. A clinical laboratory evaluation (hematology, serum chemistries, and urinalysis), a brief physical examination, a 12-lead electrocardiogram, an adverse event evaluation, and vital signs (sitting blood pressure, pulse, respiration, and temperature) assessments were performed at the completion of the study.

Sample Collection:
Blood samples were collected from each subject at 0.0 (pre-dose), 0.25, 0.5, 0.75.1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours post-drug administration

Analytical Method Performance
A suitable validated and sensitive LC-MS/MS assay method was developed for the quantitation of Baclofen in human EDTA plasma. Samples were spiked with deuterated internal standard and diluted. The compounds of interest were extracted by solid-phase extraction using the — pipettor. The extracts were evaporated to dryness under a stream of nitrogen gas and reconstituted with an acetonitrile and water solution before injection onto an LC-MS/MS. The analytical parameters are given in Table A.1.

Table A1. Analytical Method Performance

	Baclofen
Matrix	Plasma
Method	HPLC-MS/MS
Calibration curve range	2.00-500 ng/mL
Limit of Quantitation	2.00 ng/mL
Dates of analysis	July 18, 2002 - August 5, 2002.
Slope (n=30)	0.0178 (SD=0.0007)
Linearity	0.999440
Inter-day precision (%CV) n=59	3.91-5.93%
Inter-day accuracy (%RE) n=59	+1.17-+3.46
Two calibration curves and duplicate QC samples at four concentration levels were analyzed along with each batch of study samples.	

Pharmacokinetic Computations and Statistical Analysis

The pharmacokinetics of plasma baclofen were assessed by measuring the serial plasma concentrations of baclofen following the administration of the test and reference treatments. Bioequivalence was determined when the 90% confidence intervals of the ratio of products means for ln-transformed Cmax, AUC(0-t), and AUC (0-∞) for baclofen were within the range of 80-125%. The parameter values of Kel, T1/2 and Tmax were also compared between treatments.

The $AUC_{(0-t)}$ was calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (Ct). $AUC_{(0-\infty)} = AUC_{(0-t)} + Ct/Kel$, where Kel is the terminal elimination rate constant. AUC(0-t)/AUC(0-∞) was referred to as AUCR. Kel was calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. T ½ was calculated as ln(2)/Kel. A mixed linear model was applied to the logarithmic transformations of AUC(0-inf), AUC(0-t) and Cmax. Terms used in the model included sequence, subject within sequence, treatment, (subject by treatment) within sequence, period, and (sequence by period) within treatment, within subject within sequence and (subject by treatment) within sequence being defined as random effects.

The 2 one-sided hypotheses were tested at 5% level for AUC(0-inf), AUC(0-t), and Cmax by constructing 90% confidence intervals for the ratio of the Test and Reference means. The 90% CI were obtained for the antilogs of the lower and upper bounds of the 90% CI for the differences in the least-squares means of the log transformed data.

The arithmetic means and standard deviations of plasma Baclofen pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC (0-t), and AUC (0-∞) following Treatments A and B are summarized in the following table.

Table A.2.

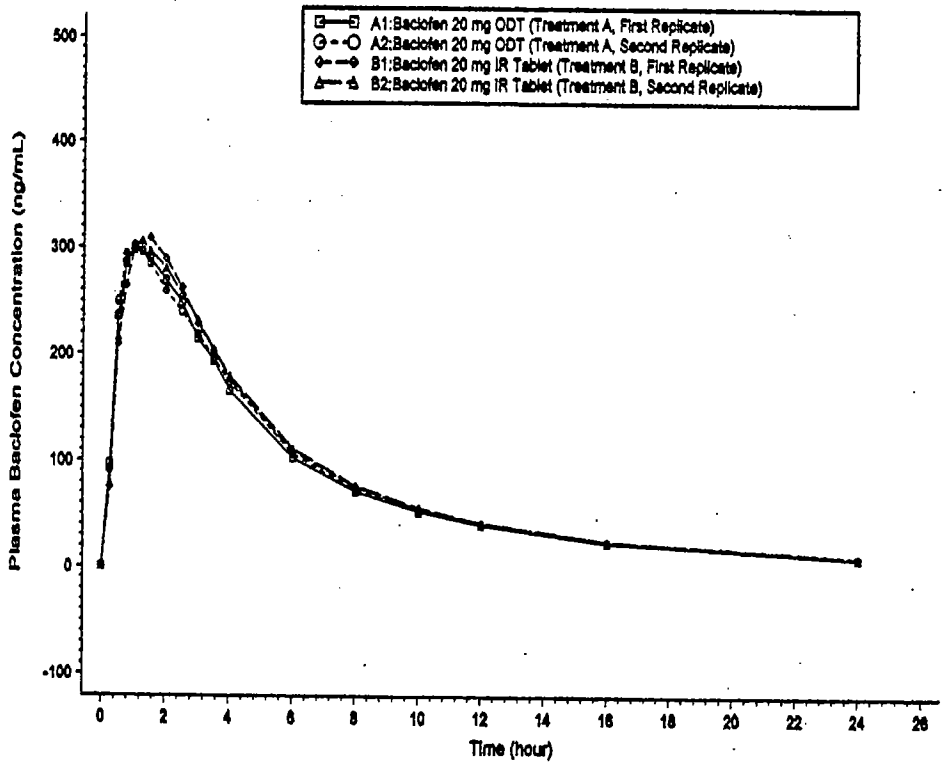
Summary of the Pharmacokinetic Parameters of Plasma Baclofen for Treatments A and B

	Plasma Baclofen									
	Treatment A				Treatment B					
	First Replicate		Second Replicate		First Replicate		Second Replicate			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI *	% Mean * Ratio
Cmax (ng/mL)	325.56	78.71	328.01	85.61	334.99	79.73	343.83	66.73		
Tmax (hr)	1.50	0.789	1.33	0.774	1.36	0.515	1.27	0.753		
AUC (0-t) (ng*hr/mL)	1817	390.0	1843	393.5	1889	325.0	1905	355.6		
AUC (0-inf) (ng*hr/mL)	1893	396.4	1919	405.1	1968	340.5	1989	373.3		
T1/2 (hr)	5.66	0.829	5.64	0.761	5.60	0.809	5.74	0.747		
Kel (1/hr)	0.125	0.0185	0.125	0.0174	0.127	0.0194	0.123	0.0173		
AUCR	0.959	0.0170	0.960	0.0142	0.960	0.0161	0.958	0.0150		
ln(Cmax)	5.757	0.2431	5.762	0.2493	5.785	0.2514	5.822	0.1981	92.2- 99.7	95.9
ln[AUC (0-t)]	7.482	0.2227	7.496	0.2256	7.530	0.1739	7.535	0.1883	91.8- 99.8	95.7
ln[AUC (0-inf)]	7.524	0.2184	7.537	0.2229	7.570	0.1738	7.578	0.1893	91.9- 99.7	95.7

Treatment A = 1 x 20 mg Baclofen CDT Administration (Schwarz Pharma, Inc.): Test
Treatment B = 1 x 20 mg Baclofen IR Tablet Administration (Watson Laboratories, Inc.): Reference
* = Based on LS means from Table 11.

The plasma concentration time curve for baclofen is shown in the following figure (Figure 2).

Figure 2
Mean Plasma Baclofen Concentrations Versus Time
(Linear Scale)



Conclusion:

Study SP 692 demonstrated that Baclofen 20 mg orally disintegrating tablets were bioequivalent to 20 mg Baclofen Immediate release tablets manufactured by Watson Laboratories under single-dose, fasting conditions when both treatments were administered with water, based on the 90% confidence intervals computed using the ratio of product means for ln-transformed data. Confidence intervals for Baclofen were between 91-100% for AUC (0-t), 92-100% for AUC (0-inf), and 93-100% for Cmax. The 90% confidence intervals were within the acceptable range of 80-125% required for determination of bioequivalence. This reviewer with help from Dr. Wendy Chou, reanalyzed this replicate design data and computed confidence intervals based on average bioequivalence approach, using a linear mixed-effects model (SAS PROC MIX). The 90% confidence intervals were similar and still within the 80-125% acceptable range. The between subject variability was 19.9% for the test product and 16.6% for the reference product. The within subject variability was 8.25% for the test product and 10.38% for the reference product.

A.2. Study No. SP741/AA03821

Title:

A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Baclofen 20 mg Given Without Water, Compared to a Marketed Immediate-Release Baclofen 20 mg Tablet Formulation (Reference), by Watson Laboratories, Inc.

Investigator:

Objective:

The objective of the study was to evaluate the single dose bioequivalence of a test 20 mg Baclofen ODT formulation taken without water, compared to the reference product, a 20 mg Baclofen tablet manufactured by Watson Laboratories taken with water.

Formulations:

Treatment A (Test Product) Baclofen 20 mg Orally Disintegrating Tablet, Manufactured by Cima Labs, Inc.; Lot 920094, Mfg. Date: May 2002, [redacted] ablet batch)

Treatment B (Reference Product) Baclofen 20 mg Immediate-Release tablet, Manufactured by Watson Laboratories, lot C2D0401 (exp. May 2004)

Study Dates:

Start Date: May 10, 2003
Ending Date: May 19, 2003

Study design:

This was a single-dose, randomized, open-label, 2-period crossover study. Eighteen subjects (14 males and 4 females) were enrolled in the study, and 17 subjects (14 males and 2 females) completed the study. The mean age of the subjects was 31 years (19-50 years), the mean height of the subjects was 70 inches (60-75 inches), and the mean weight of the subjects was 167 pounds (134-194 pounds). Subjects receiving the IR tablet (Reference) took the tablet with 240 mL of water. A mouth check was performed to ensure that the study drug was swallowed. Subjects receiving the ODT (Test) tablet had the tablet placed on the tongue until disintegrated. No water was given with the tablet. The subject was instructed not to chew or swallow the tablet. The subject notified the clinic staff when the ODT was completely disintegrated, and the staff verified the disintegration was complete and recorded the time of disintegration. The subject then swallowed the tablet without water. The clinic staff verified that the tablet was swallowed. Doses were administered after a 10.5 hour fast. Water was restricted 1 hour predose until 1.5 hours postdose. There was a 7-day washout interval between the 2 dose administrations. The subjects were confined to the clinic during each study period. A

clinical laboratory evaluation (hematology, serum chemistries, and urinalysis), a brief physical examination, a 12-lead electrocardiogram, an adverse event evaluation, and vital signs (sitting blood pressure, pulse, respiration, and temperature) assessments were performed at the completion of the study.

Sample Collection:
Blood samples were collected from each subject at 0.0 (pre-dose), 0.25, 0.5, 0.75.1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours post-drug administration. A total of 36 blood samples were drawn per subject during the study for drug analysis. Samples were collected and processed on ice bath. Plasma samples were assayed at —

Analytical Method Performance
A suitable validated and sensitive LC-MS/MS assay method was developed for the quantitation of Baclofen in human EDTA plasma. Samples were spiked with deuterated internal standard and diluted. The compounds of interest were extracted by solid-phase extraction using the — pipettor. The extracts were evaporated to dryness under a stream of nitrogen gas and reconstituted with an acetonitrile and water solution before injection onto an LC-MS/MS. The —
— , was employed in this study. Positive ions were monitored in the
— , mode. The analytical parameters are given in Table A.2.1.

Table A2.1. Analytical Method Performance	
	Baclofen
Matrix	Plasma
Method	HPLC-MS/MS
Calibration curve range	2.00-500 ng/mL
Limit of Quantitation	2.00 ng/mL
Dates of analysis	May 22, 2003 to June 7, 2003.
Slope (n=20)	0.01884 (SD=0.0012) (%CV=6.6)
Linearity	0.9978
Inter-day precision (%CV) n=20	2.0-4.9%
Inter-day accuracy (%RE) n=20	-4.8-+3.5

ODT Disintegration Times
For treatment A, one 20 mg tablet was placed on the subject's tongue. The subject was asked to notify the clinic staff when the tablet had completely disintegrated. The time when the tablet had completely disintegrated was recorded and verified by the clinic staff by visual inspection of the subject's mouth. The times to disintegration for each subject for treatment A are presented in the following table (Table A.2.2.).

TABLE A2.2. TIME FOR ODT TABLET TO DISINTEGRATE	
Subject	**Time to disintegration (seconds)**
2	—

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
Mean	91.76
SD	45.09
Minimum	
Median	89.00
Maximum	
N	17

Pharmacokinetic Computations and Statistical Analysis

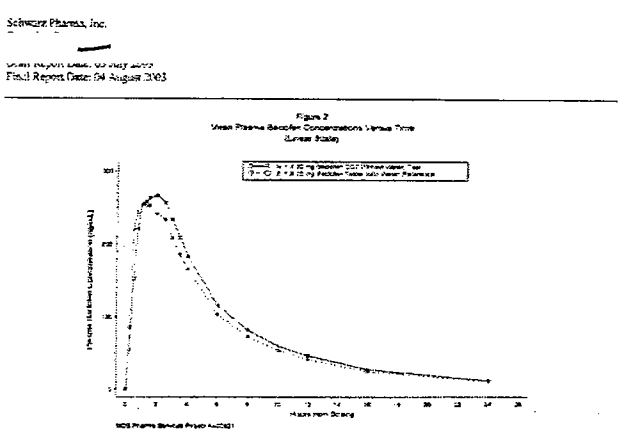
The pharmacokinetics of plasma baclofen were assessed by measuring the serial plasma concentrations of baclofen following the single dose administration of the test and reference treatments. The pharmacokinetic parameters Cmax, Tmax, AUC(0-t), AUC (0-inf), AUCR [AUC(0-t)/AUC(0-inf)], Kel, and T1/2 were calculated using noncompartmental methods. A parametric (normal-theory) general linear model was applied to the logarithmic transformations of Cmax, AUC(0-t), and AUC(0-inf) values. The analysis of variance (ANOVA) model included the following factors: sequence, subject within sequence, period, and formulation. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square). The 2 one-sided hypotheses were tested at 5% level for AUC(0-inf), AUC(0-t), and Cmax by constructing 90% confidence intervals for the ratio of the Test and Reference means. The 90% CI were obtained from the antilogs of the lower and upper bounds of the 90% CI for the differences in the least-squares means of the ln-transformed data.

Bioequivalence was concluded when the 90% confidence intervals of the ratio of the treatment geometric least squares (LS) means (test/reference) for each parameter was determined to be within the range of 80-125%. The parameter values of Kel, T1/2 and Tmax were also compared between treatments.

The arithmetic means and standard deviations of plasma Baclofen pharmacokinetic parameters and statistical comparisons of ln-transformed Cmax, AUC (0-t), and AUC (0-∞) following Treatments A and B are summarized in the following table (Table A.2.3.).

TABLE A.2.3: SUMMARY OF THE PHARMACOKINETIC PARAMETERS OF PLASMA BACLOFEN FOR TREATMENTS A AND B						
	Plasma Baclofen					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	311.82	56.86	289.47	57.19	-	-
Tmax (hr)	1.60	0.789	1.38	0.702	-	-
AUC(0-t) (ng*hr/mL)	1905.2	266.13	1796.9	295.06	-	-
AUC (0-inf) (ng*hr/mL)	2008.2	284.06	1895.1	317.31	-	-
T ½ (hr)	5.96	0.785	6.06	0.812	-	-
Kel (1/hr)	0.118	0.0172	0.117	0.0187	-	-
AUCR	0.949	0.0179	0.949	0.0167	-	-
Ln (Cmax)	5.727	0.1815	5.649	0.2052	101.23-116.51	108.6
Ln [AUC(0-t)]	7.543	0.1453	7.479	0.1819	99.98-114.82	107.1
Ln [AUC(0-inf)]	7.595	0.1503	7.532	0.1867	100.10-114.56	107.1
Treatment A=1 X 20 mg Baclofen ODT Without Water: TEST Treatment B=1 X 20 mg Baclofen Tablet With Water: Reference						

The plasma concentration time curve for baclofen is shown in the following figure (Figure 2).



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Discussion

There was a significant period effect for the AUC(0-t) and AUC (0-inf) parameters. The seven (7) day washout period appears adequate based on the average half-life of 6 hours for baclofen. The period effect was an unexplained statistical finding since predose levels in all periods were low. The mean ratios of the ln-transformed parameters for Test/Reference, resulted in similar baclofen exposure. The 90% confidence intervals for ln-transformed Cmax, AUC (0-t), and AUC(0-inf) were 108.6%, 107.1% and 107.1% respectively. This indicates similar baclofen exposure for the test and reference formulations. The 90% confidence intervals for ln(Cmax) (101.23-116.51%), AUC (0-t) (99.98-114.82%) and ln(AUC(0-inf) (100.10-114.56%) were all within the 80-125% range required for bioequivalence. Disintegration times for the orally disintegrating tablets ranged from — seconds with a mean ±SD of 91.76 ±45.09.

Conclusion:

Study SP 741/AA03821 demonstrated that Baclofen 20 mg orally disintegrating tablets administered without water were bioequivalent to 20 mg Baclofen Immediate release tablets manufactured by Watson Laboratories administered with water under single-dose, fasting conditions based on the 90% confidence intervals computed using the ratio of product means for ln-transformed data. Confidence intervals for Baclofen were between 99-115% for AUC (0-t), 100-115% for AUC (0-inf), and 101-117% for Cmax. The 90% confidence intervals were within the acceptable range of 80-125% required for conclusion of bioequivalence.

B. Dissolution studies

The firm conducted three dissolution studies. The dissolution studies accomplished several objectives. The dissolution of the 20-mg ODT was compared to the RLD using the current USP method; the 10 and 20 mg OD tablets were tested using three media of varying pH, and 10 mg OD tablets broken in half along the score line were compared to whole 10 mg OD tablets in three media. Dissolution profile comparisons (f2) were made using the following equation: $f_2=50 \cdot \log\{[1+(1/n \varphi - T_t)^2]^{-0.5} \cdot 100\}$

B.1. Study # R-A-2002-124: "Comparative Dissolution Profiles of Baclofen ODT, 20 mg, to Commercial Baclofen Immediate Release 20 mg Tablets".

Tablet Samples: Orally disintegrating tablet Lot 920094 (Schwarz) and Watson reference lot ClC0341.

Method:

Apparatus:	USP Apparatus 2 (Paddle Method)
Paddle speed:	50 rpm
Media:	0.01N HCl
Volume:	1000 mL
Sampling times:	5, 10, 15, 30 and 45 minutes (Pooled samples)

Results:

The results of two samples comprised of six pooled tablets each (n=6) are shown in the following table.

Table B1.1: Mean Results for the two pooled (n=6 samples) using the paddle method, 50 rpm and 1000 mL of 0.01N HCl as the medium

Time point (minutes)	% Baclofen Released	
	Lot 920094 (Schwartz)	Lot ClC0341 (Watson)
5	100	76
10	101	86
15	101	90
30	101	94
45	101	96
f2=42		

Conclusion

The dissolution profiles of Baclofen 20 mg and the Watson reference tablet cannot be considered similar because the similarity factor of 42 falls outside the range of 50-100. This is not unexpected when comparing an orally disintegrating tablet to a conventional tablet. Both meet the USP specification of NLT — at 30 minutes.

B.2. Study # R-A 2003-118: "Individual Tablet Dissolution of Baclofen 10-mg and 20-mg Orally Disintegrating Tablets in 0.1N HCl, pH 4.5 Acetate and pH 6.8 Phosphate Buffer."

Tablet Samples: 10 and 20 mg baclofen ODT tablet lots 920093 and 920094 respectively, stored at 25°C/60% RH for 9 months

Method

Apparatus:	Apparatus 2, paddle method
Paddle Speed:	25 rpm
Media:	0.1 N HCl; pH 4.5 acetate buffer; pH 6.8 phosphate buffer
Volume:	500 mL for 10 mg Lot 920093 1000 mL for 20 mg Lot 920094
Sampling Intervals:	2.5, 5, 10, 15, 20, 25, 30, and 45 minutes

Results:
Individual results (n=12) for each strength OD tablet are presented in the following table.

Table B2.1: 10 mg vs. 20 mg Baclofen ODT: Comparison in Three Media

		2.5	5	10	15	30	45
0.1N HCl							
10 mg tablets	Mean	79	97	99	99	99	100
	SD	8.12	3.63	2.42	2.33	2.07	2.15
	%RSD	10.3	3.7	2.4	2.4	2.1	2.2
	Range						
20 mg tablets	Mean	69	97	100	100	100	100
	SD	5.8	2.6	1.44	1.44	1.41	1.44
	%RSD	8.1	2.6	1.4	1.4	1.4	1.4
	Range						
f2=68							
pH 4.5 acetate buffer							
10 mg Tablets	Mean	66	89	95	96	98	99
	SD	6.21	5.45	3.59	3.00	2.01	2.06
	%RSD	9.4	6.1	3.8	3.1	2.1	2.1
	Range						
20 mg Tablets	Mean	54	88	98	99	100	100
	SD	6.02	5.00	2.68	2.39	1.91	1.90
	%RSD	11.1	5.7	2.7	2.4	1.9	1.9
	Range						

f2=63							
pH 6.8 Phosphate buffer							
10 mg Tablets	Mean	63	80	88	91	95	96
	SD	7.98	3.75	2.64	2.78	2.68	2.37
	%RSD	12.7	4.7	3.0	3.1	2.8	2.5
	Range						
20 mg Tablets	Mean	55	77	89	93	97	98
	SD	2.47	3.38	1.78	1.24	1.22	1.51
	%RSD	4.5	4.4	2.0	1.3	1.3	1.5
	Range						
f2=70							

Conclusion

Dissolution similarity factors of the 10 mg and 20 mg tablets (f2) were calculated to be 68 for the 0.1N HCl media, 63 for the pH 4.5 acetate media and 70 for the pH 68 phosphate buffer. The dissolution profiles of the 10-mg and 20-mg Baclofen orally disintegrating tablets are between 50 and 100 and can be considered similar based on the criteria given in the "FDA Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms". A biowaiver can be granted for the 10 mg ODT.

B3. Study R-A-2003-119: Individual Tablet Dissolution Comparison of 10-mg Baclofen Orally Disintegrating Tablets, Half vs. Whole Tablets in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate media.

Tablet samples: Scored 10-mg baclofen ODT tablets lot 730092, full-scale demonstration batch. Half tablets were broken by hand at the score. One half of the tablet was discarded and the other half was weighed and delivered into the appropriate dissolution medium.

Method

Apparatus:	Apparatus 2, paddle method
Paddle Speed:	25 rpm
Media:	0.1 N HCl; pH 4.5 acetate buffer; pH 6.8 phosphate buffer
Volume:	500 mL for whole and half tablets
Sampling Intervals:	2.5, 5, 10, 15, 20, 25, 30, and 45 minutes

Results

The results of the whole and half tablet dissolution in three media are shown in the following table (Table B3.1)

Table B3.1: Whole vs. Half Tablet Comparison in Three Media

		2.5	5	10	15	20	25	30	45
0.1N HCl									
Whole tablets	Mean	74	96	99	100	100	100	100	100
	SD	8.97	2.19	1.85	1.73	2.09	1.99	1.99	1.91
	%RSD	12.1	2.3	1.9	1.7	2.1	2.0	2.0	1.9
	Range								
Half tablets	Mean	94	101	102	103	103	103	103	103
	SD	11.06	5.92	5.20	5.77	5.51	5.24	5.12	5.30
	%RSD	11.8	5.9	5.1	5.6	5.3	5.1	5.0	5.1
	Range								
F2=55									
pH 4.5 acetate buffer									
Whole Tablets	Mean	49	70	86	92	95	97	97	99
	SD	7.61	6.55	4.98	2.91	1.23	1.51	1.44	1.72
	%RSD	15.5	9.4	5.8	3.2	1.3	1.6	1.5	1.7
	Range								
Half Tablets	Mean	73	91	97	98	98	99	100	101
	SD	8.31	7.95	6.69	6.33	6.20	6.28	5.98	6.26
	%RSD	11.4	8.7	6.9	6.5	6.3	6.3	6.0	6.2
	Range								

F2=45									
pH 6.8 Phosphate buffer									
Whole Tablets	Mean	51	70	82	86	88	90	91	94
	SD	4.78	4.15	2.15	1.95	2.02	1.92	2.11	2.02
	%RSD	9.4	5.9	2.6	2.3	2.3	2.1	2.3	2.1
	Range								
Half Tablets	Mean	60	76	85	90	92	94	95	98
	SD	5.44	3.50	3.75	3.87	3.87	3.95	4.01	3.98
	%RSD	9.1	4.6	4.4	4.3	4.2	4.2	4.2	4.0
	Range								
F2=64									

Individual tablet dissolution data (n=12) comparing half-tablet and whole tablet 10 mg orally disintegrating tablets (ODTs) were generated using USP apparatus 2, paddle method, 25 rpm and 37°C using either 0.1N HCl, 50 mM pH 4.5 acetate buffer or 50 mM pH 6.8 phosphate buffer as media. Half and whole tablet results meet the USP monograph for baclofen stage 1 dissolution specification of Q= at 30 minutes for both unit and pooled testing in all three media. Individual tablet % baclofen released results (n=12) at 30 minutes for whole tablets and weight normalized half-tablets have % RSD's of less than 3.0% in all three media. Dissolution similarity factors (f2) comparing whole 10-mg with both half 10 mg and normalized half 10-mg ODT were calculated to be greater than 50 for 0.1N HCl medium and pH 6.8 Phosphate medium, and slightly less than 50 for pH 4.5 acetate medium with some difference (large %RSD) only in the first 5 minutes.

Conclusion

Half and whole 10-mg baclofen ODTs give similar baclofen release profiles in 0.1N HCl and pH 6.8 phosphate buffer media. Half and whole 10-mg baclofen ODTs give similar baclofen release in pH 4.5 acetate buffer at 10, 20, 25, 30 and 45 minute time points while half tablets may give somewhat higher %baclofen release at 2.5 and 5 minute time points (large %RSD).

Comment

The firm has proposed the following dissolution method and specification for the OD Baclofen tablets:

Apparatus 2:	Paddle Method
Speed of Rotation:	25 rpm
Media:	50 mM acetate buffer, pH 4.5
Volume:	500 mL (10 mg tablet); 1000 mL (20 mg tablet)

Sampling time: 30 minutes
Tolerance: Q= — at 30 minutes (pooled sample)

Agency Recommended Dissolution Method and Specifications:

The firm has recommended keeping the pooled sample tolerance. This is not acceptable. Individual data submitted indicate that the dissolution of the Orally Disintegrating tablets is rapid and complete within the 30 minute time period. The orally disintegrating Baclofen tablet should meet a more stringent Q value based on the data submitted. It is recommended that the Q be increased to — in 15 minutes. The recommended dissolution method and specification for the orally disintegrating tablet should be:

Apparatus 2	Paddle Method
Paddle Speed	25 rpm
Medium:	50mM acetate buffer, pH 4.5
Medium Volume:	500 mL (10 mg) or 1000 mL (20 mg)
Sampling time:	15 minutes
Tolerance:	Q= — in 15 minutes based on individual data

C. Analytical Method Validation

An LC-MS/MS method was developed and validated for the quantification of Baclofen in human EDTA plasma. Samples were spiked with deuterated internal standard and diluted. Baclofen and the internal standard d5-Baclofen were centrifuged and then loaded into the — pipettor with the proper reagents and tips. The — would "run" and condition the — plate with methanol followed by water, add the sample and push through the plate, then wash the sample with water and push through the plate and then elute the samples with ammonium hydroxide in methanol. The samples were evaporated to dryness under a stream of nitrogen gas and reconstituted with a mixture of acetonitrile and water. These samples were injected onto the LC-MS/MS system. The —, was employed in this study. Positive ions were monitored in the — mode. Samples (1962 samples) were extracted from July 18, 2002 through August 5, 2002. Baclofen was linear over a range of 2-500 ng/mL, the limit of quantitation (LOQ) was 2 ng/mL.

The method was validated for specificity, linearity, recovery, and stability using prepared standards and quality control samples in plasma. The intra- and inter- batch precision and accuracy was determined by analyzing sets of standards and/or quality control samples. Standards were 2, 5, 10, 20, 50, 100, 200, 400 and 500 nanograms of baclofen per mL of plasma. Quality Control Samples were spiked with baclofen at 6, 60 and 375 ng/mL. Concentrations of analytes of each level of quality control sample were determined from the standard curve. Reinjection stability, bench-top stability, freeze/thaw stability, refrigeration stability and long-term stability of quality control samples spiked with baclofen at 6, 60 and 375 ng/mL were assessed. During the validation, quality control samples were stored in a freezer set at -20°C.

Intra-day Precision and Accuracy of Quality Control Samples was determined by analyzing six replicates in a single batch. The baclofen concentrations for each sample were interpolated from the standard curve. The average precision ranged from 0.6 to 4.6%. Accuracy ranged from 0.5 to 1.7%. Both intra-day precision and accuracy data are considered satisfactory.

Inter-day Precision and Accuracy of Quality Control Samples were determined by spiking blank plasma with baclofen at 6, 60, and 375 ng/mL levels. The precision (%CV) ranged from 3.8 to 5.7% for 36 sets of QC samples. The accuracy (%RE) ranged from 1.8 to 3.2%. Both the inter-day precision and accuracy data are considered satisfactory.

Selectivity and sensitivity were evaluated by spiking 6 lots of human EDTA plasma with Baclofen at 1.00 ng/mL, 2.00 ng/mL, and 500 ng/mL. At 2.0 ng/mL, 6 out of 6 were within 20% of the theoretical value when back-calculated against the calibration standards. At 500 ng/mL, 6 out of 6 lots were within 15% of the theoretical value when back-calculated against calibration standards. No interference at the retention time of Baclofen was shown for 6 out of 6 lots. The typical signal to-noise ratio at 2.00 ng/mL was 6:1

Linearity.

Prior to analysis of study samples, the method was tested to show consistent performance of the analytical method and instrumentation. A plot of baclofen concentrations versus their peak area ratios (to internal standard) demonstrated that the responses are linear

over the range specified. No significant trend or bias was observed. The regression analyses of the data showed a correlation coefficient of 0.998736 with mean slopes of 0.0238.

Extraction Recovery of baclofen was determined by comparing the responses of blank plasma spiked with 2, 50 and 500 nanograms of baclofen and then extracted to unextracted standards prepared at the same levels. Overall recovery was 85% over a concentration range of 2 –500 ng/mL for baclofen. Internal standard recovery was determined by comparing the responses of extracted and unextracted plasma samples spiked with d5- baclofen. Overall recovery of internal standard was 85%.

Reinjection/Refrigeration Stability was determined using processed spiked samples that were re-injected at least 57 hours following the initial injection. Total stability for refrigerated samples from completion of the extraction to the final injection was 71 hours. The results show area counts for Baclofen in 57 hour-old standard solutions was — — of those in freshly prepared standard solutions, indicating acceptable stability of the analytical standard in solution when stored in the refrigerator for at least 57 hours.

Benchtop Stability of Processed Quality Control Samples was determined by analyzing two sets of quality control samples. One of the replicates was left on the benchtop at ambient temperature under white light for at least 24 hours prior to processing, while the other was kept in a -20°C freezer. The mean concentrations of baclofen kept at ambient temperature for at least 24 hours were — for the three QC concentrations compared to the samples held in the freezer.

Freeze/Thaw Stability of Unextracted Quality Control Samples was determined by analyzing one set of QC samples after one freeze-thaw cycle and another set after six freeze-thaw cycles. The mean concentrations of baclofen assayed after one freeze/thaw was comparable to the baclofen assayed after six freeze/thaw cycles. This indicates that the compound is stable in plasma for at least six freeze-thaw cycles.

Long Term Stability of Quality Control Samples in a biological matrix was assessed by analyzing QC samples prepared on April 15, 2002 and stored in a -20°C freezer for 87 days. The samples were then extracted and analysed. The results demonstrate that baclofen (—) is stable at -20°C in plasma for at least 87 days.

A summary of the validation study results are given in the following tables.
Stability:

Table C.1.: Analytical Parameters

Parameter	Number of results	strength	Baclofen
Selectivity			No interference
Lower Limit of Quantitation			2 ng/mL
Standard correlation coefficient	N=5		0.9874 (0.0008)
Percent recovery	N=6 QC samples	2 ng/mL	86% (6.9%)
		50 ng/mL	81 (9.8%)
		500 ng/mL	87 (6.4%)
Interbatch Precision (%CV)	N=36 QC samples	6 ng/mL	5.7%
		60 ng/mL	3.8%
		375 ng/mL	3.9%
Interbatch Accuracy (%RE)	N=36 QC samples	6 ng/mL	1.8%
		60 ng/mL	3.2%
		375 ng/mL	2.1%

Intrabatch Precision (%CV)	N=6 QC samples	6 ng/mL	4.6%
		60 ng/mL	0.6%
		375 ng/mL	1.5%
Intrabatch Accuracy (%RE)	N=5 Calibration standards	6 ng/mL	0.5%
		60 ng/mL	1.7%
		375 ng/mL	1.3%
Refrigeration Stability of Extracted QC Samples	N=6	6 ng/mL	
		600 ng/mL	
		375 ng/mL	
Benchtop Stability of QC samples	N=6	6 ng/mL	
		60 ng/mL	
		375 ng/mL	
Freeze/Thaw Stability of QC samples	N=6	6 ng/mL	
		60 ng/mL	
		375 ng/mL	

Conclusion.
The validation report data demonstrates that the procedure for the determination of baclofen in human plasma is specific, accurate, and reproducible. The data also demonstrates that the method can be used to measure baclofen in human plasma in the range of 2 –500 ng/mL.

APPEARS THIS WAY
ON ORIGINAL

7 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

E. Filing Memo

Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-589	**Brand Name**	Baclofen orally disintegrating tablets™
OCPB Division (I, II, III)	I	**Generic Name**	Baclofen
Medical Division	Neuropharm	**Drug Class**	Antispasmodic
OCPB Reviewer	Carol Noory	**Indication(s)**	Spasticity
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Rapidly dissolving tablets 10 mg and 20 mg
Clinpharm briefing date	September 17, 2003	**Dosing Regimen**	Starting dose of 5 mg t.i.d. titrated to 20-80 mg/day
Date of Submission	December 30, 2002	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	April 30, 2003	**Sponsor**	Schwartz Pharma
PDUFA Due Date	October 31, 2003	**Priority Classification**	Standard
Division Due Date	September 30, 2003		

Baclofen orally disintegrating tablets™ are orally disintegrating 10 mg and 20 mg tablets (ODT) developed as equivalent to the RLD, Baclofen IR tablets manufactured by Watson. The firm submitted a replicate design BE study (4 way crossover) comparing the highest strength to the RLD. A dissolution study comparing the profiles of the orally disintegrating tablet and the RLD was submitted. This showed the profiles not to be similar. A study comparing the profiles of the 10 and 20 mg RDT (in 3 pH media) was also submitted which indicated that the profiles are similar. The firm submitted permeability data from the innovator and solubility data on the ODT to characterize the product as BCS class I. Waivers were requested for food effect study, lower strength BE study and a study demonstrating the effect of taking the OD tablet with and without water. The sponsor proposed dissolution specifications for this product based on pooled samples.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**1 (single dose)**	**1**		**Single dose, crossover study comparing ODT dosed without water to RLD dosed with water**
replicate design; single / multi dose:	1	**1**		**Replicate comparing 20 ODT to RLD by Watson both dosed with water**
Food-drug interaction studies:				**Waiver requested**
Dissolution:	X	**3**	**3**	**Product vs RLD; Dissolution development; half vs whole tablets**
(IVIVC):				
Bio-waiver request based on BCS				**Lower strength; food effect and study with and without water**
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**	**5**	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	This submission contains results from 1 in-vivo study: 1) Pivotal BE study using the 20 mg strength to compare the proposed orally disintegrating dosage form to the marketed immediate release dosage form 2) Dissolution study comparing the rapidly dissolving 20 mg tablet to the RLD 20 mg tablet. Second dissolution study comparing the 10 and 20 mg orally disintegrating tablet in different pH media.
Comments sent to firm ?		1. The dosage and administration section of the proposed label recommends titrating from 5 mg t.i.d. Since the 10 mg ODT is a scored tablet and needs to be split to obtain the starting dose, in vitro dissolution profiles comparing the ½ vs. whole tablet for the 10 mg strength should be provided. Individual data (N=12) should be submitted in three media. Samples should be tested at 5 minute intervals. Due to the nature of the rapidly disintegrating tablets, in conducting this dissolution study, the firm should treat the tablets in the same manner as recommended to the patient. 2. Dissolution data for the dissolution study comparing 10 and 20 mg ODTs should be provided on 12 individual tablets in three media. No individual dissolution data was submitted. While data from pooled samples have been provided, the individual data are necessary before a meaningful specification is agreed (which could be based on individual or pooled samples. All dissolution data (Comments 1 and 2) should be submitted within 3 months. 3. The Pharmacokinetic and Drug Interaction Section of the label should be updated with any additional information available from published literature.
QBR questions (key issues to be considered)	I. Is the proposed rapidly dissolving formulation of baclofen 20 mg bioequivalent to the marketed 20 mg immediate release Baclofen product manufactured by Watson? II. Are the pharmacokinetics of the proposed formulation of baclofen 20 mg altered in the presence of food and water? Can a waiver be granted on the basis of BCS classification? III. Can a waiver for in-vivo BE study be granted for the 10 mg strengths based on sponsor's argument of compositional proportionality and dissolution similarity? IV. Can a waiver be granted for a study comparing the BE when the tablet is taken with and without water. V. Are the dissolution specifications based on testing of pooled samples appropriate?	
Other comments or information not included above	A DSI inspection is requested for Study SP 692, both clinical and analytical sites, conducted by [redacted]	
Primary reviewer Signature and Date	Carol A. Noory 3/3/03	
Secondary reviewer Signature and Date		

CC: NDA 21-589 HFD-850(Lee), HFD-120(Wheelous), HFD-860(Uppoor, Mehta, Sahajwalla), CDR (B. Murphy)

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

/s/

Carol Noory
10/2/03 04:22:55 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/2/03 07:40:32 PM
BIOPHARMACEUTICS

Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-589	**Brand Name**	[redacted]
OCPB Division (I, II, III)	I	**Generic Name**	Baclofen
Medical Division	Neuropharm	**Drug Class**	Antispasmodic
OCPB Reviewer	Carol Noory	**Indication(s)**	Spasticity
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Rapidly dissolving tablets 10 mg and 20 mg
		Dosing Regimen	Starting dose of 5 mg t.i.d. titrated to 20-80 mg/day
Date of Submission	December 30, 2002	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	April 30, 2003	**Sponsor**	Schwartz Pharma
PDUFA Due Date	October 31, 2003	**Priority Classification**	Standard
Division Due Date	September 30, 2003		

[redacted] *are orally disintegrating 10 mg and 20 mg tablets (ODT) developed as equivalent to the RLD, Baclofen IR tablets manufactured by Watson. The firm submitted a replicate design BE study (4 way crossover) comparing the highest strength to the RLD. A dissolution study comparing the profiles of the orally disintegrating tablet and the RLD was submitted. This showed the profiles not to be similar. A study comparing the profiles of the 10 and 20 mg RDT (in 3 pH media) was also submitted which indicated that the profiles are similar. The firm submitted permeability data from the innovator and solubility data on the ODT to characterize the product as BCS class 1. Waivers were requested for food effect study, lower strength BE study and a study demonstrating the effect of taking the OD tablet with and without water. The sponsor proposed dissolution specifications for this product based on pooled samples.*

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
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Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	1	**1**		**Replicate comparing 20 ODT to RLD by Watson**
Food-drug interaction studies:				**Waiver requested**
Dissolution:	X	**1**	**1**	
(IVIVC):				
Bio-waiver request based on BCS				**Lower strength; food effect and study with and without water**
BCS class	**X**			**Class 1**
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**	**2**	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	This submission contains results from 1 in-vivo study: 1) Pivotal BE study using the 20 mg strength to compare the proposed orally disintegrating dosage form to the marketed immediate release dosage form 2) Dissolution study comparing the rapidly dissolving 20 mg tablet to the RLD 20 mg tablet. Second dissolution study comparing the 10 and 20 mg orally disintegrating tablet in different pH media.
Comments sent to firm ?		1. The dosage and administration section of the proposed label recommends titrating from 5 mg t.i.d. Since the 10 mg ODT is a scored tablet and needs to be split to obtain the starting dose, in vitro dissolution profiles comparing the ½ vs. whole tablet for the 10 mg strength should be provided. Individual data (N=12) should be submitted in three media. Samples should be tested at 5 minute intervals. Due to the nature of the rapidly disintegrating tablets, in conducting this dissolution study, the firm should treat the tablets in the same manner as recommended to the patient. 2. Dissolution data for the dissolution study comparing 10 and 20 mg ODTs should be provided on 12 individual tablets in three media. No individual dissolution data was submitted. While data from pooled samples have been provided, the individual data are necessary before a meaningful specification is agreed (which could be based on individual or pooled samples. All dissolution data (Comments 1 and 2) should be submitted within 3 months. 3. The Pharmacokinetic and Drug Interaction Section of the label should be updated with any additional information available from published literature.
QBR questions (key issues to be considered)	I. Is the proposed rapidly dissolving formulation of baclofen 20 mg bioequivalent to the marketed 20 mg immediate release Baclofen product manufactured by Watson? II. Are the pharmacokinetics of the proposed formulation of baclofen 20 mg altered in the presence of food and water? Can a waiver be granted on the basis of BCS classification? III. Can a waiver for in-vivo BE study be granted for the 10 mg strengths based on sponsor's argument of compositional proportionality and dissolution similarity? IV. Can a waiver be granted for a study comparing the BE when the tablet is taken with and without water. V. Are the dissolution specifications based on testing of pooled samples appropriate?	
Other comments or information not included above	A DSI inspection is requested for Study SP 692, both clinical and analytical sites, conducted by [redacted]	
Primary reviewer Signature and Date	Carol A. Noory 3/3/03	
Secondary reviewer Signature and Date		

CC: NDA 21-589 HFD-850(Lee), HFD-120(Wheelous), HFD-860(Uppoor, Mehta, Sahajwalla), CDR (B. Murphy)

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/s/

Carol Noory
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