CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-589

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

SCHWARZ
PHARMA

DUPLICATE

September 23, 2003

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Neuropharmacological Drug Products, HFD-120
1451 Rockville Pike
Rockville, MD 20852

RECEIVED
SEP 24 2003
DDR-120 / CDER

RE: Original New Drug Application 21-589
Baclofen Orally Disintegrating Tablets, 10 mg and 20 mg

Amendment 005: Revised "No Relevant Patents" Statement

NEW CORRESPONDENCE

Dear Sir or Madam,

~~Reference is made to the above-mentioned new drug application and the electronic mail messages~~ on September 16 and 17, 2003 between Teresa Wheelous, Project Manager for the Division of Neuropharmacological Drug Products, and Donna Multhauf, Regulatory Affairs Director for Schwarz Pharma Inc.

Per the mail messages, the Agency indicated that the "No Relevant Patents" statement provided in the application referenced the incorrect regulation for a 505(b)2 application. Pursuant to 21 CFR § 314.50(i)(1)(ii), SPInc hereby submits a revised "No Relevant Patents" statement.

If there are any questions regarding this submission, please contact Gary Wieczorek, Regulatory Affairs Manager, by phone at 262-238-5171 or by fax at 262-238-0957.

Sincerely,

SCHWARZ PHARMA, Inc.

Gary M. Wieczorek for

Donna K. Multhauf
Director
Regulatory Affairs

Schwarz Pharma, Inc.
Mail: P.O. Box 2038 • Milwaukee, WI 53201-2038 • 6140 West Executive Dr. • Mequon, WI 53092-4467

SCHWARZ
PHARMA

SECTION III – PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

"NO RELEVANT PATENTS" STATEMENT

As required by 21 CFR § 314.50(i)(1)(ii), Schwarz Pharma, Inc. hereby certifies that in its opinion and to the best knowledge of Schwarz Pharma, there are no patents or exclusivities that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

9-22-03

Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance

Date

Schwarz Pharma, Inc.
Mail: P.O. Box 2038 • Milwaukee, WI 53201-2038 • 6140 West Executive Dr. • Mequon, WI 53092-4467
Telephone: 262 238-9994 • Toll Free: 800 558-5114 • Fax: 262 238-0311 • www.schwarzusa.com

CIMA™

Baclofen ODT 10 mg and 20 mg Patent Submission

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

U.S. Patent No.: 6,024,981
Expiration Date: 09 April 2018
Type of Patent: Drug Product
Patent Owner: CIMA LABS Inc.
Declaration: The undersigned declares that the above stated United States Patent 6,024,981 covers the composition and formulation of Baclofen Orally Disintegrating Tablets 10 mg and 20 mg. This product is the subject of this application for which approval is sought.

U.S. Patent No.: 6,221,392
Expiration Date: 09 April 2018
Type of Patent: Drug Product
Patent Owner: CIMA LABS Inc.
Declaration: The undersigned declares that the above stated United States Patent 6,221,392 covers the composition and formulation of Baclofen Orally Disintegrating Tablets 10 mg and 20 mg. This product is the subject of this application for which approval is sought.

Signed: Thomas A. Rendos
Thomas A. Rendos, Esq.

Date: 25 November 2002

Title: Intellectual Property Counsel

CIMA LABS INC.®
Corporate Offices: 10000 Valley View Road • Eden Prairie, MN 55344-9361 • 952-947-8700, fax 952-947-8770
Research: 7325 Aspen Lane N • Brooklyn Park, MN 55428 • 763-488-4700, fax 763-488-4800

SCHWARZ
PHARMA

SECTION III – PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

"NO RELEVANT PATENTS" STATEMENT

As required by 21 CFR § 314.53 and 314.54, Schwarz Pharma, Inc. hereby certifies that in its opinion and to the best knowledge of Schwarz Pharma, there are no patents or exclusivities that claim the listed drug referred to in this application or that claim the use of the listed drug.

Steven R. Pollock
Vice President, Medical, Regulatory & Quality Assurance

November 11, 2002
Date

Mail P.O. Box 2038 • Milwaukee, WI 53201-2038 • 6140 West Executive Dr. • Mequon, WI 53092-4467
Telephone 262-238-9994 • Toll Free 800-558-5114 • Fax 262-238-0311
www.schwarzusa.com

EXCLUSIVITY SUMMARY for NDA # 21-589

Trade Name:

Generic Name: Baclofen Tablets

Applicant Name: Schwarz Pharma

Approval Date:

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)?

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

      YES /___/ NO /_X__/

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

      This is a 505 (b) 2 application that provided the data from two bioequivalence studies.

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

   d) Did the applicant request exclusivity?

      YES /__/ NO /_X__/

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

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

YES /__/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex,

chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

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

NDA # 17-851

2. Combination product.

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

YES /___/ NO /___/

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

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #
NDA # _____ Study #

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

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

Investigation #1

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

Investigation #2

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

CDR Teresa Wheelous
Signature of Preparer Date: October 17, 2003
Title: Sr. Regulatory Management Officer

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

SCHWARZ
PHARMA

CERTIFICATION STATEMENT

As Required By The

GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to Section 306 (k) of the Federal Food, Drug and Cosmetic Act as amended by the Generic Drug Enforcement Act of 1992, Schwarz Pharma, Inc. hereby certifies that it did not, and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Additionally, during the previous five years, neither the applicant nor any affiliated person responsible for the development or submission of this application, has been convicted of the offenses described in subsection (a) or (b) of the Generic Drug Enforcement Act of 1992.

Schwarz Pharma, Inc. further certifies that it will promptly amend this certification as necessary in light of new information.

Mary Cyrier
Vice President
Human Resources

October 11, 2002
Date

Ron Stratton, Ph.D.
President & COO

October 11, 2002
Date

Mail P.O. Box 2038 • Milwaukee, WI 53201-2038 • 6140 West Executive Dr. • Mequon, WI 53092-4467
Telephone 262-238-9994 • Toll Free 800-558-5114 • Fax 262-238-0311
www.schwarzusa.com

CIMA™

Certification Required By Generic Drug Enforcement Act of 1992

Pursuant to section 306(k) of the Generic Drug Enforcement Act of 1992, CIMA LABS INC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 subsections (a) and (b) of the Federal Food, Drug, and Cosmetic Act.

We also certify that during the previous 5 years, we have not sustained a conviction that is described in subsections (a) and (b) of the Generic Drug Enforcement Act of 1992. In addition, CIMA LABS INC does not and will not knowingly use services of any person who has been convicted on an offense described in subsections (a) and (b) of the Generic Drug Enforcement Act of 1992

Jackie Toffin

Jackie Toffin
Director, Quality Systems

02Aug02
Date

13.9.2002

SCHWARZ PHARMA INC.
6140 West Executive Drive
Mequon, WI 53092

DEBARMENT CERTIFICATION

certifies that to the best of its knowledge, neither nor its employees connected with the development or submission of any drug application, has been convicted of any crime described in section 306, subsections (a) and (b) of the Generic Drug Enforcement Act of 1992.

does not and will not knowingly use, in any capacity, the services of any person debarred under section 306, subsections (a) and (b) of the Generic Drug Enforcement Act of 1992.

To: Our Valued Customers

Date: March 12, 2002

RE: Employees Criminal Conviction and Disbarment by the FDA

— does not knowingly employ individuals that have been convicted of any crime or have been disbarred by the FDA under Sections 306 (a) or (b) of the Generic Drug Enforcement Act of 1992. Prior to employment at — potential employees are required to complete a pre-employment document that states they have not been convicted or have been disbarred under Sections 306 (a) or (b) of the Generic Drug Enforcement Act of 1992.

Therefore, no one who has been convicted of a crime or has been disbarred by the FDA under Sections 306 (a) or (b) of the Generic Drug Enforcement Act of 1992 will knowingly be associated with any Sponsor project at —

If you need any additional information, please do not hesitate to contact your Project Development representative or myself at — For your convenience, more detailed information concerning — can be found at our website address listed above.

October 9, 2002

Laurie W. Nelsen, M.P.M.
Project Manager
Schwarz Pharma, Inc.
6140 West Executive Drive
Mequon, WI 53092-4467

Re: SP692: Baclofen
Debarment Statement

Dear Ms. Nelsen:

This letter will certify that — and its employees, affiliates, and agents have never been debarred or convicted of a crime for which a person can be debarred, under Section 306 (a) or 306 (b) of the Generic Drug Enforcement Act of 1992. — represents that it has never been and, to the best of its knowledge after due inquiry, none of its employees, affiliates, or agents has ever been threatened to be debarred or indicted for a crime or otherwise engaged in conduct for which a person can be debarred, under Section 306 (a) or (b).

Very truly yours,

March 12, 2002

Mr. Jeff Peason
CIMA Labs
10000 Valley View Road
Eden Prairie, Minnesota 55344-9361

SUBJECT: GMP, GLP, & FDA Generic Drug Enforcement Act Compliance

Dear Mr. Pearson,

cGMP COMPLIANCE

— and all of its medical device and pharmaceutical clients are required to operate in accordance with cGMPs (current Good Manufacturing Practices) regulations — is committed to perform all testing in accordance with our understanding of the GMPs. A comprehensive body of Standard Operating Procedures covers all aspects of our laboratory operations. The FDA, EPA, BSI and many client auditors routinely inspect us.

— does not assume any responsibility for the appropriateness and /or regulatory acceptance of any client's testing program. It is the responsibility of each client to assess the testing and test validation requirements of their products and quality control systems. — will endeavor to alert clients of testing programs that may need further consideration to determine conformance to cGMPs.

GLP COMPLIANCE

For some submissions, the FDA and EPA require that testing be performed in accordance with GLP (Good Laboratory Practice) regulations. It is the client's responsibility to determine when GLP treatment is required and to inform — in writing of this requirement at the time of sample submission. — will perform testing in accordance with the GLPs when requested by the client. There is an additional charge for GLP treatment.

DEBARMENT NOTIFICATION

— certifies that neither the firm nor any person employed by — has been convicted of any crime described in section 306 (a) and (b) of the Generic Drug Enforcement Act of 1992. — does not, has not and will never use the services of any person debarred under section (a) or (b) of section 306.

— Is committed to offering excellence in testing to all of our clients. Please contact me if any additional information is needed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schwarz Pharma, Inc.	9/23/03
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(262) 238-5171	(262) 238-0957
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
6140 W. Executive Drive Mequon, WI 53092 Mailing Address: P.O. Box 2038 Milwaukee, WI 53201	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-589

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Baclofen	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
4-amino-3-(4-chlorophenyl)-butanoic acid

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Orally Disintegrating Tablets	10 mg and 20 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Baclofen is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis

PRODUCT DESCRIPTION

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

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Baclofen Tablets, USP Holder of Approved Application Watson Labs

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

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

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

REASON FOR SUBMISSION
Amendment 005: Revised Patent Statement

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

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

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

N/A

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

DMF # —
DMF # —
DMF # —
DMF # —
DMF # —

NDA 17-851 (Lioresal Tablets/Novartis)
ANDA 73-093 (Baclofen Tablets/Watson Labs)

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Schwarz Pharma, Inc.
6140 W. Executive Drive
Mequon, WI 53092

Mailing Address:
P.O. Box 2038
Milwaukee, WI 53201

2. TELEPHONE NUMBER *(Include Area Code)*

(262) 238-5171

3. PRODUCT NAME

Baclofen Orally Disintegrating Tablets, 10 mg and 20 mg

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021589

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Gary M. Wiegand for	Donna K. Multhauf Director of Regulatory Affairs	09/23/2003

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-3456

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-589		
Drug: **Baclofen Orally Disintegrating Tablets 10 mg & 20 mg**	Applicant: **SCHWARZ PHARMA**	
RPM: T. Wheelous	HFD- 120	Phone # 594-5504
Application Type: ( ) 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): Lioresal 17-851 ANDA 73-093 Watson Labs Baclofen, U.S.P.	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
•	
❖ User Fee Goal Dates Oct. 31, 2003	
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes ( ) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	( ) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) (X) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	

4 Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖5 Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NONE
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖6 Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖7 Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖8 Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖9 Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖10 Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖11 Memoranda and Telecons	
❖12 Minutes of Meetings	
• EOP2 meeting (N/A)	
• Pre-NDA / Pre-IND meeting (July 2, 2002) CMC 10/3/02	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖N/A Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
N/A Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
❖ 13 Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ 14 Clinical review(s) *(indicate date for each review)*	10-16-03
❖ NA Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ 15 Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ NA Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ 16 Statistical review(s) *(indicate date for each review)*	
❖ 17 Biopharmaceutical review(s) *(indicate date for each review)*	10-02-03
❖ NA Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ 18 Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	7-22-03; 4-11-03
CMC Information	
❖ 19 CMC review(s) *(indicate date for each review)*	
❖ 20 Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NA Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ 21 Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ 22 Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ 23 Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ 24 Nonclinical inspection review summary	
❖ 25 Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ 26 CAC/ECAC report	

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: October 31, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850

Subject: NDA 21-859 KEMSTRO Baclofen Orally Disintegrating Tablets Approval Letter

Total no. of pages including cover:

Donna or Gary,
The following is a copy of the approval letter for Kemstro.

Thank you,
Teresa Wheelous

Document to be mailed: ☐ YES ☑ NO

10/28103

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: Sept. 17, 2003	**DESIRED COMPLETION DATE:** Oct. 27, 2003 **PDUFA DATE:** Oct. 30, 2003	**ODS CONSULT #:** 03-0168-1 and 03-0268

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Teresa Wheelous
Project Manager
HFD-120

PRODUCT NAME: **Kemstro** (Baclofen) Orally Disintegrating Tablets 10 mg and 20 mg **NDA #:** 21-589	**SPONSOR:** Schwarz Pharma

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Kemstro" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Kemstro. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

2. DMETS recommends the implementation of the label and labeling recommendations outlined in section III of this review.

3. DDMAC finds the name "Kemstro" acceptable from a promotional perspective.

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

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 24, 2003

NDA NUMBER: 21-589

NAME OF DRUG: **Kemstro**
(Baclofen) Orally Disintegrating Tablets
10 mg and 20 mg

NDA SPONSOR: Schwarz Pharma

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products, for an assessment of the proprietary name "Kemstro" regarding potential name confusion with other proprietary or established drug names. The Container labels as well as carton and package insert labeling (including , were also reviewed for possible interventions to minimize medication errors. An evaluation of the trademark "Kemstro" conducted by was also submitted to DMETS for review and comment.

This is the fourth name submitted for this product. DMETS did not recommend the use of the previously submitted names (see ODS Consult # 03-0016, dated March 18, 2003 and 03-0168, dated July 22, 2003).

PRODUCT INFORMATION

Kemstro contains baclofen, and is indicated for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Kemstro is formulated for oral administration, in which the tablet disintegrates within seconds after placement on the tongue, allowing it to be swallowed with or without water. The proposed product will be available as 10 mg and 20 mg orally disintegrating tablets. The optimal dosage requires individual titration; however, the following titration schedule is suggested:

5 mg three times a day for 3 days, then
10 mg three times a day for 3 days, then
15 mg three times a day for 3 days, then
20 mg three times a day for 3 days.

The total daily dose should not exceed a maximum of 80 mg daily (20 mg four times a day).

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound alike or look alike to "Kemstro" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

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

1. The Expert Panel identified one proprietary name, Kestrone, as having the potential for confusion with Kemstro. The product is listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have any concerns with Kemstro in regard to promotional claims.

---

[i] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

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

Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Kemstro	**Baclofen Orally Disintegrating Tablets 10 mg and 20 mg**	**Individual Dose Titration** **5 mg tid for 3 days, then** **10 mg tid for 3 days, then** **15 mg tid for 3 days, then** **20 mg tid for 3 days.** **Max Dose: 80 mg/day (20 mg qid)**	
Kestrone-5	Estrone	***No longer marketed.***	**S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONOLOGIC AND ORTHOGRAPHIC COMPUTER ANALYSIS

As part of the assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. At this time of this review, the database was not available. Therefore, Kemstro was not evaluated using this method.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Kemstro with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Kemstro (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

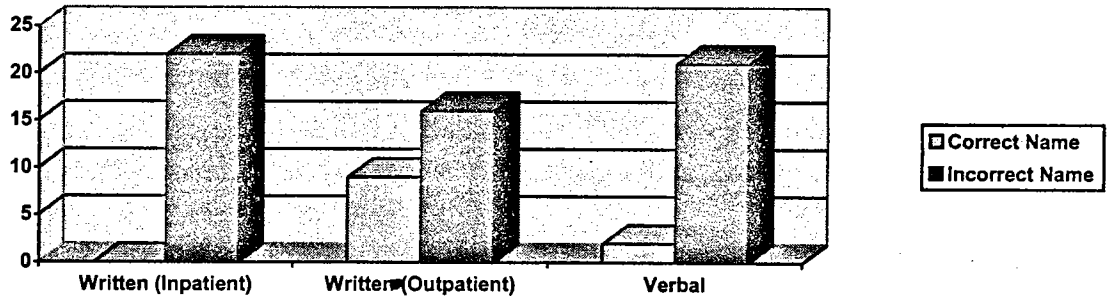
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Kemstro 10mg 1 po TID #30	Kemstro 10 mg, take one by mouth three times a day, dispense #30.
Inpatient RX: Kemstro 10mg po tid	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	22 (51%)	0 (0%)	22 (100%)
Written Outpatient	41	25 (61%)	9 (36%)	16 (64%)
Verbal	43	23 (53%)	2 (9%)	21 (91%)
Total	127	70 (55%)	11 (16%)	59 (84%)



Among the verbal prescription study participants for Kemstro, 21 of 23 (91%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Kemstro". The incorrect responses *were Chemstro (16), Camstro, Kenstr, Kemstirl, Kestro,* and *Kensrove.*

Among the written inpatient prescription study participants for Synaptra, 100 % of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of

"Kemstro". The incorrect responses were *Renstro, Kenistro (6), Remistro, Kenstro (10), Renistio, Renistro (2),* and *Kenestro.* None of the interpretations are similar to a marketed drug product.

Among the written outpatient prescription study participants for Synaptra, 16 of 25 (64%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Kemstro". The incorrect responses were *Kearstro (6), Keurstro (5), Kenstro (2), Keenstro, Keorsto,* and *Keemstro.*

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Kemstro", the primary concerns raised were related to one look-alike and/or sound-alike name: Kestrone-5. DMETS contacted the manufacturer of Kestrone-5 and discovered that the drug product is no longer manufactured. Kestrone-5 does not appear in the 2003 online version of Facts and Comparisons, Orange Book, or Physician Desk Reference. Additionally, we conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Kestrone-5 and Kemstro. Therefore, DMETS believes that the potential for confusion between Kestrone-5 and Kemstro is minimal.

E. — Evaluation

At the request of Schwarz Pharma, —
— evaluated the trademark of Kemstro. The trademark vulnerability evaluation was performed using the — model of analysis, which is a modification of Failure Mode and Effects Analysis (FMEA). FMEA is a technique used to uncover design flaws or other product defects in such a way that may predict and limit the consequences of human error. As such, the — models brings to light potential problems related to the safe use of the proposed product trademarks. The proposed proprietary name Kemstro received a low vulnerability score of 5 which indicates that Kemstro may co-exist in the U.S. market with reasonable assurance that it will not create confusion that could lead to medication errors.

DMETS response:

DMETS concurs with — evaluation in that the proposed proprietary name Kemstro has minimal potential for confusion.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and package insert labeling for Kemstro, DMETS has focused on safety issues relating to possible medication errors, and has identified areas of possible improvement, which might minimize potential user error. The following comments were also included in DMETS consult 03-0168-1 yet not addressed by the sponsor in the latest draft labels and labeling submitted for review.

A. GENERAL COMMENT

The — color utilized for the strength on labels and labeling does not provide sufficient contrast against the — background. Thus, the strength does not appear prominently on the principal display panel. Revise to utilize a different color that will make the strength as prominent as the proprietary and established names on all labels and labeling.

B. UNIT DOSE CARTON LABELING

1. The — is distracting and interferes with the readability of the name. The color of the letter constituting the proprietary name should all be the same.

2. The presentation of strengths on the carton labeling is difficult to read as it is not prominently displayed. Additionally, the color presentation of the 10 mg — and 20 mg — does not provide adequate contrast with the — background. Please increase the prominence of the strengths.

IV. RECOMMENDATIONS

4. DMETS has no objections to the use of the proprietary name Kemstro. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

5. DMETS recommends the implementation of the label and labeling recommendations outlined in section III of this review.

6. DDMAC finds the name "Kemstro" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at (301) 827-3242.

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
10/28/03 03:22:11 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/28/03 03:28:18 PM
DRUG SAFETY OFFICE REVIEWER

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Monday, October 27, 2003 1:23 PM
To: Gary Wieczorek
Subject: Baclofen Phase 4

Gary,

The following is a clinical request regarding a Phase 4 commitment:, in response to their fax of 10/24/03:

Schwarz Pharma submitted in September 2003 under IND 63,882 Baclofen ODT

The addition of special monitoring for oral mucosa side effects in that study would qualify for the phase IV commitment. Is it possible to amend Protocol to add that monitoring?

Thanks,
Teresa

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Monday, October 27, 2003 11:11 AM
To: Gary Wieczorek
Subject: New CMC Comment

Gary,

The following are CMC comments regarding Baclofen, NDA 21-589:

Based on our review of all stability data submitted, an expiration dating period of [redacted]. For tablets packaged in [redacted] bottles, we will not approve an expiration dating period greater than 18 months until you provide either:

a) Full shelf life stability data on at least three batches of each strength, pilot or production scale, that demonstrates the product will conform to the acceptance criteria of not more than [redacted]

b) Supporting data (e.g.,, [redacted] to demonstrate that a [redacted] than proposed in the regulatory specification does not adversely impact on the physical stability of the tablets.

Although the manner in which the regression analyses were performed does not impact on our decision regarding product expiry, we note that all stability analyses involved pooling of data for both strengths. During review of the stability data we noted differences in physical and chemical properties, e.g. [redacted] between 10 mg and 20 mg tablets Therefore, the individual strengths should analyzed separately in future submissions to this application,

Please respond before Wednesday, when the reviewer plans to conclude her review.

Thank you,

CDR Teresa Wheelous, R. Ph.
Senior Regulatory Management Officer
Division of Neuropharmacological Drug Products
(301) 594-2850

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Monday, October 27, 2003 8:30 AM
To: Gary Wieczorek
Subject: Baclofen

Gary,

We have the following comments regarding the Baclofen application:

While the data for males and females do not show much difference, the sponsor has not done appropriate analysis to evaluate gender effect (test for significance). Therefore, we propose to leave out of the label.

Regarding dissolution, we have still not heard from the sponsor, whether they are going to accept our revised method, based on INDIVIDUAL samples.

Let me know your reply as soon as possible.

Thanks,
Teresa

MODE = MEMORY TRANSMISSION START=OCT-21 14:19 END=OCT-21 14:20

FILE NO.= 036

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	S	912622380957	001/001	00:00'17"

-FDA/DNDP -

********** - - ***** - 3015942859- *********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: October 21, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850

Subject: NDA 21-859 Baclofen Orally Disintegrating Tablets – 2nd Phase 4 Commitment Request

Total no. of pages including cover: 1

Donna or Gary,
The following is another request for a Phase 4 commitment:

In anticipation of the upcoming PDUFA goal date for your application, we request that you commit to perform a clinical study during Phase IV to better characterize the adverse event of petechiae in the oral mucosa after multiple administration of the orally disintegrating tablet. This adverse event was observed only after taking the orally disintegrating tablet with no water, and was not observed when the orally disintegrating tablet was taken with water, or with baclofen "conventional" tablets.

Your response should be in writing and must include an anticipated submission date of this information following approval of the NDA.

Thank you,
Teresa Wheelous

Document to be mailed: ☐ YES ☑ NO

MODE = MEMORY TRANSMISSION START=OCT-20 12:48 END=OCT-20 12:49

FILE NO.= 011

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	a	912622380957	001/001	00:00'17"

-FDA/DNDP -

********** - ***** - 3015942859- **********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: October 20, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850

Subject: NDA 21-859 Baclofen Orally Disintegrating Clinical Pharmacology Comment Clarification Fax

Total no. of pages including cover: 1

Donna or Gary,

The following are Clinical Pharmacology & Biopharmaceutics comments that were faxed to you on Oct. 6, 2003. However, point one has been clarified to state that the dissolution specs are for individual tablet data and not pooled data.

1. Adopt new dissolution specs, as recommended by OCPB. (Q= — at 15 minutes vs. proposed ~ at 30 minutes). 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.

2. Conduct a subgroup analysis of the PK studies by gender to investigate for a gender effect, and include this in labeling if one exists.

Thank you,
Teresa Wheelous

Document to be mailed: ☐YES ☑NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: October 6, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850

Subject: NDA 21-859 Baclofen Orally Disintegrating Tablets Phase 4 Commitment Request

Total no. of pages including cover: 1

Donna or Gary,
The following is a request for a Phase 4 commitment:

In anticipation of the upcoming PDUFA goal date for your application, we request that you commit to perform a complete genotoxicity battery (per ICH guidelines) during Phase IV. Your response should be in writing and must include an anticipated submission date of this information following approval of the NDA.

Thank you,
Teresa Wheelous

Document to be mailed: ☐ YES ☑ NO

OFS ✓

MODE = MEMORY TRANSMISSION START=OCT-06 13:15 END=OCT-06 13:15

FILE NO.= 163

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	a	912622380957	001/001	00:00'17"

-FDA/DNDP -

********** - ***** - 3015942859- *********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: October 6, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850
Subject: NDA 21-859 Baclofen Orally Disintegrating Clinical Pharmacology Comment Fax	
Total no. of pages including cover: 1	

Donna or Gary,

The following are clinical pharmacology & biopharmaceutics comments that require your immediate attention:

1. Adopt new dissolution specs, as recommended by OCPB. (Q= —% at 15 minutes vs. proposed — at 30 minutes).
2. Conduct a subgroup analysis of the PK studies by gender to investigate for a gender effect, and include this in labeling if one exists.

Thank you,
Teresa Wheelous

Document to be mailed: ☐YES ☑NO

DFS ✓

Wheelous, Teresa A

From: Wheelous, Teresa A
Sent: Friday, October 03, 2003 10:31 AM
To: 'Gary Wieczorek'
Subject: RE: Baclofen (NDA 21-589) Stability Questions

Gary,

This is being sent in reply to your voice mail message regarding the CMC Info Request Letter:

Based on the certificate of analysis provided in the NDA for baclofen Lot No. 70351076, we are aware that a [redacted] is available to the drug substance manufacturer. The baclofen ODT formulation is considered a new dosage form subject to the recommendations provided in the following giudances, which are available on the CDER website (http://www.fda.gov/cder/guidance/index.htm):

Guidance for Industry: NDAs: Impurities in Drug Substances
Q3A Impurities in New Drug Substances

-----Original Message-----
From: Gary Wieczorek [mailto:GWieczor@schwarzusa.com]
Sent: Monday, September 22, 2003 2:56 PM
Subject: Baclofen (NDA 21-589) Stability Questions

Teresa,

[redacted]r our earlier telephone conversation, we have [redacted] stability data to report. The [redacted]egression analysis of the [redacted] stability data support a shelf life greater than [redacted] A program written by Moh-Jee-Ng of the FDA's Division of Biometrics was used for this analysis, as well as the [redacted] data analysis submitted in the NDA. The statistician Schwarz used to perform both regression analyses noted that while the final shelf life estimates are correct using this program, the output is not complete. In some cases, the program does not give the intercept and/or the slope for individual configurations. This was observed for both the [redacted] analyses. The statistician indicated that an older version of SAS does not have this problem.

The questions we would like you to forward to the reviewer are as follows:

Should we use the FDA program to calculate the regression analysis for the [redacted] data, as was done for the [redacted] data regression analysis? Alternatively, we can redo the analysis, using an older version of SAS, or we can present the analysis using both versions. Which approach would the reviewer prefer? Both versions will give the same result for the final shelf life estimate.

Also, is it possible to submit the [redacted] data now and have it reviewed without impacting the October 31 target date of the action letter?

Gary

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-589

INFORMATION REQUEST LETTER

Schwartz Pharma Inc.
Attention: Donna K. Multhauf
Director, Regulatory Affairs and Quality Assurance
6140 Executive Drive
Mequon, WI 53092

Dear Ms. Multhauf:

Please refer to your December 30, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for baclofen orally disintegrating tablets, 10 mg and 20 mg.

We also refer to your submission dated August 18, 2003.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1) With respect to the drug substance specification, acceptance criteria for impurities should include a limit of not more than (NMT) ~ w/w for unspecified impurities. All impurities that may be present at levels greater than ~ w/w should be identified and listed individually in the specification.

2) With respect to the drug product specification, we have the following comments:

   a) Acceptance criteria for impurities should include a limit of not more than (NMT) ~ w/w for unspecified impurities. All impurities that may be present at levels greater than ~ w/w should be identified and listed individually in the specification.

   b) The ~ used for *Assay, Content Uniformity, Related substances,* and *Dissolution* should include a test for resolution between baclofen and aspartame as part of the system suitability criteria.

3) The post approval stability protocol should include accelerated stability testing for the first three production batches.

4) You propose an expiration dating period of — Based on the available stability data, we can approve a tentative expiration dating period of 18 months. Any further extension based on data from pilot scale stability batches will require prior approval.

5) With regard to the package insert (PI), the following revisions are requested:

   a) **DESCRIPTION** Section (paragraph 1)

   TRADENAME (baclofen orally disintegrating tablets) is a muscle relaxant and antispastic. —

   b) **DOSAGE AND ADMINISTRATION** (Administration)

   Using dry hands, the patient should be instructed to place the tablet on the tongue, where it will disintegrate and can then be swallowed with or without water.

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

Maryla Guzewska, Ph.D.
Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Maryla Guzewska
9/23/03 01:44:12 PM

A

15 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

MEMORANDUM

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

DATE: July 22, 2003

FROM: Nilufer M. Tampal, Ph.D.
Toxicologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Supplement to DSI memorandum for NDA 21-589, Baclofen Orally Disintegrating Tablets, 10 and 20 mg, Sponsored by Schwarz Pharma, Inc.

TO: Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (HFD-120)

The following information supplements DSI's memorandum dated 05/29/03 regarding NDA 21-589 (Baclofen Orally Disintegrating Tablets).

From April 21 through 25, 2003, DSI audited the clinical and analytical portions of a bioequivalence study in NDA 21-589 performed by —. Following the inspection, Form 483 was issued. Recently, DSI received written responses (attachment 1) to the 483 item from —. Below is an evaluation of the — written responses:

Form 483 item: Failure to demonstrate stability of stock solution of baclofen in that the assay used to evaluate stability was not stability indicating.

—. **Response:** — has conducted additional stock solution stability study using a stability indicating assay (HPLC/MS/MS). — has been determined that baclofen is stable in solution for 296 days.

Conclusion:

DSI evaluated and found that the — written responses have provided adequate stock solution stability data for baclofen. The data from study SP692 should be accepted for your review.

After your review, please attach this memo to the original NDA submission.

Nilufer M. Tampal, Ph.D.

cc:
HFD-45/RF
HFD-48/Tampal(2)/Himaya/CF
HFD-120/Wheelous
HFD-860/Uppoor
Draft: NMT 07/21/03
Edit: MKY 7/23/03
DSI: — , O:\BE\EIRCOVER\21589 — res

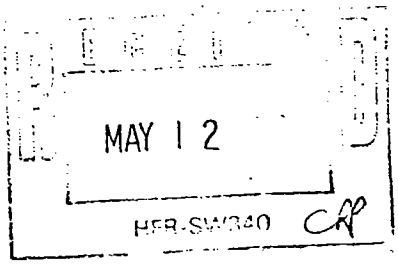
Attachment 1

(Please note that the raw data and chromatograms received as part of the responses are not included in the attachment but are available upon request).

483 Response

RECEIVED
MAY 12 2003

May 9, 2003



Mr. Charles W. Sedgewick
District Director
Kansas City District
U.S. Food & Drug Administration
11630 West 80th Street
Lenexa, KS 66214-3340

Re: Response to FDA Inspection

Dear Mr. Sedgewick:

FDA Investigator Linda R. Kuchenthal, from the Kansas City office, and FDA Pharmacologist Nilufer M. Tampal, Ph.D., of the Division of Scientific Investigations conducted a detailed inspection of a clinical trial and bioanalytical project performed at — . The inspection began April 21, 2003, and concluded March 25, 2003. One inspectional observation was listed on a Form FDA 483 issued at the conclusion of the inspection. During the wrap-up meeting, we discussed the observation and agreed to send our written response to the observation.

The observation was:
"In regards to ' 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. (Project 27930)'. 1. Failure to demonstrate stability of stock solution of baclofen in that the assay used to evaluate stability was not stability indicating".

Response:
We are writing working instructions to our SOP — covering method validation to specify that the method used to determine stock stability must have sufficient specificity to show different instrumentation responses for the analyte compared to expected breakdown products. Additionally we did locate and retest the baclofen stock standard solutions that were used for this study. The results in the attached table demonstrate that the stock solutions are stable for at least 296 days.

If possible, we request that this response be attached to the associated Form FDA 483 when copies of the Form FDA 483 are requested through the Freedom of Information Act or other sources.

We appreciate the opportunity this inspection offered to examine our procedures, as well as the courtesies extended to —

Sincerely,

bab

Enclosure

c: Linda R. Kuchenthal, Food and Drug Administration

Baclofen Primary Stock Standard Comparisons

Baclofen/D5-Baclofen Peak Area Ratios

	Stock 10730-114A	Stock 10730-114B	Stock 10730-114C	Stock 10730-128A	Stock 10730-128B	Stock 10730-128C
Mean	10.180	10.470	10.700	10.270	10.480	10.540
C.V. %	2.7	2.9	2.0	4.2	2.0	2.0
N	6	6	6	6	6	6

Stock Comparisons (Ratios)

114A/114B	97.2	114B/114C	97.9	114C/128A	104	128A/128B	99.4
114A/114C	95.1	114B/128A	102	114C/128B	102	128A/128C	101
114A/128A	99.1	114B/128B	99.9	114C/128C	102	128B/128C	100
114A/128B	97.1	114B/128C	99.3				
114A/128C	96.6						

Stocks 10730-114A, B & C were prepared on 10-Jul-2002 and were used for the audited study
Stocks 10730-128A, B & C were prepared on 02-May-2003

09-July-2003

Nilufer M. Tampal, Ph.D.
Pharmacologist, US FDA
DSI/OMP/CDER/HFD-048
MPN 1, Room 108
7420 Standish Place
Rockville, MD 20855

Re: NDA 21-589, MDSPS Project 27930_1

Dear Dr. Tampal,

I have reviewed the memo that you sent to me dated 02-July-2003 regarding the response on the FDA 483 for the above-mentioned project. The stability of the baclofen stock standard solution was conducted as follows.

On 05-May-2003, testing solutions containing baclofen stock standards prepared on 10-Jul-2002 (reference as 10730-114 A, B & C) and baclofen stock standards prepared on 02-May-2003 (reference as 10730-128 A, B & C) were prepared by mixing approximately 0.1 mL of each stock solution (the actual volume was varied to account for the varying concentrations of each stock solution) with 0.1 mL of a 2° d-5 baclofen internal standard solution (which was prepared on 02-May-2003 reference as 10730-130G). This mixture was diluted to a final volume of 50 mL with 4:1 (ethanol:glacial acetic acid). The solutions were identified as follows:

TST B = Stock Solution 10730-114A + Internal Standard 10730-130G
TST C = Stock Solution 10730-114B + Internal Standard 10730-130G
TST D = Stock Solution 10730-114C + Internal Standard 10730-130G
TST E = Stock Solution 10730-128A + Internal Standard 10730-130G
TST F = Stock Solution 10730-128B + Internal Standard 10730-130G
TST G = Stock Solution 10730-128C + Internal Standard 10730-130G

30 µL of each solution was injected six times on a — instrument on 05-May-2003. Baselines were drawn by Analyst® software. I have attached the Audit Trail from the Analyst® software along with all chromatography to indicate which program alterations were made. There were no manual alterations in the baseline drawing process.

I have attached both the printout from Analyst® showing the Analyte Peak Area (counts) and the IS Peak Area (counts) as well as a summary of the Analyte and IS peak areas. Please note that we did not compare the stability of the internal standard solution as the stability of a stable isotope internal standard is usually inferred from the stability of the non-deuterated analyte.

Please let me know if you have any further questions regarding this issue. I can be reached at (402) 437-4722.

Best regards,

C –
Mr. Charles W. Sedgewick, District Director FDA, Kansas City District.

Wheelous

COMPLETED JUN 2 6 2003

MEMORANDUM

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

DATE: May 29, 2003

FROM: Nilufer M. Tampal, Ph.D.
Toxicologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Jain for 6/19/03
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-589,
Baclofen Orally Disintegrating Tablets, 10 and 20 mg
Sponsored by Schwarz Pharma, Inc.

TO: Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted audit of the following bioequivalence study:

Protocol 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. (Project 27930).

The clinical and analytical portions of Protocol SP692 were conducted at —

Following the inspection at — (04/21-25/03), Form 483 was issued. Our evaluation of the significant finding is as follows:

1. **Failure to demonstrate stability of stock solution of baclofen in that the assay used to evaluate stability was not stability indicating.**

Stability of stock solution of baclofen used to prepare calibration standards was evaluated after 125 days of

storage by measuring ultraviolet absorbance at 266 nm using a spectrophotometer. This assay did not adequately address stability as the molar extinction coefficient at 266 nm would not change significantly after changes in the

/

— and was

therefore not stability indicating.

At the inspection closeout meeting, —
stated they would respond to the Form 483 observation. HFD-48 will evaluate the response and forward the recommendation to HFD 120 and HFD 860 shortly after the response is received.

Conclusions:

Based on the above finding DSI recommends that the data **not** be accepted for Agency review until the stability issue discussed above is resolved by the site satisfactorily.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Nilufer M. Tampal, Ph.D.

Final Classification:
VAI - —

cc:
HFD-45/RF
HFD-48/Tampal(2)/Himaya/CF
HFD-120/Wheelous
HFD-860/Uppoor
HFR-SW350/Kuchenthal
Draft: NMT 05/30/03
Edit: MKY 6/18/03
DSI:5463; O:\BE\EIRCOVER\21589sch.bac
FACTS ID: —

B

35 Page(s) Withheld

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

__✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

M E M O R A N D U M

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

DATE: April 11, 2003

TO: Director, Investigations Branch

FROM: C.T. Viswanathan, Ph.D. CTV 4/11/03
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2003, **High Priority CDER User Fee NDA,** Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-589
DRUG: Baclofen Orally Disintegrating Tablets, 10 and 20 mg
SPONSOR: Schwarz Pharma, Inc.

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study. **Due to the user fee deadline, this inspection should be completed before September 5, 2003.**

Protocol: 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. (Project 27930).

Clinical Site

Clinical Investigator:

Please check the batch numbers of both the test and the reference drug formulations used in the study with descriptions in the documents submitted to the Agency. Samples of both the

test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site:

Analytical Investigator:

Instrumentation: LC-MS/MS

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background material will be forwarded directly. **A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: Jacqueline A. O'Shaughnessy, Ph.D.
(301) 827-5463 or 5460

cc:
HFD-45/RF
HFD-48/O'Shaughnessy(2)/Himaya/CF
HFD-120/Wheelous/NDA 21-589
HFR-SW350/Montgomery (please send by fax)
Draft: JAO 4/11/03
Edit: MKY MKY 4/11/03
DSI:5463 O:\BE\assigns\bio21589.doc

FACTS 1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE I

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2003

To: Donna Multhauf or Gary Wieczorek	**From:** Teresa Wheelous
Company: Schwarz Pharma, Inc	Division of Division of Neuropharmacological Drug Products
Fax number: 262-238-0957	**Fax number:** 301-594-2859
Phone number: 262-238-5171	**Phone number:** (301) 594-2850

Subject: NDA 21-859 Baclofen Orally Disintegrating Tablets Clinical Pharmacology Comments

Total no. of pages including cover: 1

Donna or Gary,
The following are Clinical Pharmacology & Biopharmaceutics comments :

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.

Thank you,
Teresa Wheelous

Document to be mailed: ☐ YES ☑ NO

NDA NO DEFICIENCY TELECON

NDA: **21-589**

SPONSOR: Schwarz Pharma Inc.
Mr. Gary Wieczorek (262) 238-5171

DRUG: Baclofen Orally Disintegrating Tablets 10 mg and 20 mg

DATE: February 25, 2003

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 25, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

GROUP LEADER: **Dr. Armando Oliva**
MEDICAL OFFICER: **Dr. Eric Bastings**
CMC Team Leader: **Dr. Maryla Guzewska**
CHEMIST: **Dr. Martha Heimann**
PHARMACOLOGIST: **Dr. Barry Rosloff**
CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS TEAM LEADER:
Dr. Ramana Uppoor
CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEWER:
Dr. Carol Noory

COMMENTS:

1. We remind you that your submission indicates that the Cima Labs facilities will not be ready for inspection until April 14, 2003. The failure to have all facilities ready for inspection at time of application submission may cause delays in the inspection process.

2. Based upon prior experience with DMETS, it is recommended that you not use the term — as part of the proposed product name. Please submit an alternative product name.

3. Additional Clinical Pharmacology & Biopharmaceutics will be faxed to the sponsor in the near future (see the March 4, 2003 facsimile).

{See appended signature page}

Teresa Wheelous,
Sr. Regulatory Management Officer
Division of Neuropharmacology, HFD-120

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

/s/

Teresa Wheelous
3/11/03 03:56:08 PM
CSO

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: February 24, 2003

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Dr. Armando Oliva, Group Leader, HFD-120 AOliva

FROM: Teresa Wheelous, Regulatory Management Officer, HFD-120
TWheelous

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-589
Bacoflex Tablets 10 and 20 mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Protocol	Project
SP692;		27930

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by September 31, 2003. We intend to issue an action letter on this application by **October 31, 2003.**

Should you require any additional information, please contact Teresa Wheelous.

Concurrence: (Optional)
Dr. Ramana Uppoor Clinical Pharmacology & Biopharmaceutics Team Leader

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-589

Schwarz Pharma, Inc.
Attention: Donna K. Multhauf
Director of Regulatory Affairs
6140 W. Executive Drive
Mequon, WI 53902

Dear Ms. Multhauf:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Baclofen orally disintegrating tablets 10 mg and 20 mg
Review Priority Classification:	Standard (S)
Date of Application:	December 30, 2002
Date of Receipt:	December 31, 2002
Our Reference Number:	NDA 21-589

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 25, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 31, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Teresa Wheelous, Regulatory Management Officer, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander
Supervisory Regulatory Health Officer
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Teresa Wheelous
2/21/03 01:08:14 PM
Teresa Wheelous (for) Robbin Nighswander

MEMORANDUM OF TELECON

DATE: October 3, 2002

APPLICATION NUMBER: IND 63,882, Baclofen Orally Disintegrating Tablets

BETWEEN:

Name: Mr. Pollack,
Jeff Seefer,
Barry Bankin,
Elaine Cibulka – Regulatory Affairs
Phone: Called Us
Representing: Schwarz Pharma

AND

Name:
Teresa Wheelous, Regulatory Management Officer
Dr. Maryla Guzewska, CMC Team Leader
Dr. Mona Zarifa, CM Reviewer
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Reply to August 27, 2002 submission regarding the need for additional stability data to support an NDA.

BACKGROUND:
As a follow up to the July 10, 2002 pre-IND meeting, in which Schwarz Pharma was informed that their stability data proposal was not acceptable, Schwarz Pharma submitted a detailed stability proposal, dated August 27, 2002, for CMC consideration.

Excerpt from the July 10, 2002 pre-IND meeting minutes

- *The proposal to file the NDA with — stability data on — of the drug product — is not acceptable. We concur that there is "a great deal of CMC information available to the Agency on the drug substance", and therefore, no stability data on the active component of the drug are being requested in the NDA submission. The drug product, however, is a new formulation of baclofen (Orally Disintegrating Tablets vs. the approved Tablets). The new formulation contains six (6) new excipients (including aspartame) as compared to the approved tablets, and therefore, stability studies should be performed as outlined in both: FDA and ICH guidances (refer to www.fda.gov/cder/guidance/index.htm). The sponsor is encouraged to discuss the new, revised stability protocol with the review chemist prior to initiating the stability studies.*

- *It was noted that the formulation of Baclofen Orally Disintegrating Tablets contains aspartame, which might interact with the drug substance and/or other excipients. The sponsor responded that all potential degradation products (including those related to the aspartame by-products) are being monitored, and the results will be presented in the NDA submission.*

Schwarz would like to submit the following data for inclusion in the 505(b) 2 NDA:

- ✓ of data on the baclofe —

- — of data on the 20 mg — scale (prototype) lot
- — of data from the two — scale demonstration batches of each strength at both conditions in — packaging —

Stability data proposed by Schwartz Pharma are insufficient for evaluation of stability of the drug product.

DISCUSSION:

- Guidance Recommendations for new drugs (NMEs) are 12 months of long-term data. Schwarz would like to have an exception to the normal requirements because baclofen has been on the market for over 20 years.

- The marketed products, which contain the same drug substance as Schwarz's product, do not have the same excipient combination as Schwarz's formulation. Therefore, this is a new formulation for which we do not have long-term historical stability data. As a new formulation a reduced stability database at submission time may be acceptable in certain justified cases.

- Schwarz was suggested to submit the complete stability package proposal along with a justification for accepting less than the usual amount of stability data for review. This information will be shared with the upper management of ONDC and their decision will be relayed to Schwarz.

ACTION ITEM:

1. Schwarz Pharma will submit a stability package proposal and reduced stability package justification for review by the Division and upper management.
2. After discussing Schwarz's forth coming submission with upper management, the Division will relay the final decision to Schwarz about the amount of stability data required to support a 505(b) 2 NDA for baclofen orally disintegrating tablets.

MEETING MINUTES

DATE: July 2, 2002

TIME: 10 AM

LOCATION: WOC II conference Room E

APPLICATION: 63,882

TYPE: Pre-IND

ATTENDEES

FDA
Dr. R. Katz - Division Director
Dr. A. Oliva – Group Leader
Dr. E. Bastings – Medical Reviewer
Dr. B. Rosloff – Pharmacology / Toxicology Team Leader
Dr. M. Guzewska – CMC Team Leader
Dr. M. Zarifa – CMC Reviewer
Dr. R. Uppoor – Clinical Pharmacology & Biopharmaceutics Team Leader
Dr. V. Sekar - Clinical Pharmacology & Biopharmaceutics Reviewer
T. Wheelous – Regulatory Management Officer

SCHWARZ Pharma, Inc. REPRESENTATIVES
Elaine Cibulka - Regulatory Affairs Manager
Cherie Godin - Regulatory Affairs Associate
Phillip A. Johns, Ph.D., J.D. - Regulatory and Toxicology Consultant
Kathleen Kastenholz, Pharm.D., M.S. - Associate Director, Drug Safety
Jack R. Luderer, M.D. - Associate Vice President for Research, Consultant
Donna Multhauf - Director, Regulatory Affairs and Quality Assurance
Steven R. Pollock - Vice President, Medical and Regulatory Affairs
Jeff Siefert - Director, Pharmaceutical Development
Ron Stratton, Ph.D. - President & COO

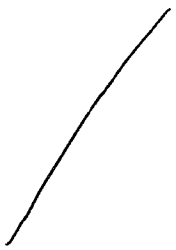
BACKGROUND:
The April 12, 2002 meeting request was granted on April 23, 2002. The May 30, 2002 meeting package was submitted in preparation for this July 2, 2002 meeting. The objective of this meeting is to discuss Schwarz's proposal to submit a 505(b)(2) application for a new dosage form of baclofen tablets, 10-mg and 20 mg. The approved product Lioresal (baclofen) tablets has been withdrawn by Novartis, and baclofen tablets owned by Watson Labs is designated as the new reference listed drug.

DISCUSSION QUESTIONS:

1. *The sponsor has evaluated the existing preclinical package and has determined that, although the existing preclinical studies may not have been conducted according to current ICH standards, the intent and aims of the current guidelines have been met. Thus, the sponsor's position is that existing preclinical data are sufficient to support a 505(b)(2) application. At the meeting, the sponsor will review the existing data and provide the basis for the sponsor's conclusion. The sponsor seeks Agency concurrence on the acceptability of the preclinical package as defined in this Information Package.*

   - The Division concurs with the sponsor's proposal, i.e., to conduct a complete genotoxicity battery phase IV.

2. *The sponsor intends to conduct a Bioavailability Study comparing the new dosage form to Watson Labs' Baclofen Tablets, USP, 20 mg, the RLD, to support the filing of a 505(b)(2) application. A biowaiver will be filed for the lower 10-mg strength. The sponsor feels that a waiver of pediatric studies is justified due to the intended use of the drug. Information to support a pediatric waiver is included in this Information Package. The application will seek the same indications, strengths, and dosing as the RLD. Thus, the sponsor has determined that no further clinical studies are required to support approval of the 505(b)(2) application. The sponsor seeks Agency concurrence for this proposal.*



   - Although the sponsor's proposal (to conduct a bioequivalence study comparing the new dosage form to the RLD and requesting a biowaiver for the 10 mg strength) is acceptable, the granting of biowaiver for the 10 mg strength will be a review issue based on results from the proposed BA/BE study and the dissolution data in multiple pH media.

   - A food effect study on the 20 mg strength of the new to-be-marketed formulation is recommended. If this study is not conducted, a suitable justification should be provided.

   - A study to assess the effect of coadministration with and without water for the new to-be-marketed formulation is recommended. If this study is not conducted, a suitable justification should be provided.

- Attempts should be made to develop a suitable, discriminatory dissolution test for the proposed new formulation strengths. A complete report describing these efforts should be submitted. Specifications for this product will depend on the generated data (not necessarily the same as USP specification for Baclofen tablets).

3. ***The sponsor intends to product Baclofen Orally disintegrating tablets in 10 mg and 20 mg strengths. Baclofen is not a new chemical entity. The drug substance and conventional immediate release tablets are compendial items and Lioresal® (baclofen) Tablets have been approved since November 22, 1977. Therefore, there is a great deal of CMC information available to the Agency on both the drug substance and the current approved formulations. The formulation proposed by the sponsor uses a common blend for both the 10-mg and 20 mg strengths. In light of these facts, the sponsor is proposing to produce 10-mg strength of the 20-mg strength as support for the CMC portion of the application. In addition, the sponsor proposes to file the application with — of Accelerated and Controlled Room Temperature stability data on the drug product, with stability updates provided to the application during the review process. Is this proposal acceptable to the Agency?***

- The proposal to file the NDA with — of stability data on — of the drug product / —) is not acceptable. We concur that there is "a great deal of CMC information available to the Agency on the drug substance", and therefore, no stability data on the active component of the drug are being requested in the NDA submission. The drug product, however, is a new formulation of baclofen (Orally Disintegrating Tablets vs. the approved Tablets). The new formulation contains six (6) new excipients (including aspartame) as compared to the approved tablets, and therefore, stability studies should be performed as outlined in both: FDA and ICH guidances (refer to ww.fda.gov/cder/guidance/index.htm). The sponsor is encouraged to discuss the new, revised stability protocol with the review chemist prior to initiating the stability studies.

- It was noted that the formulation of Baclofen Orally Disintegrating Tablets contains aspartame, which might interact with the drug substance and/or other excipients. The sponsor responded that all potential degradation products (including those related to the aspartame by-products) are being monitored, and the results will be presented in the NDA submission.

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

/s/

Russell Katz
7/17/02 04:05:39 PM