CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-793

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Schwarz Pharma, Inc.
Mequon, WI 53092

PATENT INFORMATION

21 CFR § 314.54(v)

Signed patent declaration forms FDA 3542a regarding patent information are herein submitted for each patent number (6,024,981 and 6,221,392) as required under section 505(b) of the Federal Food Drug & Cosmetic Act and 21 CFR § 314.53 and 314.54. The patents cover the composition and formulation of Reglan RPT, 5 mg and 10 mg. Accordingly, the applicant requests that this information be published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) upon approval of the application.

A certification stating that there are no relevant patents or exclusivities that claim the listed drug or the use of the listed drug referred to in this application, Reglan® Tablets, is also included.

CIMA™

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DEBARMENT STATEMENT
Certification Required by Generic Drug Enforcement Act of 1992

CIMA LABS INC.®, (the "Drug Product Manufacturer"), hereby certifies as follows:

(i) The Drug Product Manufacturer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application; and

(ii) There are no convictions of the type described in section 306 (a) and (b) of the Federal Food, Drug and Cosmetic Act, which occurred within 5 years prior to the date of this Certificate, of the Drug Product Manufacturer or any affiliated person responsible for the development or submission of such application.

IN WITNESS WHEREOF, the undersigned has signed this certificate on behalf of CIMA LABS INC.®, on the 28th of April, 2004.

By: Jackie Torfin
Jackie Torfin, Director Quality Assurance

DIANE F. KEITH
NOTARY PUBLIC-MINNESOTA
MY COMMISSION EXPIRES 1-31-2005

Diane F. Keith 4/28/04

CIMA LABS INC.®
Corporate Offices: 10000 Valley View Road, Eden Prairie, MN 55344• 952-947-8700, Fax: 952-947-8770
Research: 7325 Aspen Lane, Brooklyn Park, MN 55428•952-947-8950, Fax: 952-947-8970

EXCLUSIVITY SUMMARY

NDA # 21-793 SUPPL # N/A HFD #

Trade Name Reglan [redacted] Orally Disintegrating Tablets

Generic Name metoclopramide

Applicant Name Schwarz Pharma

Approval Date, If Known 6/10/05

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☒

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.

The firm conducted a fasting bioequivalence study to compare Reglan Orally Disintegrating Tablets with Reglan Tablets. The sponsor is relying on the Agency's findings of safety and efficacy for Reglan Tablets (NDA 17-854).

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 ☒

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 ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☒ NO ☐

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

NDA# 17-854 Reglan (metoclopramide) Tablets

NDA# 17-862 Reglan (metoclopramide) for Injection

NDA#

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).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☐

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

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 ☐

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

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"):

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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

==========

Name of person completing form: Susan Daugherty
Title: Regulatory Project Manager
Date: 6-10-05

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Joyce Korvick
7/12/05 02:15:34 PM

SCHWARZ
PHARMA

RECEIVED
AUG 02 2004
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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

3/11/04
Date

Ron Stratton, Ph.D.
President & COO

3/11/04
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.schwarzus.com

Sharp

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

Sharp Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sincerely,

Kathleen C Baszczewski

Date: 6/28/04

Kathleen C. Baszczewski
Director of Compliance
SHARP CORPORATION

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-793 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: August 10, 2005 Action Date: June 10, 2005

HFD 180 Trade and generic names/dosage form: Reglan [redacted] (metoclopramide) Orally Disintegrating Tablets

Applicant: Schwarz Pharmaceuticals Therapeutic Class: motility modifiers

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: for the relief of symptomatic gastroesophageal reflux

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☒ No: Please check all that apply: ____Partial Waiver _X_Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 18	**Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): June 10, 2010 for children ≥ 1 year old; June 10, 2013 for children < 1 year old

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager

cc: NDA 21793
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: for the relief of symptoms associated with diabetic gastroparesis (Diabetic Gastric Stasis)

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☒ **No: Please check all that apply: ____Partial Waiver _X_Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 18	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): June 10, 2010

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Susan Daugherty
Regulatory Project Manager

cc: NDA 21-793
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Susan B. Daugherty
4/25/05 12:26:29 PM

Memorandum of Telecon

Meeting Date: June 9, 2005

Application Number: NDA 21-793 TRADENAME (metoclopramide orally disintegrating tablets)

Between

Steve Pollock, Vice President, Medical/Regulatory and Quality Assurance
Barry Behnken, Vice President, New Products
Donna Multhauf, Director, Regulatory Affairs
Lisa Schmitt, Project Manager, New Products
Lucrezia Hinman, Manager, Regulatory Affairs
Ketaki Karpe, Manager, Drug Information
Erwin Sahagun, Product Manager, Marketing

Representing: Schwarz Pharma, Inc.

And

Ruyi He, M.D., Medical Team Leader
Lolita Lopez, M.D. Medical Reviewer
Shannon Benedetto, Pharm.D., DDMAC Reviewer
Susan Daugherty B.S.N.; Regulatory Project Manager

Representing: Division of Gastrointestinal and Coagulation Drug Products

Subject:

Labeling submitted by Schwarz Pharma via electronic mail today.

Background:

NDA 21-793 for metoclopramide orally disintegrating tablets on July 30, 2004, received on August 10, 2004, for the relief of symptomatic gastroesophageal reflux and of symptoms associated with diabetic gastroparesis (diabetic gastric stasis).

In a letter dated May 17, 2005, an advice letter was issued to the sponsor with the following comments:

General Comments

1. Ensure that the labeling for Reglan Orally Disintegrating Tablets is distinct from Reglan Tablets to minimize the potential for medication selection error.

2. Print the established name in letters that are at least half as large as the proprietary name in the labeling, to be in accordance with 21 CFR 201.10 (g)(2).

3. Decrease the prominence of the purple circle graphic since it is more prominent than the proprietary name. The drug name and strength should be the most prominent information on the labeling.

4. Design and implement an educational campaign to raise the awareness of health care providers and patients of the differences between the two product formulations.

Container Label – 5 mg and 10 mg (100 count)

Relocate the location of the net quantity so that it is not in close proximity to the product strength in order to avoid confusion between the two.

Sample Blister Carton – 5 mg and 10 mg

1. The net quantity is absent from the carton. Include the net quantity statement on the principal display panel.

2. The orange colored font, along with the white colored font, on the purple background does not provide sufficient contrast which makes it difficult to read. Similarly, the blue colored font on the purple background is also difficult to read. Adjust the colors to improve the readability of the printed information.

3. Remove the following product indication statements from the sample carton:

4. Remove the following statement from the sample carton:

5. Provide directions for patients on how to remove a tablet from this sample carton.

Sample Display Carton – 5 mg and 10 mg

1. Revise the net quantity to read, sample packs. Each sample pack contains 6 tablets".

2. [redacted]

On June 2, 2005, a teleconference was held between representatives of Schwarz Pharma and this Division to discuss the submitted package insert. In that meeting, text for the package insert (PI) was agreed upon. The sponsor was asked to submit the proposed PI and labeling as soon as possible.

On June 9, 2005, the sponsor provided the PI and updated carton and container labeling via electronic mail. The submitted PI was as agreed upon in the June 2, 2005 teleconference. The sponsor made most of the requested revisions to the labeling from the May 17, 2005, letter, as above; however, the blister sample cartons contained new text that was not acceptable, as follows:

1. [redacted]
2.
3.
4.
6.
7.
8.
9.

In addition, all indication statements were removed except ' [redacted] ', which was revised to read, "For the relief of symptoms associated with the short-term treatment of gastroesophageal reflux (GER) when adult patients fail to respond to conventional therapy, and for adults with diabetic gastroparesis."

The Call:

The sponsor was informed that, in order to keep the indication statement, [redacted]

In addition, the sponsor was asked to remove statements 1-9, as above, from the 5 mg and 10 mg sample blister carton labeling because of the promotional nature or lack of fair balance. The sponsor agreed.

The call was ended.

Susan Daugherty
Regulatory Project Manager

Ruyi He, M.D.
Medical Team Leader

UPDATE:
On June 9, 2005, the sponsor faxed a letter indicating their agreement to the above labeling revisions to the 5 mg and 10 mg sample blister carton labeling.

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

/s/

Susan B. Daugherty
7/11/05 12:01:07 PM
CSO

Ruyi He
7/11/05 01:14:47 PM
MEDICAL OFFICER

Memorandum of Telecon

Meeting Date: June 6, 2005

Application Number: NDA 21-793 TRADENAME (metoclopramide orally disintegrating tablets)

Between

Steve Pollock, Vice President, Medical/Regulatory and Quality Assurance
Barry Behnken, Vice President, New Products
Kathleen Kastenholz, Associate Director, Drug Safety and Clinical Management
Donna Multhauf, Director, Regulatory Affairs
Lisa Schmitt, Project Manager, New Products
Lucrezia Hinman, Manager, Regulatory Affairs

Representing: Schwarz Pharma, Inc.

And

Brian E. Harvey, M.D., Ph.D., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Lolita Lopez, M.D. Medical Reviewer
Susan Daugherty B.S.N.; Regulatory Project Manager

Representing: Division of Gastrointestinal and Coagulation Drug Products

Subject:

Request for waiver of pediatric studies for NDA 21-793 metoclopramide orally disintegrating tablets.

Background:

NDA 21-793 for metoclopramide orally disintegrating tablets on July 30, 2004, received on August 10, 2004, for the relief of symptomatic gastroesophageal reflux and of symptoms associated with diabetic gastroparesis (diabetic gastric stasis). The application contained a request to waive the pediatric study requirement. In a letter dated December 13, 2004, the sponsor was informed that their request for a waiver of pediatric studies was denied "because metoclopramide has applicability to the pediatric population and it represents a meaningful therapeutic benefit over existing therapies especially for pediatric patients with GERD. Unlike proton-pump inhibitors and H2-receptor

antagonists which suppress gastric acid secretion, metoclopramide stimulates the motility of the upper gastrointestinal tract." In that letter we also requested that the sponsor submit a pediatric plan. The sponsor did not respond to the request for a pediatric plan submission.

On June 2, 2005, a teleconference was held between representatives of Schwarz Pharma and this Division to discuss the submitted package insert. The sponsor was asked to agree to conduct postmarketing pediatric studies to fulfill requirements indicated by the Pediatric Research Equity Act (PREA). At that time, the sponsor indicated they would need to have an internal discussion before agreeing to conduct postmarketing pediatric studies and would submit a pediatric plan as soon as possible.

On June 6, 2005, Schwarz faxed a letter to the Division, requesting – again – a waiver for pediatric studies. The purpose of today's call is to discuss the pediatric study waiver request.

The Call:

The Division informed the sponsor that we do not agree with their request to waive pediatric studies for the reasons stated in the letter issued December 13, 2004, as above. In addition, metoclopramide is on the list for NIH studies due to needed pediatric information. The Division philosophy is that a waiver would close the door on needed pediatric studies, but that we could defer the studies as postmarketing commitments and, thereby, continue this discussion with the sponsor.

The Division assured the sponsor that a large efficacy study would not be needed to collect the necessary data, but that the knowledge acquired from such studies was important. It was suggested that all age ranges may not need to be studied.

The sponsor stated they would send a letter agreeing to conduct pediatric studies as postmarketing commitments in principle and would like to have additional dialogues regarding the pediatric studies.

The call was ended.

Susan Daugherty
Regulatory Project Manager

Ruyi He, M.D.
Medical Team Leader

UPDATE:

On June 7, 2005, the sponsor faxed a letter indicating their agreement to conduct postmarketing pediatric studies. They plan to request a meeting with the Division to discuss pediatric studies soon.

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

/s/

Susan B. Daugherty
7/11/05 11:57:18 AM
CSO

Ruyi He
7/11/05 01:11:41 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

Schwarz Pharma, Inc.
Attention: Donna Multhauf
Director, Regulatory Affairs
6140 West Executive Dr.
Mequon, WI 53092-4467

Dear Ms. Multhauf:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan (metoclopramide) Orally Disintegrating Tablets.

We request a letter agreeing to the following post-marketing commitments:

1) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged 1 to 16 years.

Protocol submission by:	December 10, 2005 (6 mos. post-approval)
Study start:	June 10, 2006 (1 year post-approval)
Final report submission:	June 10, 2010 (5 years post approval)

2) Single and multiple-dose pharmacokinetics (PK), pharmacodynamics (PD) and safety study in pediatric patients aged less than 1 year.

Protocol submission by:	December 10, 2005 (6 mos. post-approval)
Study start:	June 10, 2007 (2 years post-approval)
Final report submission:	June 10, 2013 (8 years post approval)

We are open to discussing these pediatric studies in the future. If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III

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/s/

Joyce Korvick
6/7/05 09:07:16 AM
For Dr. Brian E Harvey

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

Schwarz Pharma, Inc.
Attention: Lucrezia Hinman
Regulatory Affairs Manager
6140 West Executive Dr.
Mequon, WI 53092-4467
USA

Dear Ms. Hinman:

Please refer to your July 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan (metoclopramide) Orally Disintegrating Tablets.

We also refer to your submission dated May 9, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments.

1. Your justification for the scoring on the 10 mg drug product is unacceptable and the scoring should be removed. Scoring on the 10 mg drug product raises concerns regarding potential off-label use and quality issues.

2. The proposed dissolution limit of NLT [redacted] in 15 minutes is unacceptable. The dissolution limit should be NLT [redacted] in 15 minutes based on the test results.

3. The proposed acceptance criteria for the disintegration specification are unacceptable. The acceptance criteria for the disintegration specification should be less than [redacted] based on the test results.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
5/20/05 03:10:50 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

DISCIPLINE REVIEW LETTER

Schwarz Pharma, Inc.
Attention: Lucrezia Hinman
Regulatory Affairs Manager
6140 West Executive Dr.
Mequon, WI 53092-4467
USA

Dear Ms. Hinman:

Please refer to your July 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan [redacted]™ (metoclopramide) Orally Disintegrating Tablets.

The review of the proposed proprietary name, Reglan [redacted]™, is complete and we find it unacceptable. Please consider proposing an alternate proprietary name and submitting it to NDA 21-793.

In addition we have the following recommendations regarding your labeling.

General Comments

1. Ensure that the labeling for Reglan Orally Disintegrating Tablets is distinct from Reglan Tablets to minimize the potential for medication selection error.

2. Print the established name in letters that are at least half as large as the proprietary name in the labeling, to be in accordance with 21 CFR 201.10 (g)(2).

3. Decrease the prominence of the purple circle graphic since it is more prominent than the proprietary name. The drug name and strength should be the most prominent information on the labeling.

4. Design and implement an educational campaign to raise the awareness of health care providers and patients of the differences between the two product formulations.

Container Label – 5 mg and 10 mg (100 count)

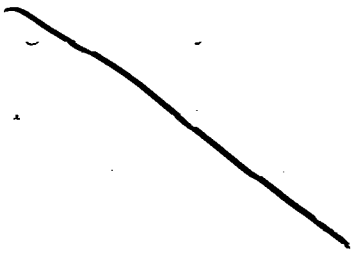
Relocate the location of the net quantity so that it is not in close proximity to the product strength in order to avoid confusion between the two.

Sample Blister Carton – 5 mg and 10 mg

1. The net quantity is absent from the carton. Include the net quantity statement on the principal display panel.

2. The orange colored font, along with the white colored font, on the purple background does not provide sufficient contrast which makes it difficult to read. Similarly, the blue colored font on the purple background is also difficult to read. Adjust the colors to improve the readability of the printed information.

3. Remove the following product indication statements from the sample carton:
   -
   -
   -
   -
   -



4. Remove the following statement from the sample carton:

5. Provide directions for patients on how to remove a tablet from this sample carton.

Sample Display Carton – 5 mg and 10 mg

1. Revise the net quantity to read, sample packs. Each sample pack contains 6 tablets".

2. The white font color contrasted with the yellow/orange background color of the "Top Panel" is difficult to read. Revise the background color to improve readability of the proprietary name, established name, and strength.

If you have any questions, call Susan Daugherty, Regulatory Health Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
5/17/05 11:47:25 AM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 09/29/04 **DATE OF DOCUMENT:** 07/30/04	**DESIRED COMPLETION DATE:** 03/29/05 **PDUFA DATE:** 06/10/05	**ODS CONSULT #:** 04-0262

TO: Joyce Korvick, M.D.
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Susan Daugherty
Project Manager
HFD-180

PRODUCT NAME: **Reglan** [redacted] ™ (Metoclopramide Orally Disintegrating Tablets) 5 mg, 10 mg **NDA#:** 21-793	**NDA SPONSOR:** Schwarz Pharma

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1. Although DMETS has no objections to the use of the proprietary name, Reglan [redacted], from a sound-alike or look-alike perspective, DMETS strongly urges the sponsor to exercise prudence in packaging, labeling, and advertising this product in order to prevent medication errors between the currently marketed Reglan and Reglan [redacted] DMETS also recommends an educational campaign to raise the awareness of health care providers and patients of the differences between the two product formulations. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Reglan [redacted] acceptable from a promotional perspective.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 4439664

12 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Jinhee Jahng
5/3/05 11:06:35 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/3/05 04:19:53 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/3/05 04:24:51 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

DISCIPLINE REVIEW LETTER

Schwarz Pharma, Inc.
Attention: Lucrezia Hinman
Regulatory Affairs Manager
6140 West Executive Dr.
Mequon, WI 53092-4467
USA

Dear Ms. Hinman:

Please refer to your July 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan [redacted] (metoclopramide) Orally Disintegrating Tablets.

We also refer to your submissions dated February 17, and March 8, 2005.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Explain the rationale for conducting a test "Half-Tablet Versus Whole-Tablet Dissolution of Metoclopramide 10 mg Tablets" as described in Volume 5, page 241. We recommend that the scoring not be used in the commercial product.

2. The specification for the degradation products of the drug products should be tightened based on your batch test results.

3. Provide details of the new test method for the impurities [redacted] metoclopramide. Update the specification for the degradation products using the new test method.

4. The specification for the drug dissolution should be tightened based on your test results (e.g [redacted] (Q) at 15 min).

5. The specification for the disintegration time should be reduced based on your batch test results [redacted]

6. Update the stability protocol with the updated regulatory specification.

7. [redacted] months expiration time may be warranted based on your current stability data. The expiration time can be extended when more stability data become available pending resolution of the tablet scoring concern addressed in question #1.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
4/25/05 12:27:01 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-793

Trade Name: Reglan [redacted] ™ Orally Disintegrating Tablet
Generic Name: metoclopromide
Strengths: 5 mg and 10 mg

Applicant: Schwarz Pharma, Inc.

Date of Application: July 30, 2004
Date of Receipt: August 2, 2004
Date clock started after UN: August 10, 2004
Date of Filing Meeting: September 17, 2004
Filing Date: October 9, 2004
User Fee Goal Date: June 10, 2004

Indication(s) requested: For the Relief of Symptomatic Gastroesophageal Reflux and of Symptoms Associated with Diabetic Gastroparesis (Diabetic Gastric Stasis)

Type of Original NDA: (b)(1) ___X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

___ NDA is a (b)(1) application OR ___ NDA is a (b)(2) application

Therapeutic Classification: S ___X___ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___3___
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: ***YES***

User Fee Status: Paid ___X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? ***NO***

  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? ***NO***

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***N/A***

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? ***NO***
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? ***N/A***

- Does the submission contain an accurate comprehensive index? ***YES***

- Was form 356h included with an authorized signature? ***YES***
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? ***YES***

  If no, explain:

- If an electronic NDA, does it follow the Guidance? ***N/A***
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? ***YES***

- Is it an electronic CTD? ***NO***
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted on form FDA 3542a? ***YES***

- Exclusivity requested? ***NO***
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? ***YES***
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? ***YES***
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? ***YES***

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? ***YES***
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? ***YES***

- List referenced IND numbers:

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? ***YES***

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? ***YES***

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? ***N/A***

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***N/A***

If Rx-to-OTC Switch application: **N/A**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? ***N/A*** YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A**

Chemistry

- Did applicant request categorical exclusion for environmental assessment? ***YES***
  If no, did applicant submit a complete environmental assessment? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? ***YES***

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **N/A**

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 17, 2004

BACKGROUND:
NDA 17-854 for Reglan (metoclopromide) Tablets was approved on December 30, 1980, for the indications of short-term treatment (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. This application was transferred from A.H. Robins Company to Schwarz Pharma, Inc (SPI) on December 27, 2001.

SPI submitted NDA 21-793 for Reglan [redacted] (metoclopromide) Orally Disintegrating Tablets for the relief of symptomatic gastroesophageal reflux and of symptoms associated with diabetic gastroparesis (diabetic gastric stasis)on July 31, 2004, received August 4, 2004. The PDUFA goal date is June 10, 2004 because the application fee was received and posted on August 10, 2004. The sponsor relies on the Agency's findings of safety and efficacy from NDA 17-854 Reglan (metoclopromide) Tablets, and has submitted bioequivalence data to support approval of this application.

In addition, the sponsor has requested that we waive the need for pediatric studies per the Pediatric Research Equity Act (PREA).

ATTENDEES:
Joyce Korvick, M.D., Acting Director; Ruyi He, M.D., Medical Team Leader; Lolita Lopez, M.D., Medical Reviewer; Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader; Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer; Jasti Choudary, Ph.D., B.V.Sc., Supervisory Pharmacologist; Yash Chopra, Ph.D., Pharmacology Reviewer; Liang Zhou, Ph.D., Chemistry Team Leader; Zhengfang Ge, Ph.D., Chemistry Reviewer; Susan Daugherty, B.S.N., Regulatory Project Manager

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Lolita Lopez, M.D.
Statistical:	N/A
Pharmacology:	Yash Chopra, Ph.D.
Chemistry:	Zhengfang Ge, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Tien-Mien Chen, Ph.D.
Microbiology, sterility:	N/A
Regulatory Project Management:	Susan Daugherty, B.S.N.

Consults: DSI/Biopharmaceutics; DDMAC (labeling/tradename); DMETS (labeling/tradename)

Per reviewers, are all parts in English or English translation? ***YES***
If no, explain:

CLINICAL FILE ___X_ REFUSE TO FILE _____

- Clinical site inspection needed: ***NO***
- Advisory Committee Meeting needed? YES, date if known _____ ***NO***
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? ***N/A***

CLINICAL MICROBIOLOGY NA __X__ FILE _____ REFUSE TO FILE _____

STATISTICS NA __X__ FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE _____

- Biopharm. inspection needed: ***YES***

PHARMACOLOGY NA ___X___ FILE _____ REFUSE TO FILE _____

- GLP inspection needed: YES ***NO***

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? ***YES***
- Microbiology ***N/A***

ELECTRONIC SUBMISSION: ***NO***
Comments: The following were submitted electronically as well; cover letter, FDA Form 356h, case report tabulations, field copy certification, User Fee Cover Sheet, financial information, and meeting minutes.

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X__ No filing issues have been identified.

ACTION ITEMS:

1. Document no filing issues conveyed to applicant by Day 74.
2. Include the following chemistry information request in the 74-Day letter:
   "In our filing review, we have identified that the submitted stability data do not support your proposed expiration. Provide additional stability data ([redacted]) to support your proposed expiration date, when they become available."

Susan Daugherty
Regulatory Project Manager, HFD-180

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/s/

Susan B. Daugherty
4/15/05 04:27:34 PM
CSO

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/s/

Shannon Benedetto
4/12/05 02:35:02 PM
DDMAC REVIEWER

1) A brief summary or information of Post marketing Experience of Reglan tablets in the U.S. (This should include information such as the estimated *number of patients* who had used the tablet formulation and the estimated *number of prescriptions* dispensed through 2004, and a review of the Adverse Experience Reports received by the sponsor for patients treated with the tablet formulations.)

2) A summary/ narrative report of the following safety evaluations done at baseline and end of treatment period:
   -vital signs, laboratory evaluation and EKG.

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/s/

Susan B. Daugherty
4/11/05 03:49:21 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-793	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug:Reglan (metoclopramide) Orally Disintegrating Tablets		Applicant: Schwarz Pharma	
RPM: Susan Daugherty .		HFD- 180	Phone # (301) 827-7310
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	June 10, 2005
❖ 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	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) 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.	(X) 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) ( ) (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)	7-11-05
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	4-15-05

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	6-10-05
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC 4-12-05; DMETS 5-3-05; Label mtg min
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	6-7-05
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
Outgoing correspondence (i.e., letters, E-mails, faxes)	X
Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	11-8-02
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	6-10-05
❖ Clinical review(s) *(indicate date for each review)*	5-13-05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Pg 23 clinical review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	4-25-05
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	4-26-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	3-18-05

CMC Information	
CMC review(s) *(indicate date for each review)*	4-19-05; 5-19-05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4-19-05
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 12-22-04 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **(X)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	5-22-05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

Schwarz Pharma, Inc.
Attention: Donna Multhauf
Director, Regulatory Affairs
6140 West Executive Dr.
Mequon, WI 53092-4467

Dear Ms. Multhauf:

Please refer to your submission dated July 30, 2004, requesting a waiver for pediatric studies for Reglan (metoclopromide) Orally Disintegrating Tablets.

We have reviewed the submission and do not agree that a waiver of pediatric studies is justified for Reglan (metoclopromide) Orally Disintegrating Tablets for the relief of symptomatic gastroesophageal reflux and of symptoms associated with diabetic gastroparesis (Diabetic Gastric Stasis) because metoclopramide has applicability to the pediatric population and it represents a meaningful therapeutic benefit over existing therapies especially for pediatric patients with GERD. Unlike proton-pump inhibitors and H2-receptor antagonists which suppress gastric acid secretion, metoclopramide stimulates the motility of the upper gastrointestinal tract.

Accordingly, a waiver for pediatric studies for this application is denied under 21 CFR 314.55 at this time. Please submit your pediatric drug development plan.

If you have questions, please call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
12/13/04 01:40:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-793

Schwarz Pharma, Inc.
Attention: Donna Multhauf
Director, Regulatory Affairs
6140 West Executive Dr.
Mequon, WI 53092-4467

Dear Ms. Multhauf:

Please refer to your July 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reglan [redacted]™ (metoclopromide) Orally Disintegrating Tablet.

We also refer to your submission dated August 24, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on October 9, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified that the submitted stability data do not support your proposed expiration. Provide additional stability data (e.g. 9 month, 12 month) to support your proposed expiration date, if they become available.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.
If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III

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/s/

Julieann DuBeau
10/5/04 02:58:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-793

Schwarz Pharma, Inc.
Attention: Donna Multhauf
Director, Regulatory Affairs
6140 West Executive Dr.
Mequon, WI 53092-4467

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:	Reglan [redacted] (metoclopromide) Orally Disintegrating Tablet, 5 mg and 10 mg
Review Priority Classification:	Standard (S)
Date of Application:	July 30, 2004
Receipt Date of User Fees:	August 10, 2004
Our Reference Number:	NDA 21-793

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received on August 10, 2004, all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 9, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 10, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan B. Daugherty
8/18/04 05:37:03 PM
Signing for Julieann DuBeau, MSN, RN, Chief Project Management Staff

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 8, 2002

TIME: 1:00 – 2:30 PM

LOCATION: Potomac Conference Room, Parklawn Building

APPLICATION: NDA: 17-854; Reglan (metoclopramide) Orally Disintegrating Tablets 5 mg and 10 mg

TYPE OF MEETING: Pre NDA meeting

MEETING CHAIR: Dr. Robert Justice

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (DGCDP; HFD-180)

Robert L. Justice, M.D., Division Director
Hugo Gallo-Torres, M.D. – Gastrointestinal Team Leader
Liang Zhou, Ph.D. - Chemistry Team Leader
Diane Moore – Regulatory Health Project Manager
Susan Daugherty – Regulatory Health Project Manager
Jasti Choudary, B.V.Sc., Ph.D. – Supervisory, Pharmacologist
Suresh Doddapaneni, Ph.D. - Pharmacokinetic Team Leader,
Suliman Al-Fayoumi, Ph.D. – Pharmacokinetic Reviewer

Division of Biometrics II

Tom Permutt, Ph.D. - Team Leader

Office of Pharmaceutical Science

Donald Hare – Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Schwarz Pharma. Inc.

Barry Behnken - Vice President, New Products
Hugo Friehe, Dr. Med. Vet. - Scientific Director, Toxicology
Lucrezia Hinman - Regulatory Affairs Manager
Jack R. Luderer, M.D. - Associate Vice President for Research, Western Michigan University
Eleanor Meyer - Regulatory Affairs Associate
Donna Multhauf - Director, Regulatory Affairs and Quality Assurance
Steven R. Pollock - Vice President, Medical and Research

BACKGROUND:

Reglan® Tablets was approved December 30, 1980. Ownership of NDA 17-854 was transferred to Schwarz Pharma Inc. (SPInc) on December 27, 2001. Reglan® Tablets (NDA 17-854) is indicated as short-term (4 to 12 weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. Reglan® Tablets, is also indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The firm requested this pre-NDA meeting to discuss a proposed new dosage form of orally disintegrating tablets. SPInc plans to cross-reference the efficacy and safety data contained in NDA 17-854 in support of a 505(b)(2) application for the new dosage form. The background package for this meeting was submitted October 7, 2002, and received October 8, 2002. Revised questions from the sponsor were submitted November 1, 2002, (received November 1, 2002) in a telefacsimile. The sponsor decided to not pursue the 5 mg orally disintegrating tablet dose and revised the questions to be more appropriate to the new scenario.

MEETING OBJECTIVE:

To discuss the proposed New Drug Application by Schwarz Pharma for Reglan Orally Disintegrating Tablets.

DISCUSSION ITEMS:

The sponsor plans to manufacture a 10 mg orally disintegrating tablet that is scored.

QUESTIONS POSED BY THE FIRM in the NOVEMBER 1, 2002, telefacsimile and FDA RESPONSES: (FDA responses are bolded).

1) SPInc has evaluated the existing preclinical package and has determined that, although the existing preclinical studies may not have been conducted according to current standards, the intent and aims of the current guidelines have, for the most part, been met. Thus, SPInc's position is that existing preclinical data are sufficient to support the new drug application. SPInc seeks Agency concurrence on the acceptability of the preclinical package as defined in the pre-meeting package.

   FDA Response:
   If the pharmacokinetic (PK) profiles for the two formulations (i.e., 10 mg Reglan Tablet and the 10 mg orally disintegrating Tablet) are the same, the preclinical studies for the original NDA may be sufficient to support the new formulation. However, if the PK profiles differ, additional preclinical toxicology studies might be needed. Adequacy and appropriateness of the existing studies need to be examined closely.

2) The proposed indications, strengths and dosing for Reglan orally disintegrating tablets are the same as those contained in the approved labeling for conventional Reglan Tablets. The indications are supported by clinical studies submitted to NDA 17-854. It is SPInc's position that these studies are adequate to support the new drug application for the orally disintegrating tablets. To support this, a pharmacokinetic trial will demonstrate therapeutic equivalence of the conventional tablet and the proposed orally disintegrating tablet. A review of the clinical information found in NDA 17-854 will be included in the pre-meeting package. SPInc seeks Agency concurrence on the acceptability of the clinical package.

FDA Response:
If the sponsor shows that the PK profile is the same, the original clinical studies could support the new formulation. However, if the PK profile is different, additional clinical studies may be necessary.

3) The pre-meeting package will include a review of existing publications which address pediatric use of metoclopramide, a considerable amount of which discusses metoclopramide use in the young pediatric population. While SPInc recognizes that metoclopramide appears on the Agency's *List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population*, SPInc will present information in the pre-meeting package to suggest that more suitable therapies are currently available and approved for pediatric patients. SPInc will seek Agency agreement on the adequacy of the published information and available pediatric therapies, as well as the merits of conducting additional studies in the pediatric population.

FDA Response:
The Division cannot comment on how the Pediatric Rule might apply. Information on pediatric usage would be of value. The Division encourages the sponsor to submit a proposed pediatric study request (PPSR) for a gastroparesis indication.

4) Three lots of Reglan Orally Disintegrating tablets, 10 mg will be produced to support the submission. Tablets will be packaged into bottles of 100 and professional sample blisters. Stability samples of the demonstration batches will be stored under ICH accelerated and controlled room temperature conditions. To support a proposed [redacted] month expiration date, the sponsor proposes submitting [redacted] months of stability data, updating the application with additional stability data as it becomes available. The application will also includ [redacted] months of accelerated stability data on a prototype batch. The sponsor will be seeking Agency concurrence on this proposal.

FDA Response:

a. **In general, [redacted] months of primary stability data are required for a NDA submission.**

b. **Specifications for Impurities need to be tightened based on the batch test data.**

c. **For Dissolution methods, data from several batches need to be submitted.**

d. **Other specification acceptance criteria need to be reviewed with additional chemistry, manufacturing and quality Control (CMC) information such as impurities and test methods. The sponsor should provide justification for the use of non compendial excipients. The Division recommends the sponsor refer to the draft Guidance for Industry entitled "Guidance on Nonclinical Studies for Development of Pharmaceutical Excipients."**

e. **The Division recommends the applicant submit CMC information to a new IND for Reglan Orally-disintegrating Tablets for review and comment.**

Additional comment: The sponsor should consider developing a release test to determine the *in vivo* release of the proposed orally-disintegrating tablets.

5) The safety profile of metoclopramide has been well established in the over 20 years of marketing experience of various dosage forms. The safety profile of Reglan Orally Disintegrating Tablets is not expected to differ from that of the currently approved conventional Reglan Tablets. SPInc will adhere to the postmarketing adverse drug experience reporting requirements of 21 CFR § 314.80 for Reglan Orally Disintegrating Tablets. Thus, SPInc proposes no additional risk management activities. The sponsor will be seeking Agency concurrence on this proposal.

FDA Response:
The Division cannot comment at this time. The data must be reviewed prior to a decision regarding this matter.

6) As noted previously, SPInc believes the preclinical and clinical study data included in NDA 17-854 is adequate to support the efficacy and safety of metoclopramide. Thus, SPInc plans to cross-reference the efficacy and safety data contained in NDA 17-854 for this 505(b)(2) application. The 505(b)(2) application will also include the published preclinical and clinical pediatric data contained in this pre-meeting package. SPInc seeks Agency concurrence that this proposal is acceptable and no further documentation will be needed.

FDA Response:
The sponsor should clarify the intent of submitting published clinical pediatric data.

The adequacy and appropriateness of the available data from the preclinical studies of metoclopramide needs to be examined closely.

The 505(b)(2) application is submitted under 505(b)(1) and therefore must contain full reports. If the preclinical data in the listed drug's application does not meet today's standards, the pharmacologist may request any data needed so that the proposed (b)(2) application will meet the "full reports" requirement.

Additional Comments:

The sponsor should refer to 21 CFR 206 regarding embossing or imprinting of the tablets.

The sponsor should refer to the International Conference on Harmonisation (ICH): Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products.

The sponsor should refer to the ICH Q3A Guideline for Industry entitled, "Impurities in New Drug Substances" regarding drug impurities.

ACTION ITEMS:

1. SPInc will request a separate Pre-NDA chemistry and manufacturing meeting to discuss chemistry questions.
2. SPInc is not currently seeking a pediatric application, [redacted] pediatric patients. They will notify the Division regarding their plans for a PPSR.
3. SPInc will consider submitting an IND for the orally-disintegrating tablets.

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

drafted: dm/11/12/02
revised: J.Dubeau 11.22.02
initialed: J.Dubeau 11.22.02/J.Choudary, S.Daugherty, S.Al-Fayoumi 11.26.02/T.Permutt 11.27.02 D.Hare 11.28.02/.Justice 11.27.02
Finalized: December 6, 2002
Filename: N20210TC5702.doc

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/s/

Diane V. Moore
12/6/02 03:04:55 PM

Robert Justice
12/11/02 05:50:44 PM