

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-712

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

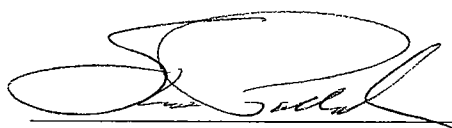
PATENT INFORMATION
21 CFR § 314.54(v)

Signed patent declaration forms FDA 3542a regarding patent information is 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 Famotidine Orally Disintegrating Tablets, 20 mg and 40 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, Pepcid, is also included.

SCHWARZ
P H A R M A**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.



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

11.12.03
Date

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

N021712

NAME OF APPLICANT / NDA HOLDER

Schwarz Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

FLUXID™

ACTIVE INGREDIENT(S)

Famotidine

STRENGTH(S)

20 mg and 40 mg

DOSAGE FORM

Orally Disintegrating Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, please above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,024,981

b. Issue Date of Patent
2/15/2000

c. Expiration Date of Patent
4/9/2018

d. Name of Patent Owner

CIMA LABS INC.

Address (of Patent Owner)
7325 Aspen Lane

City/State
Brooklyn Park, MN

ZIP Code
55428

FAX Number (if available)
(763) 488-4770

Telephone Number
(763) 488-4700

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

the patent referenced above a patent that has been submitted previously for the
proved NDA or supplement referenced above?

☐ Yes

☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration
date a new expiration date?

☐ Yes

☒ No

025
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



11-20-03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

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

Address

Schwarz Pharma, Inc.
6140 West Executive Drive

City/State

Mequon, WI

ZIP Code

53092-4467

Telephone Number

(262) 238-5206

FAX Number (if available)

(262) 238-0957

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

N021712

NAME OF APPLICANT / NDA HOLDER

Schwarz Pharma, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

FLUXID™

ACTIVE INGREDIENT(S)

Famotidine

STRENGTH(S)

20 mg and 40 mg

DOSAGE FORM

Orally Disintegrating Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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1. GENERAL

a. United States Patent Number

6,221,392

b. Issue Date of Patent

4/24/2001

c. Expiration Date of Patent

4/9/2018

d. Name of Patent Owner

CIMA LABS INC.

Address (of Patent Owner)

7325 Aspen Lane

City/State

Brooklyn Park, MN

ZIP Code

55428

FAX Number (if available)

(763) 488-4770

Telephone Number

(763) 488-4700

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the same or a related NDA or supplement referenced above?

☐ Yes

☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

☐ Yes

☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

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Date Signed



11-20-03

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Check applicable box and provide information below.

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☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

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

Address

Schwarz Pharma, Inc.
6140 West Executive Drive

City/State

Mequon, WI

ZIP Code

53092-4467

Telephone Number

(262) 238-5206

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

EXCLUSIVITY SUMMARY FOR NDA # 21-712

Trade Name: Fluxid™ Generic Name: Famotidine Orally Disintegrating Tablets, 20 mg, 40 mg

Applicant Name: Schwarz Pharma HFD # 180 DGCDP

Approval Date If Known: September 24, 2004

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES /X/ NO /___/

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

505(b)(2)

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 bioequivalence study (see clinical pharmacology review dated July 13, 2004). The sponsor has not made an argument otherwise to our knowledge, (see cover letter of submission dated November 24, 2003).

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:

N/A

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?

N/A

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

YES / X / 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? **NO**

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 / X /**

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 / X / NO /___/

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

NDA 19-462 Pepcid® (famotidine) Tablets, 20 mg, 40 mg
NDA 19-510 Pepcid® (famotidine) Injection, 10 mg/mL
NDA 19-527 Pepcid® (famotidine) Oral Suspension, 40 mg/5 mL
NDA 20-249 Pepcid® (famotidine) Injection, 0.4 mg/mL preservative free

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.)

N/A YES / / NO / /

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

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 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 / X / NO / X /

Signature: Joyce Korvick, M.D., M.P.H.
Title: Acting Division Director, DGCDP

Date: September 24, 2004

**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

9/24/04 04:56:56 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA: #21-712

Stamp Date: November 24, 2003

Action Date: September 24, 2004

HFD-180 Trade and generic names/dosage form:

Fluxid™ (famotidine orally disintegrating tablets), 20 mg, 40 mg

Applicant: Schwarz Pharma Inc.

Therapeutic Class: H 2-receptor antagonist

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 5

Indication #1: Short term treatment of active duodenal ulcer

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

X Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ 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:

X 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. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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): _____

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}

Betsy Scroggs, Pharm.D.
Regulatory Project Manager

cc: NDA 21-712

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: Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer

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

X Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ 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:

X 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. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	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): _____

*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}

Betsy Scroggs, Pharm.D.
Regulatory Project Manager

cc: NDA 21-712
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)

Attachment A

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

Indication #3: Short term treatment of active benign gastric ulcer

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

X Yes: Please proceed to Section A.No: Please check all that apply: ☐ Partial Waiver ☐ 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:

X 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. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	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): _____

*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}

Betsy Scroggs, Pharm.D.
Regulatory Project Manager

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

(revised 10-14-03)

Attachment A

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

Indication #4: Short term treatment of gastroesophageal reflux disease (GERD) with or without esophagitis

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

X Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ 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:

X 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. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ 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): _____

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}

Betsy Scroggs, Pharm.D.
Regulatory Project Manager

cc: NDA 21-712
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)

Attachment A

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

Indication #5: Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)

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

X Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ 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**X 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. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	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): _____

*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}

Betsy Scroggs, Pharm.D.
Regulatory Project Manager

cc: NDA 21-712

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)

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

/s/

Betsy Scroggs
9/24/04 01:30:36 PM

SCHWARZ
P H A R M A**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

01/23/03

Date



Ron Stratton, Ph.D.
President & COO

10-23-03

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-712	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: Fluxid™ (famotidine orally disintegrating tablets)		Applicant: Schwarz Pharma, Inc.
RPM: Betsy Scroggs	HFD-180	Phone # 301-827-1250
Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct. (X) Confirmed	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA # 19-462 Pepcid® Tablets	
❖ Application Classifications:		
• Review priority		(X) Standard () Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		September 25, 2004
❖ 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 () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
• User Fee		() Paid UF ID number
• User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception		() Orphan designation (X) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
❖ 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)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) (X) Verified 21 CFR 314.50(i)(1) (X) (ii) () (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)). <i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i> (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? <i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i> <i>If "No," continue with question (3).</i> (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	() N/A (no paragraph IV certification) () Verified () Yes () No () Yes () No () Yes () No

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)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes
• 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)	(X) 9/16/2004
• Most recent applicant-proposed labeling	(X) 9/17/2004
• Original applicant-proposed labeling	(X) 11/24/2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	(X) DDMAC 8/31/2004, 9/21/2004 DMETS 9/20/2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	(X) NDA 19-462 NDA 19-527 NDA 20-752
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	(X) 11/24/2003, 9/02/2004
• Reviews	(X) See CMC DR dated 8/09/2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• 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	
N/A	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	(X) Pre-IND 4/02/2003
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
N/A	

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
• Exclusivity summary	☒ (X)
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ (X) No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☐ () Yes, Application # _____ ☒ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	☒ (X) 09/15/2004, updated 09/28/2004

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	(X) 9/24/2004
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	(X) 7/16/2004, 8/20/2004
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	(X) see MOR dated 8/20/2004
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	(X) 9/24/2004
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	(X) 7/13/2004, 9/16/2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	(X) 9/02/2004
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	(X) 8/06/2004, 9/22/2004
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	(X) See CMC DR dated 8/06/2004
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: 7/26/2004 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested 4/02/2004 () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	(X) 9/03/2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 22, 2004

To: Ms. Elizabeth Weil for Ms. Donna Multhauf	From: Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company Schwarz Pharma	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (262) 238-0957	Fax number: (301) - 827-1305
Phone number: (262) 238-5225	Phone number: 301-827-1250

Subject: NDA 21-712

**Total no. of
pages including 4
cover:**

DOCUMENT TO BE MAILED? NO

We have the following comments and recommendations regarding the carton labeling for the 20mg and 40mg tablet strengths for NDA 21-712, Fluxid. Please respond ASAP by fax followed by submission of hard copy.

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

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

2 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☒ § 552(b)(4) Draft Labeling

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

/s/

Betsy Scroggs
9/22/04 10:00:56 AM
CSO

CONSULTATION RESPONSE

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

DATE RECEIVED:

February 09, 2004

DESIRED COMPLETION DATE:

June 05, 2004

ODS CONSULT #: 04-0040

PDUFA DATE: September 25, 2004

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

THROUGH: Betsy Scroggs, PharmD.
Project Manager
HFD-180

PRODUCT NAME:

Fluxid™ (Primary)
— (Secondary)
(Famotidine Orally Disintegrating Tablets)
20 mg and 40 mg

NDA SPONSOR: Schwarz Pharma, Inc.

NDA#: 21-712

SAFETY EVALUATOR: Linda M. Wisniewski, RN

METS RECOMMENDATIONS:

1. DMETS has no objection to use of the name Fluxid. However, DMETS does not recommend the use of the proprietary name —. Please note: DMETS does not routinely evaluate secondary names if the first name has been found acceptable. Due to the anticipated approval of this product, we included both. 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 and its associated labels and labeling 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 IV of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proposed proprietary names Fluxid and — acceptable from a promotional perspective.

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

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 02, 2004

NDA#: 21-712

NAME OF DRUG: Fluxid™ (Primary)
— (Secondary)
(Famotidine Orally Disintegrating Tablets)
20 mg and 40 mg

NDA HOLDER: Schwarz Pharma, Inc.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public. ***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for assessment of the proprietary names, "Fluxid" (Primary), and — (Alternate), regarding potential name confusion with other proprietary or established drug names. When addressing name confusion, each drug will be addressed separately. Otherwise, "Fluxid —" will be used synonymously. Draft container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Fluxid™ — (famotidine orally disintegrating tablets) is a histamine H₂-receptor antagonist, and is an orally administered formulation of famotidine which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. Famotidine is a white to pale yellow crystalline compound. Each orally disintegrating tablet contains either 20 mg or 40 mg of famotidine. It will be supplied in bottles of 30 tablets (unit-of-use), and bottles of 100 tablets.

Fluxid™ — is indicated for use in the following:

1. *Short-term treatment of active duodenal ulcer.*
2. *Maintenance therapy of duodenal ulcer patients at reduced dosage after healing of an active ulcer.*
3. *Short-term treatment of active benign gastric ulcer.*
4. *Short-term treatment of gastroesophageal reflux disease (GERD).*
5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).*

Fluxid™ — is also indicated for the short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy.

Product Dosing:

Duodenal Ulcer:

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime, but also can be dosed as 20 mg twice a day.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Benign Gastric Ulcer:

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD):

The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg two times a day for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 mg or 40 mg two times a day for up to 12 weeks.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Fluxid. — 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 was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. 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.

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, Drugs@FDA,

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Fluxid and —. Potential concerns regarding drug marketing and promotion related to the proposed names were 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. DDMAC finds the proposed proprietary names Fluxid and — acceptable from a promotional perspective.
2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Fluxid. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.
3. The Expert Panel identified six proprietary names that were through to have potential for confusion with —. These products are listed in Table 2 (see page 5), along with the dosage forms available and usual dosage.

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

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Fluxid	Famotidine Orally Disintegrating Tablets, 20 mg and 40 mg for oral use	20 mg daily or b.i.d. or 40 mg daily or twice daily.	N/A
Flexeril	Cyclobenzaprine Hydrochloride Tablets 5 mg and 10 mg for oral use	5 mg to 10 mg three times a day. Not recommended to be used for more than two or three weeks.	LA
Floxin	Ofloxacin Tablets: 200 mg, 300 mg, 400 mg Injection: 200 mg/50 mL D ₅ W, 400 mg in water for injection in 10 mL single-use vials; 400 mg in 100 mL D ₅ W. Ophthalmic Solution: 0.3%. Otic Solution: 0.3%	Cervicitis and urethritis: 300 mg orally or intravenously every twelve hours for seven days. Sexually Transmitted Diseases: Uncomplicated Gonorrhea: 400 mg orally or intravenously as a single dose. Conjunctivitis: 1 to 2 drops every two to four hours for two days, then q.i.d. for up to 5 additional days. Otitis Media: 5 to 10 gtts in affected ear b.i.d. for 10 days.	SA/LA
Fluonid	Fluocinolone Acetonide Gel: 0.025% Cream: 0.025% Ointment: 0.025% Solution: 0.01%	No longer marketed. ANDA's withdrawn after approval on: ANDA # 87-300: 03/03/1988 ANDA # 87-156: 10/25/2000 ANDA # 87-157: 10/25/2000 ANDA # 87-158: 05/31/2002	LA
Luxiq	Betamethasone Valerate Foam: 1.2 mg/g	Apply twice daily, once in the morning and once at night.	SA
			S/A
Flexon	Orphenadrine Citrate Injection: 30 mg per mL IM or IV	60 mg may repeat every 12 hours.	LA/SA
*Frequently used, not all inclusive. ** L/A (look-alike), S/A (sound-alike).			
*** NOTE: This review contains proprietary and confidential information that should not be released to the public. ***			

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☐ § 552(b)(4) Draft Labeling

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified Fluocin, Flaxedil, and Fluidil which were considered to have significant phonetic or orthographic similarities to Fluxid. These products are listed in Table 3 (see below), along with the dosage forms available and usual dosage.

Table 3: Potential Sound-Alike/Look-Alike Names Identified by POCA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Fluxid	Famotidine Orally Disintegrating Tablets 20 mg and 40 mg for oral use	20 mg daily or b.i.d. or 40 mg daily or twice daily.	N/A
Fluocin	Fluocinonide Cream: 0.05% Gel: 0.05% Ointment: 0.05% Solution: 0.05%	Apply sparingly to affected areas two to three times a day. NDA's withdrawn unapproved: # 87-330 on 6/30/94 # 87-331 on 6/30/94.	SA/LA
Fluidil	Cyclothiazide Tablets: 2 mg	No dosing available. NDA# 18-173 withdrawn by the commissioner on 2/9/87.	SA/LA
Flaxedil	Gallamine Triethiodide Injection: 20 mg/mL 100 mg/mL	No dosing available. NDA# 7-842 withdrawn by the commissioner on 9/22/99.	SA/LA

*Frequently used, not all-inclusive.

**L/A (look-alike), S/A (sound-alike)

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Fluxid:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Fluxid with currently marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 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 Fluxid (see page 7). 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.

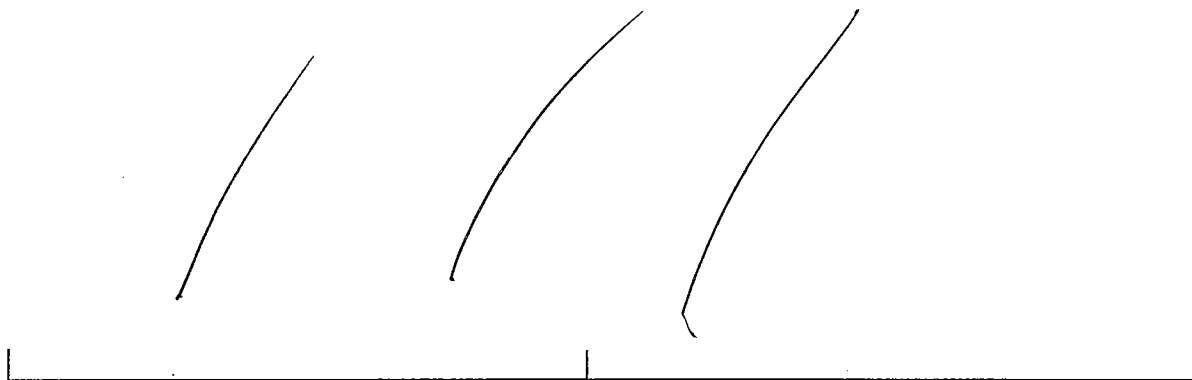
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Fluxid 40mg 1 po qhs #30	Fluxid 40 mg Sig: Take one po hs. #30
Inpatient RX: ~~Fluxid 20mg po QHS # 15~~	

2. Results:

Two respondents from the written inpatient study interpreted the proposed name as Flexeril. Flexeril is a currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

3. Methodology for —





4. Results:



E. SAFETY EVALUATOR RISK ASSESSMENT

1. Fluxid

In reviewing the proprietary name Fluxid, the primary concerns related to look-alike and sound-alike confusion with Flexeril, Floxin, Fluonid, Luxiq, — and Flexon. The POCA tool identified the names Fluocin, Fluidil and Flaxedil as having significant phonetic or orthographic similarity. Upon further review of the names gathered from EPD and POCA, the names: Fluidil and Flaxedil were not evaluated further because their applications were withdrawn on 2/9/87, 9/22/99, 10/25/00; 10/25/00, 5/31/02, and 3/3/88, respectively. No additional information is available for either of these names through commonly used reference sources such as The Physicians Desk Reference (PDR) and Facts and Comparison. The product

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Fluxid could be confused with Flexeril. Two respondents from the Fluxid inpatient written study misinterpreted the name as Flexeril, a currently marketed product. The remaining interpretations were misspelled or phonetic variations of the proposed name.

- a. Floxin may look similar when scripted, and sound similar when spoken, to Fluxid. Floxin is an antibiotic used to treat a variety of infections. Both names begin with the same two letters (fl), and are followed by letters that may look similar when written (uxi vs. oxi). Additionally, the last letter of each name (d vs. n) may look similar, if the 'n' is exaggerated or the upstroke of the 'd' is not prominent (see page 9). However, post-marketing research has not described orthographic confusion between the letters 'n and d'. Both names share the letters 'fl and x' which contributes to the phonetic similarities

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.

between these two names. However, the pronunciation of the vowels 'o vs. u' will help to differentiate these two names when spoken (ox-in vs. ux-id). Additionally, there are product characteristics that may help to minimize confusion, such as dose (1-10 gtts and 300 mg to 400 mg, vs. 20 mg or 40 mg), and strength (200 mg/50 mL, 400 mg/20 mL, 400 mg/100 mL, 200 mg, 300 mg, and 400 mg vs. 20 mg or 40 mg). Thus, the orthographic differences, dose, and strength of these two products will help to minimize confusion.

fluonid
fluxid

- b. Fluonid may look similar to Fluxid when scripted. Fluonid, although no longer marketed, was indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. However, there are generic and other proprietary named products that contain the same active ingredient at the same strength. Therefore, if a practitioner receives a prescription for Fluxid that they interpret as Fluonid, they may fill it with a generically equivalent product. Both names begin with the letters 'flu' and end with letters 'id'. Additionally, the middle letters 'x vs. on' can also look similar (see below) when scripted. Although both products may be administered twice daily, there are some differentiating product characteristics, such as dose (sparing amount vs. 20 mg or 40 mg), dosage form (cream, ointment, or solution vs. tablet), strength (0.01%, 0.025%, and 0.2% vs. 20 mg and 40 mg), route of administration (topical vs. oral), and indication of use (inflammatory and pruritic dermatoses vs. gastric ulcer and GERD). An order may be scripted for Fluxid to be used twice daily and be misinterpreted as Fluonid. However, the dosage form (cream, ointment, and solution) and /or strength would likely be included in the order. This may help decrease the potential for error. If it were not included in the order, the practitioner would need further clarification prior to dispensing a generic product. Although the names may look similar and have overlapping frequency of administrations, the dosage form and strength may help to minimize confusion between Fluonid and Fluxid.

fluxid
fluonid

- c. Flexeril may look similar to Fluxid when scripted. Two respondents in the written inpatient study misinterpreted Fluxid as Flexeril (see Appendix A). Flexeril is used as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute painful musculoskeletal conditions. Both names begin and end with letters that look similar when scripted (flexe vs. fluxi and ril vs. xud) (see page 10). Additionally, there are some overlapping product characteristics, such as dosage form (tablet), route of administration (oral), and storage location (oral solids). However, other product characteristics may help to differentiate the two products, such as dose and/or strength (5 mg and 10 mg, vs. 20 mg and 40 mg), frequency of administration (three times a day

vs. once or twice daily), and indication of use (relief of muscle spasm vs. treatment of ulcers and GERD). Although there are orthographic similarities, the dose, strength, and frequency of administration may help to minimize confusion between Fluxid and Flexeril.

Fluxid
Flexeril

- d. Luxiq may sound similar to Fluxid when spoken. Luxiq is indicated for the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive scalp dermatoses. Both names may sound similar when pronounced. The prefix “flux” may sound like “lux” particularly if the letter ‘f’ is indistinguishable. Although both drugs are administered twice daily, there are product characteristics that will help to differentiate them. Such characteristics include dosage form (tablet vs. aerosol foam), daily dose (20 mg or 40 mg vs. small amount), strength (20 mg or 40 mg vs. 1.2 mg/g), route of administration (oral vs. topical), and indication of use (gastric ulcers and gastroesophageal reflux disease vs. scalp dermatitis). Additionally, prescriptions for Fluxid will likely need a strength identified before dispensing. In contrast, Luxiq prescriptions do not require that a strength to be noted. Thus, the different product characteristics of Fluxid may help to decrease the potential for confusion between these two products.
- e. Flexon may look similar when scripted and sound similar when spoken to Fluxid. Flexon is indicated as an adjunct to rest, physical therapy and other measures for relief of discomfort associated with acute, painful musculoskeletal conditions. Both names begin with the same two letters (fl), followed by similarly looking letters (ex vs. ux and id vs. on) (see below). Moreover, these two-syllable names share phonetic similarities due to the similar spelling (f l _ x _) and identical character length (6 letters). Although there are orthographic similarities, and both products may be administered every twelve hours, there are product characteristics that may help to differentiate them. These include dose (60 mg vs. 20 mg or 40 mg), strength (30 mg/mL vs. 20 mg or 40 mg), dosage form (injection vs. tablet), route of administration (intravenous or intramuscular vs. orally), and indication of use (muscle spasm vs. gastric ulcer and gastroesophageal reflux disease). The product characteristics will help to distinguish the two products and minimize the potential for confusion.

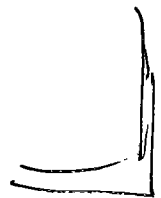
fluxid
flexon

- f. Fluocin may look similar when written and sound similar when spoken to Fluxid. Fluocin is a topical corticosteroid and is used to help relieve redness, swelling, itching, and discomfort of many skin problems. Each name begins with the same three letters “flu”. However, the rest of the letters are different (ocin vs. xid), but the orthographic presentation may look similar (see page 11). If the upstroke of the ‘d’ in Fluxid is clearly scripted, it may help to distinguish the two names when written. The phonetic similarity stems from similar spelling; each name contains the same four letters (flui), in the same order, with different placement. However, the different syllable length (3 vs. 2) makes the rest of the name phonetically different. Both drugs have the potential to have overlapping frequencies of administration (twice daily), but differentiating product characteristics such as dose (sparing amount vs. 20 mg or 40 mg); dosage form (cream, gel, ointment, and

solution vs. tablets), strength (0.05% vs. 20 mg or 40 mg), route of administration (topical vs. oral), and indication of use (redness, swelling, itching, and discomfort of many skin problems vs. gastric ulcer and GERD) may help to minimize confusion.

fluorid
fluorid

2.



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DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

- A. DMETS has no objection to use of the name Fluxid. However, DMETS does not recommend the use of the proprietary name — Please note: DMETS does not routinely evaluate secondary names if the first name has been found acceptable. Due to the anticipated approval of this product, we included both. 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 and its associated labels and labeling 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.
- B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
- C. DDMAC finds the proposed proprietary names Fluxid and — acceptable from a promotional perspective

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

Fluxid: NDA 21-712

ODS Consult: 04-0040

Voice	Inpatient	Outpatient
Flexid	Flexeril	Flurid
Flexid	Flexeril	Fluxia
Flexid	Flexerol	Fluxid
Flexid	Flexid	Fluxid
Flexid	Fluped	Fluxid
Flexid	Flurid	Fluxid
Flexid	Fluriol	Fluxid
Flexid	Fluxed	Fluxid
Flexid	Fluxed	Fluxid
Flexil	Fluxed	Fluxid
flexir	Fluxed	fluxid
Flexis	Fluxed	Fluxid
Floxcid	Fluxed	Fluxid
Floxid	Fluxid	Fluxid
Fluxed	Fluxid	Fluxid
Fluxes	Fluxid	Fluxid
Fluxid	Fluxid	Fluxid
Fluxid	Fluxid	Fluxid
Fluxid	Fluxid	Fluxid
Fluxid	Fluxid	Fluxid
Fluxid	Fluxid	Fluxid
		Fluxid

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/s/

Linda Wisniewski
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/20/04 01:57:08 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/20/04 03:48:04 PM
DRUG SAFETY OFFICE REVIEWER



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 20, 2004

To: Ms. Elizabeth Weil for Ms. Donna Multhauf	From: Betsy Scroggs, Pharm.D. Consumer Safety Officer
Company Schwarz Pharma	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (262) 238-0957	Fax number: (301) - 827-1305
Phone number: (262) 238-5225	Phone number: 301-827-1250
Subject: NDA 21-712	

**Total no. of
pages including
cover:** 3

DOCUMENT TO BE MAILED? NO

Please find our additional draft labeling recommendations based on review by the Division of Medication Errors and Technical Support (DMETS). We look forward to discussing these recommendations with you.

- I. We find the use of the name "Fluxid™" acceptable.
- II. We recommend implementation of the following label and labeling revisions to minimize potential errors with the use of this product.

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

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/s/

Betsy Scroggs
9/20/04 05:57:22 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #: 21-712

Trade Name: Fluxid™

Generic Name: famotidine orally disintegrating tablets

Strengths: 20 mg and 40 mg

Applicant: Schwarz Pharma

Date of Application: November 24, 2003

Date of Receipt: November 25, 2003

Date clock started after UN: N/A

Date of Filing Meeting: January 19, 2004

Filing Date: January 23, 2004

Action Goal Date (optional): Friday, August 24, 2004 User Fee Goal Date: September 25, 2004

Indication(s) requested:

Adults

- Duodenal ulcer
- Benign Gastric Ulcer
- Gastroesophageal Reflux Disease (GERD)
- Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)

Pediatrics

- GERD with or without esophagitis

Type of Original NDA: (b)(2)

Therapeutic Classification: S

Resubmission after withdrawal? No Resubmission after refuse to file? No

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) No

Form 3397 (User Fee Cover Sheet) submitted: Yes

User Fee Status?..... Exempt per 505(b)(2) exemption

?	Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application?	No
?	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).....	N/A
?	Is the application affected by the Application Integrity Policy (AIP)? If yes, explain. N/A	No
?	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:	N/A
?	If an electronic NDA, does it follow the Guidance?	Yes
	If an electronic NDA, all certifications must be in paper and require a signature.	
	Which parts of the application were submitted in electronic format?	
	1. Labeling	
	2. Datasets	
	Additional comments:.....	None
?	If in Common Technical Document format, does it follow the guidance? ..	N/A
?	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:.....	N/A
?	Patent information submitted on form FDA 3542a?.....	Yes

- | | | |
|---|---|-----|
| ? | Exclusivity requested?..... | No |
| | <i>NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | |
| ? | Correctly worded Debarment Certification included with authorized signature? | No |
| | <i>Comment: 5 certifications provided. Second of 5 must be reworded.</i> | |
| | <i>Pending from Sponsor: has committed to provide updated certification for MDS Pharma Services ASAP.</i> | |
| ? | 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 |
| ? | Drug name/Applicant name correct in COMIS?..... | Yes |
| ? | List referenced IND numbers: | N/A |
| ? | End-of-Phase 2 Meeting?..... | No |
| ? | Pre-NDA Meeting(s)?..... | Yes |
| | <i>The firm cancelled the scheduled April 3, 2004 meeting having received our faxed responses on April 2, 2004. They accepted our written responses in lieu of a face-to-face meeting. The official date of the "meeting" is April 2, 2004.</i> | |

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?..... | No |
| ? | 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

? Has DOTCDP been notified of the OTC switch application?..... N/A

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

? Establishment Evaluation Request (EER) submitted to DMPQ?..... Yes

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

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)?..... Yes

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and any NDAs or aNDAs: NDA 19-462 Pepcid® (famotidine) Tablets, 20 mg and 40 mg

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?..... Yes

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? Yes

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?..... N/A

*If "No," please contact the Director, Division of Regulatory Policy II, ORP.
Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved?..... N/A

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? N/A
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II to ORP? N/A

*If "No," please contact the Director, Division of Regulatory Policy II, ORP.
Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? N/A

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug?..... N/A

6. Describe the change from the listed drug(s) provided for in this (b)(2) application:
This application provides for a change in dosage form to an "orally disintegrating tablet".
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9))..... No
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). No
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))?..... No
10. Are there certifications for each of the patents listed for the listed drug(s)?..... Yes
11. Which of the following patent certifications does the application contain?
(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- v 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.
(Paragraph II certification) *The applicant has submitted signed form 3542a for Patent Number 6,221,392 issued 4/24/2001 with and expiration of 4/9/2018 for CIMA LABS INC, 5325 Aspen Lane, Brooklyn Park, MN 55428 (763) 488-4700.*

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.
(Paragraph III certification)

_____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

_____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?..... Yes
- Submit a statement as to whether the listed drug(s) identified No
has received a period of marketing exclusivity?

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?..... Yes
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).? N/A
13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A
- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a)..... N/A
 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval N/A
 - EITHER
- The number of the applicant's IND under which the studies essential to approval were conducted. No
- OR
- A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?.. No
14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?..... Yes

ATTACHMENT

MEMORANDUM OF FILING MEETING

MEETING DATE: January 19, 2004

TIME: 10:00 AM to 11:00 AM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 21-712

TYPE OF MEETING: Filing Meeting

MEETING CHAIR: Gary Della'Zanna, M.D. Acting GI Team II Team Leader

MEETING RECORDER: Brian Strongin, R.Ph. M.B.A., CPMS
(covering for Paul Levine, Jr., R.Ph., JD., Regulatory Health Project Manager)

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

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

Robert L. Justice, M.D., M.S. Director, Division
Joyce Korvick, M.D., M.P.H. Deputy Director
Lolita Lopez, M.D., Medical Officer
Jasti Choudary, B.V.Sc., Ph.D., Supervisory, Pharmacologist
Ronald Honchel, Ph.D., Pharmacologist
Brian Strongin, R.Ph., M.B.A. Chief, Project Management Staff

Division of New Drug Chemistry II (DNDC II)

Liang Zhou, Ph.D., Chemistry Team Leader
Raymond Frankewich, Ph.D., Chemist

Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)

Tien Mien Chen, Ph.D., Biopharmaceutics Reviewer
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

BACKGROUND: In this submission, the sponsor seeks approval of a new famotidine formulation, an orally disintegrating tablet (ODT), Fluxid™ 20 mg and 40 mg under a 505(b)(2) application. The sponsor relies on the Agency's finding of safety and efficacy for conventional immediate release famotidine tablets, Pepcid® tablet, originally approved in 1986. Pepcid® is available as injection, tablets,

oral suspension and previously as orally disintegrating tablets. The latter was approved on May 28, 1998 (under NDA 20-752) but the company voluntarily ceased its marketing in the U.S., no reason was provided; however, no safety issues were identified. The sponsor has no proposed changes to the indications and administration schedule of the Pepcid®.

To support approval, the sponsor conducted a fasting bioequivalence study comparing the 40 mg tablets of the approved Pepcid® and proposed famotidine 40mg orally disintegrating tablets (ODT) dosage forms, Fluxid™. The sponsor requested a waiver of in vivo bioequivalence studies for the 20 mg strength of the drug product. The sponsor has proposed the proprietary name "Fluxid™" and proposes a second choice "_____ " if the former is not acceptable.

MEETING OBJECTIVE:

To discuss the fileability of NDA 21-712, and to identify and discuss potential review issues regarding the submission. Identified issues will be conveyed to the sponsor in a regulatory letter.

DISCUSSION POINTS:

Regulatory Project Management (RPM):

- The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing from a regulatory standpoint.
- The supplement will have a 10-month review. Reviews will be due August 20, 2004. The PDUFA User Fee Goal Date is Saturday, September 25, 2004. Action will be taken on or before Friday, September 24, 2004.
- 60 day filing date is January 23, 2004, 74 day letter is due February 5, 2004.
- Next team meeting is in March.
- This NDA submission (project management) will be transferred from Paul Levine to Betsy Scroggs on January 19, 2004.

1. Clinical

- The supplement is fileable.
- No studies submitted, relying on Pepcid®.
- Need volumes 1.11 and 1.12 copies.
- May have information requests, will email to RPM if needed.

2. Chemistry, Manufacturing and Quality Control

- The supplement is fileable. No issues.
- Need acceptance criteria for dissolution test.
- Is the disintegration time too long? Should be less than 2 minutes.
- Needs IR, not a filing issue Will email to RPM.
- EER needed.

3. Pharmacology

- The supplement is fileable. No issues.
- References the MSD NDA.

4. Clinical Pharmacology and Biopharmaceutics

- The supplement is fileable. Additional information will be requested. Will email to RPM.
- Firm has submitted one bioequivalence study, 3-way cross-over with and without water and fasting.
- DSI audit of bioequivalence study needed.

CONCLUSION:

1. The application is filable.
2. A “no review issues found” letter should be sent to the sponsor on or before February 5, 2004.

ACTION ITEMS:

1. A filing issues letter will be sent to the sponsor delineating that no issues were identified during the filing meeting for NDA 21-712.
2. An information request letter will be sent to the sponsor requesting volume 1.11 & 1.12 desk copies.
3. Information requests will be drafted for Chemistry, Manufacturing and Controls, Clinical, Biopharmaceutics, and Clinical pending RPM receipt of specific requests from each discipline respectively.
4. DGICDP will request DSI to inspect the bioequivalence study site.
5. DGICDP will consult DMETS for tradename review.
6. Chemistry, Manufacturing and Controls will send for EER

Betsy Scroggs, Pharm.D., CSO *(recorded on behalf of Brian Strongin, CPMS)*

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/s/

Betsy Scroggs
9/10/04 04:05:24 PM
CSO

MEMORANDUM

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

DATE: August 31, 2004

TO: Joyce A. Korvick, M.D., MPH
Acting Director
Division of Gastrointestinal Coagulation Drug
Products (HFD-180)

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

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

SUBJECT: Review of EIRs Covering NDA 21-712, Famotidine
Orally Disintegrating Tablets (20 and 40 mg),
Sponsored by Schwarz Pharma, Inc.

At the request of HFD-180 and HFD-870, the Division of
Scientific Investigations audited the following
bioequivalence study:

Study Number: SP701

Study Title: A Pharmacokinetic Study to Evaluate the
Bioequivalence of a Unique New Formulation
(Test), Orally Disintegrating Tablet (ODT),
of Famotidine 40 mg, Administered with and
without Water, Compared to a Marketed
Famotidine 40 mg Tablet Formulation
(Reference), Pepcid®, by Merck.

Both the clinical and analytical portions of the study were
conducted at _____
Following the inspection at _____ (8/16-
20/2004), there were no objectionable observation in the
clinical portion of the study. In the analytical portion,
however, one objectionable observation was uncovered, and

Form 483 was issued to — (Attachment 1). The objectionable observation and our evaluation are as follows:

1. The chromatograms in run FAM031 (repeat analysis for subject 14) were not integrated in a consistent manner. FAM031 would have failed to meet the run acceptance criteria if the chromatograms were integrated consistently.

— acknowledged that the chromatograms in run FAM031 were not integrated consistently, and that the run should not have been accepted. During the inspection, — excluded the data from subject 14 (generated in run FAM031) and recalculated the bioequivalence statistics. The results of the data reanalysis (Attachment 2) showed that the test dosage forms (40 mg Famotidine Orally Disintegrating Tablet administered with and without Water) remained bioequivalent to the reference product, Pepcid® (40 mg famotidine tablet administered with water).

Conclusion:

DSI recommends that data from Study SP710 be accepted for review if the results from the bioequivalence data reanalysis provided by — during the inspection (see Attachment 2) can be confirmed and verified independently by the OCPB reviewer.

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

Martin K. Yau, Ph.D.

Final Classification:

—
- VAI

Page 3 of 3 - NDA 21-712, Famotidine Orally Disintegrating
Tablets (20mg, 40 mg), Sponsored by Schwarz Pharma, Inc.

CC:

HFA-224

HFD-45/RF

HFD-48/Yau(2)/Himaya/CF

HFD-180/NDA 21-712/Levine

HFD-870/Doddapaneni

HFR-SE350/Montgomery/Evitt

Draft: MKY 8/31/04

DSI:5531; O:\BE\eircover\21712sch.fam.doc

FACTS: 524631

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/s/

Amalia Himaya

9/2/04 03:03:37 PM

CSO

Dr. Viswanathan signed the paper copy on 9/2/04 and
is available upon request.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-712

DISCIPLINE REVIEW LETTER

Schwarz 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 November 23, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Famotidine Orally Disintegrating Tablets 20 mg and 40 mg.

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

- 1. Provide a complete response to all the issues communicated in the Information Request letter dated July 26, 2004, regarding this NDA.**
- 2. Amend the drug product specification such that USP <701> is the analytical procedure for Disintegration Time, and the acceptance criterion is — seconds for the average of at least six samples (Stage 1), or sixteen samples (Stage 2). The current procedure used to determine Disintegration Time may be regarded an alternate analytical procedure.**

The following information is not required for approval of this application but should be submitted as soon as possible, preferably within six months of the approval of the application:

- 3. Provide validation data demonstrating that your analytical procedure for Related Impurities by HPLC in the drug product (ATM-558) is capable of determining any impurities in famotidine that have not been previously identified. Please contact your drug substance supplier — regarding identified impurities**

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 Betsy Scroggs, Pharm.D., Consumer Safety Officer, at 301-827-1250.

Sincerely,

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

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/s/

Liang Zhou
8/9/04 05:19:27 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-712

Schwarz Pharma, Inc.
Attention: Donna K. Multhauf
Director, Regulatory Affairs and Quality Assurance
P.O. Box 2038
6140 W. Executive Drive
Mequon, WI 53092 -4467

Dear Ms. Multhauf:

We have received your submission dated February 16, 2004, requesting a waiver for pediatric studies for Famotidine Orally Disintegrating Tablets, 20 mg and 40 mg.

We have reviewed the submission and agree that a waiver is justified for Famotidine Orally Disintegrating Tablets, 20 mg and 40 mg for treatment of GERD with or without esophagitis and peptic ulcer in pediatric patients because there are other age appropriate formulations (such as suspension) for famotidine products available on the market that adequately address pediatric dosing information.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
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
7/26/04 05:18:02 PM
for Dr. Robert Justice



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-712

INFORMATION REQUEST LETTER

Schwarz Pharma, Inc.
Attention: Donna K. Multhauf
Director, Regulatory Affairs and Quality Assurance
P.O. Box 2038
Milwaukee, WI 53201-2038

Dear Ms. Multhauf:

Please refer to your November 24, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Famotidine Orally Disintegrating Tablets, 20 mg and 40 mg.

We also refer to your submissions dated March 10, 2004 and July 20, 2004.

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.

Comments and Requests



F

2 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling

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/s/

Liang Zhou

7/26/04 11:44:00 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-712

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 November 24, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for famotidine orally disintegrating tablets, 20 mg and 40 mg.

We also refer to your submission dated March 10, 2004.

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

Perform a disintegration test for each batch of both strengths of dosage form using the test for Disintegration currently provided in USP (<701> in Physical Tests and Determination, in the General Chapters). Submit the results as soon as possible.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer, at 301-827-1250.

Sincerely,

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

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/s/

Liang Zhou

7/2/04 11:26:27 AM

MEMORANDUM

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

OST
Request to Field 4/16/04
Keune

DATE: April 16, 2004

TO: Director, Investigations Branch
Kansas District Office
11630 West 80th Street
Lenexa, KS 66214

FROM: C.T. Viswanathan, Ph.D. *CTV 4/16/04*
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2004, **High Priority CDER User Fee NDA**, Pre-Approval
Data Validation Inspection, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 21-712
DRUG: Famotidine Orally Disintegrating Tablets,
20 and 40 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 July 2, 2004.**

Study: SP701, A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Famotidine 40 mg, Administered with and without Water, Compared to a Marketed Famotidine 40 mg Tablet Formulation (Reference), Pepcid®, by Merck.

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: Nilufer M. Tampal, Ph.D.
(301) 594-2457

CC:

HFD-45/RF

HFD-48/Tampal (2)/Himaya/CF

HFD-180/Levine/NDA 21-712

HFD-870/Doddapaneni

HFR-SW350/Montgomery (please send by fax)

Draft: JAO 4/16/04

Edit: MKY

DSI:5531 O:\BE\assigns\bio21712.doc

FACTS: 524631

Memorandum

Date: March 18, 2004

To: Viswanathan, CT., Ph.D., Director
Division of Bioequivalence Branch of DSI (HFD-048)

From: Suresh Doddapaneni, Ph.D., Biopharm Team Leader *via*
Paul E. Levine, Jr., R.Ph., J.D., Regulatory Project Manager

Subject: Request for Audit of Biopharmaceutical Study Sites for NDA 21-712

The following protocol/sites essential for approval have been identified for inspection. These sites are listed in order of priority. This supplement provides for a new dosage form of famotidine, (Famotidine Orally Disintegrating Tablets; proposed name, FLUXID), 20/40mg in maintenance therapy for duodenal ulcer patients and the treatment of pathological hypersecretory conditions.

<u>Indication</u>	<u>Pivotal Protocol #</u>	<u>Site (Investigator's Name/Address)</u>
<u>(above)</u>	<u>SP701</u>	

<u>(above)</u>	<u>SP701</u>	
----------------	--------------	--

International Inspections: We have requested inspections because (please check appropriate statements): N/A

_____ There are insufficient domestic data; or

_____ Only foreign data are submitted to support an application; or

_____ Domestic and foreign data show conflicting results pertinent to decision-making; or

_____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **August 01, 2004**. We intend to issue an action letter on this application by (action goal date) **September 25, 2004**.

Should you require any additional information, please contact Betsy Scroggs, Pharm.D., Regulatory Project Manager or Paul E. Levine, Jr., R.Ph., J.D., Regulatory Project Manager, at (301) 827-7310.

Concurrence: Division Director

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Suresh Doddapaneni
3/22/04 03:55:08 PM



NDA 21-712

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 November 24, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (Famotidine) Orally Disintegrating Tablets.

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.

Comments

The specification for both the 20 mg and 40 mg tablets contains a test for Disintegration Time (similar to the USP test, <701>). However, there is no acceptance criterion associated with this test (under acceptance criterion it says "report results").

You have provided certificates of analysis (COAs) from all four of the registration/stability batches produced in support of this application (two batches of 20 mg tablets, two batches of 40 mg tablets). In each COA, a result for Disintegration Time is provided. For each batch, the result is between — seconds.

Request

Revise the specification for the drug product such that it contains an appropriate acceptance criterion for the Disintegration Time test.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer,
at 301-827-1250.

Sincerely,

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

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/s/

Liang Zhou

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION		
(Division/Office): OPSS/DMETS Attention: Sammie Beam, HFD-420 (Rm. 15B23 PKLN Bldg.)			FROM: Paul E. Levine, Jr., R.Ph., J.D. and Betsy Scroggs, Pharm.D. Project Managers: HFD-180		
DATE February 4, 2004	IND NO.	NDA NO. 21-712	TYPE OF DOCUMENT	DATE OF DOCUMENT November 25, 2003	
NAME OF DRUG Famotidine Orally Disintegrating Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE June 05, 2004	
NAME OF FIRM:					
REASON FOR REQUEST					
I. GENERAL					
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW): Trade name review					
III. BIOPHARMACEUTICS					
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES ☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST					
IV. DRUG EXPERIENCE					
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS					
V. SCIENTIFIC INVESTIGATIONS					
☐ CLINICAL			☐ PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: We are requesting a trade name review of the brand name Fluxid™ for the proposed drug product. If there is objection to the proposed proprietary name "Fluxid™", the applicant proposes a second choice, _____ Background: NDA 21-712 was submitted on November 25, 2003 (received November 25, 2003) as a 505(b)2 application for famotidine orally disintegrating tablets, a histamine H ₂ -receptor antagonist. FLUXID™ is an orally administered formulation of famotidine which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. The proposed indications are the same as that for Pepcid (treatment of duodenal and gastric ulcers). A copy of the cover letter is attached for your convenience. Thank you in advance for your attention to this matter.					
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

Betsy Scroggs
2/4/04 02:20:41 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-712

Schwarz Pharma, Inc.
Attention: Donna K. Multhauf
Director, Regulatory Affairs and Quality Assurance
P. O. Box 2038
Milwaukee, WI 53201-2038

Dear Ms. Multhauf:

Please refer to your November 24, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Famotidine Orally Disintegrating Tablets, 20mg and 40mg.

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 January 24, 2004, 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.

If you have any questions, call Betsy Scroggs, Pharm. D., Consumer Safety Officer at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R. Ph., M.B.A.
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/

Brian Strongin
2/5/04 02:12:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Ack 1/13/04

NDA 21-712

Schwarz Pharma, Inc.
Attention: Donna K. Multhauf
Director, Regulatory Affairs and Quality Assurance
P.O. Box 2038
6140 W. Executive Drive
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: Famotidine Orally Disintegrating Tablets, 20mg, 40mg

Review Priority Classification: Standard (S)

Date of Application: November 24, 2003

Date of Receipt: November 25, 2003

Our Reference Number: NDA 21-712

Unless we notify you within 60 days of our 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 January 24, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 25, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until November 25, 2005. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

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/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Paul E. Levine, Jr., R.Ph., J.D.
Regulatory Health Project Manager
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Paul Levine

1/13/04 04:06:01 PM

pre-IND mtg.
Responses
were accepted
in lieu of
the meeting



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET**DATE:** April 2, 2003**To:** Donna K. Multhaupt**From:** Paul E. Levine, Jr., R.Ph.**Company:** Schwarz Pharma, IncDivision of Division of Gastrointestinal &
Coagulation Drug Products**Fax number:** (262) 238 - 0311**Fax number:** (301) 827-1305**Phone number:****Phone number:** 301-443-8347**Subject:** Meeting Comments**Total no. of pages including cover:** 4**Comments:****Document to be mailed:**☒ YES☐ NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Pre-IND

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

Dear Ms. Multhauf:

We received your January 03, 2003, correspondence on January 06, 2003, requesting a meeting to discuss the clinical development of Famotidine Orally Disintegrating Tablets as an alternative dosage form to Pepcid® (famotidine) Tablets.

Attached are the FDA answers to your questions. You have the option of canceling our meeting of April 03, 2003, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss or reach agreement on such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling the meeting.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment:

Famotidine Orally Disintegrating Tablets
Pre-IND

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ATTACHMENT

- 1) SPInc has evaluated the existing preclinical package which includes the approval information for the RLD, Pepcid, along with additional published literature and has determined that it is sufficient to support the new drug application. This pre-meeting background package includes a review of the existing data and provide the basis for SPInc's conclusion. SPInc seeks Agency concurrence on the acceptability of the preclinical package as defined in the pre-meeting package.

Division's Response: For a 505b(2) application, the pre-clinical package is sufficient for review.

- 2) The proposed indications, strengths and dosing for Famotidine Orally Disintegrating Tablets are the same as those contained in the approved labeling for the RLD, Pepcid. The indications are supported by clinical studies submitted to the Pepcid application, NDA 19-462. 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 proposed orally disintegrating tablet and Pepcid Tablets. A review of the clinical information in approval packages along with additional published literature is included in this pre-meeting package. SPInc seeks Agency concurrence on the acceptability of the clinical package.

Division's Response: For a 505b(2) application, the clinical package is sufficient for review. Your other option is a 505(J) application, which would include a citizen petition to determine whether the listed product is not being marketed due to safety or efficacy.

- 3) The sponsor intends to produce Famotidine Orally Disintegrating Tablets in 20 mg and 40 mg strengths. Famotidine is not a New Chemical Entity. The drug substance and conventional immediate release tablets are compendial items and Pepcid Tablets have been approved since October 15, 1986. Several dosage forms of Famotidine have been approved since 1986, including an orally disintegrating tablet, Pepcid RPD. (Pepcid RPD is included in the Orange Book's list of discontinued drug products and is no longer available in the marketplace.) Thus, 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 20 mg and 40 mg strengths. In light of these facts, the sponsor is proposing to produce two batches of the 20 mg strength and two batches of the 40 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 to support a 24 month expiration period. SPInc seeks Agency concurrence on the acceptability of this proposal.

Famotidine Orally Disintegrating Tablets
Pre-IND

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Division's Response: For a 505b(2) application, we recommend — s long-term
and — accelerated stability data on 3 batches of drug
product.

In addition, the CMC section should follow 21 CFR 314.50.

APPEARS THIS WAY
ON ORIGINAL