

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-855**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**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

21-855

NAME OF APPLICANT / NDA HOLDER

Banner Pharmacaps, 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)

Loperamide Hydrochloride Soft Gelatin Capsules

ACTIVE INGREDIENT(S)

Loperamide HCl

STRENGTH(S)

1 mg and 2 mg

DOSAGE FORM

Capsule, Oral

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 submit 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, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	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 approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> 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)**

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?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		
	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)		
	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?		<input type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 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?	<input type="checkbox"/> Yes	<input type="checkbox"/> 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 proposed 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.	<input checked="" type="checkbox"/> 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)

*Shelly K. Meachum*

Date Signed

8/2/2005

**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

Shelly K. Meachum, Director, Regulatory Affairs

Address

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City/State

High Point, NC

ZIP Code

27265

Telephone Number

(336) 812-8700

FAX Number (if available)

(336) 812-9091

E-Mail Address (if available)

skmeachum@banpharm.com

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.*



**505(b)(2) NEW DRUG APPLICATION**  
**LOPERAMIDE HCl SOFT GELATIN CAPSULES,**  
*1 mg and 2 mg*

**SECTION VIII**  
**PATENT INFORMATION**

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[21 CFR § 314.50 (h); § 314.54 (a)(1)(v)].

There are no relevant patents that claim the drug products, Loperamide HCl Soft Gelatin Capsules, 1 mg and 2 mg, or which claim a method of using the drug products.



**505(b)(2) NEW DRUG APPLICATION**  
**LOPERAMIDE HCl SOFT GELATIN CAPSULES,**  
*1 mg and 2 mg*

**SECTION IX**  
**PATENT CERTIFICATION**

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[21 CFR § 314.50 (i); § 314.54 (a)(1)(vi)]

A patent certification with respect to the reference listed drug – McNeil Consumer Healthcare's Imodium® A-D 2 mg tablets (caplets) – on which investigations were relied upon in this application, is provided on the following page.

## EXCLUSIVITY SUMMARY

NDA # 21-855

SUPPL #

HFD # 180

Trade Name Loperamide

Generic Name Loperamide

Applicant Name Banner Pharacaps, Inc.

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(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

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.

N/A; There were no disagreements with the sponsor concerning exclusivity

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

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

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

YES  NO

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

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

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

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

NDA# 19-860

Imodium A-D (loperamide hydrochloride) 2mg

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

summary for that investigation.

YES  NO

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

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

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

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Giuseppe Randazzo

Title: Project Manager/Consumer Safety Officer

Date: 7/19/2005

Name of Office/Division Director signing form: Brian E. Harvey MD. PhD

Title: Division Director, Gastrointestinal and Coagulation Blood products

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



Banner Pharmacaps Inc.  
4125 Premier Dr.  
High Point, NC 27265

PHONE 336.812.8700  
FAX 336.812.9091

## Debarment Certification Statement

- Banner Pharmacaps, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this NDA.

Asia/Pacific

Canada

*Shelly K. Meachum*

Europe

Shelly K. Meachum  
Director, Regulatory Affairs.

*11/15/2004*

**Date**

India

Mexico/Latin America

United States

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-855 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: October 4, 2004 Action Date: August 4, 2005

HFD-180 Trade and generic names/dosage form: Loperamide Soft Gelatin Capsules, 1mg and 2 mg

Applicant: Banner Pharmacaps, Inc. Therapeutic Class: Type 3

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: controls symptoms of diarrhea, including Travelers' Diarrhea

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

- 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
- 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 < 1 MTH kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max ≤ 6 YRS 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: Over-the-counter self-treatment of diarrhea with loperamide may be unsafe

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 being partially waived:

Min < 1 MTH kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max ≤ 6 YRS 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: Over-the-counter self-treatment of diarrhea with loperamide may be unsafe

Comments:

Note: The proposed pediatric age range for this product is from 6 years to 18 years.

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}

\_\_\_\_\_  
Regulatory Project Manager

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: \_\_\_\_\_

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

- 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
- 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: \_\_\_\_\_

*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}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-855  
HFD-960/ Grace Carmouze

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

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research**

---

**DATE:** 08/04/2005

**FROM:** Brian E. Harvey, MD, PhD  
DGCDP/ODE III

**SUBJECT:** Division Director Approval Comments  
NDA 21-855

**APPLICANT:** **Banner Pharmacaps, Inc.**

**DRUG:** Loperamide soft gelatin capsules

**DIVISION RECOMMENDATION:**

The division recommends that this application be approved. Specially, this approval action is for the 1 mg loperamide soft gelatin capsule dose in the over-the-counter (OTC) treatment of diarrhea in adults and pediatric patients over 6 years old, and for the 2 mg loperamide soft gelatin capsule dose in the OTC of diarrhea in adults and pediatric patients over 12 years old. In addition, the division recommends a partial waiver for the assessment of loperamide soft-gelatin capsules in the OTC treatment of diarrhea in pediatric patients from birth to 6 years old, under the Pediatric Research Equity Act of 2003 (PREA).

**I. Background:**

The sponsor, Banner Pharmacaps Inc., submitted a 505(b)(2) application in support of oral loperamide soft gelatin capsules in the OTC treatment of diarrhea in adults and children over 12 years old. This NDA contained one bioequivalent study (Study R03-724) in 30 healthy adult men and adult women.

**II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:**

**A. Chemistry and Manufacturing:**

Based on the CMC data provided, this NDA was recommended for approval.

The interim specifications approved for the 1 mg soft gelatin capsules are for a period of one year. The applicant has made a post marketing commitment as follows: After one year of approval of the application, the applicant will submit a prior approval supplement to establish the final dissolution specification for the 1 mg strength based on additional data from newly manufactured drug product batches.

**B. Biopharmaceutics:**

Since the proposed indications and dosing regimen for loperamide SGC were the same as Imodium A-D caplet, a biowaiver for the lower strength, loperamide 1 mg SGC, in vitro comparative dissolution data between loperamide SGC 1 and 2 mg was submitted. The BE study No. R03-724 was a randomized, single-dose, open-label, 2x2 crossover study comparing test product, loperamide 2 mg SGC (Treatment A) and RLD, Imodium A-D 2 mg caplet (Treatment B) under fasting conditions with a washout period of 2 weeks in 30 healthy subjects (17 males and 13 females). Twenty eight subjects completed the study.

The results of the BE study demonstrated that loperamide 2 mg SGC is bioequivalent to the currently marketed Imodium A-D 2 mg caplet under fasting conditions based on the Agency's two one-sided tests procedure acceptance criteria. The in vitro dissolution comparisons also showed comparable dissolution data between loperamide 1 and 2 mg SGC. Biowaiver for the lower strength of loperamide, 1 mg SGC was granted. The partial waiver request for pediatric study in children from birth to 6 years old was also granted.

**C. Clinical/Statistical:**

The information in this application provides support that the loperamide soft-gelatin capsules are bioequivalent to Imodium A-D caplets. In summary, of the 30 subject in the bioequivalent study, there were no deaths, no serious adverse events, and no significant adverse events associated with the use of loperamide soft-gelatin capsules. It was reported, that two patients withdrew from the study, but their discontinuations were not related to study treatment. In the bioequivalent study, the data supports the claim that safety of loperamide soft-gelatin capsules is similar to Imodium A-D caplets which is the reference listed drug product. There are no significant safety signals for Loperamide in the United States in the past 30 years, which includes 17 years as an OTC drug.

**D. Pediatric Use:**

The data in this application supported the use of the 1 mg loperamide soft gelatin capsule dose in the OTC treatment of diarrhea in pediatric patients over 6 years old, as well as the use of the 2 mg loperamide soft gelatin capsule dose in the OTC treatment of diarrhea in pediatric patients over 12 years old. Based upon the data provided, a partial waiver is supported under PREA for the assessment of loperamide soft-gelatin capsules in the OTC treatment of diarrhea in pediatric patients from birth to six years old.

**III. Summary Comments:**

I concur with the conclusions of the review team as outlined in this memo and for the approval of this application. I also support the previous postmarketing study commitment in the submission dated July 20, 2005. Finally, I support the administrative procedure proposed that with the approval of this application, the oversight of this NDA will be transferred to the Office of Nonprescription Products.

**IV. Labeling Recommendations:**

I concur with the negotiated label as attached to the approval letter dated 08/04/05 for this NDA 21-855.

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/s/

-----  
Giuseppe Randazzo

8/4/05 10:21:28 AM

CSO

I placed this into DFS for Dr. Brian Harvey  
due to technical problems.



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of OTC Drug Products  
Office of Drug Evaluation V**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 21, 2005**

<b>To: Shelly K. Meachum Director, Regulatory Affairs</b>	<b>From: Keith Olin Regulatory Project Manager</b>
<b>Company: Banner Pharmacaps</b>	Office of Nonprescription Products
<b>Fax number: (336) 812-9091</b>	<b>Fax number: (301) 827-2315</b>
<b>Phone number: (336) 812-8700 ext. 3312</b>	<b>Phone number: (301) 827-2293</b>

**Subject: Labeling Comments NDA 21-855**

**Total no. of pages including cover:2**

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**Document to be mailed:**       YES       NO

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N21-855- Labeling Comments

07/21/05

Page 2

We have attached the reviewer's comments related to the labeling submitted July 11, 2005.

The labeling revisions submitted for the 1 mg and 2 mg Loperamide Hydrochloride Soft Gelatin Capsules for the 6 and 72 count cartons included in this submission are in accordance with the agency's requested revisions faxed in the July 6, 2005 correspondence, except for the following:

- 1) Fully extend the barlines separating each of the headings in the "Drug Facts" box such that the barlines reach each end of the box, as required by § 201.66(d)(8).

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible. You can also fax your labeling changes to Keith Olin at (301) 827-2315.

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/s/

-----  
Keith Olin  
7/22/05 01:27:38 PM

## MEMORANDUM OF TELECON

**DATE: July 20, 2005**

**APPLICATION NUMBER: NDA 21-855**

**BETWEEN:**

Name: Shelly K. Meachum and Dr. Dale Kruep

Phone: 336-812-8700

Representing: Banner Pharmacaps, Inc. (BPI)

AND

FDA: Dr. Suresh Doddapaneni, Dr. Liang Zhou,  
Dr. Ramesh Raghavachari, and Giuseppe Randazzo

Division of Gastrointestinal and Coagulation Drug Products,  
HFD-180

**BACKGROUND:**

On June 16, 2005 the agency delivered a Chemistry, Manufacturing and Controls (CMC) discipline review letter for NDA 21-855 to Banner Pharmacaps, Inc.

On June 23, 2005, I received an email from Shelly Meachum requesting a teleconference to clarify some of the deficiencies.

On June 27, 2005 a telecon was held between the agency and Banner. Banner agreed to submit a response by July 12, 2005 addressing the CMC deficiencies. (Two submissions were eventually submitted addressing the deficiencies: July 1, 2005 and July 12, 2005)

Upon review, CMC requested we again speak with Banner regarding dissolution specification for the 1 mg strength.

**TELECONFERENCE**

DATE: July 20, 2005

The following were agreed upon between the agency and Banner Pharmacaps, Inc.:

Meeting Minutes 7/20/05

BPI:

Based on the 18 month stability data submitted in BPIs amendment dated July 12, 2005, the 1 mg product dissolution data supported a need to set the dissolution specification as \_\_\_\_\_ minutes, while the dissolution specification for the 2 mg product is T=30 minutes. BPI is submitting a revised 1 mg finished product specification which sets the dissolution as an interim specification at \_\_\_\_\_ seconds, with a requirement to collect full dissolution profile data.

FDA:

If approved, please submit a written postmarketing commitment to provide interim dissolution specifications for the 1 mg strength product and to finalize the dissolution specifications within 1 year of the NDA approval date. We recommend that the same dissolution specifications (T=30 minutes) are established for both the 1mg and 2 mg soft gel tablets.

BPI:

We commit to evaluating the dissolution data for the 1 mg strength and set a final specification within one year of approval, based on the data. This specification change is for the 1 mg strength only, and the 2 mg strength dissolution specifications will remain at T = 30 minutes.

---

SIGNER'S NAME  
TITLE

---

SIGNER'S NAME  
TITLE

Drafted: GR 7.22.05

Revised: GR 8.1.05

Initialed: SD 8.1.05

File: C:\Data\My Documents\NDAs\218551operimide\telecon CMC PMC 7.20.05.doc

**Division of OTC Drug Products Labeling Review for an NDA**

**NDA 21-855/N-000 (BL)**

**Submission Date:** July 11, 2005  
**Received Date:** July 11, 2005  
**Drug product:** Loperamide Hydrochloride Soft Gelatin Capsules, 1 mg and 2 mg  
**Active ingredient:** loperamide HCl  
**Pharmacological category:** anti-diarrheal  
**Sponsor/Contact:** Shelly K. Meachum  
Director, Regulatory Affairs  
Banner Pharmacaps, Inc.  
4125 Premier Drive  
High Point, NC 27265  
(336) 812-8700 ext. 3312  
**Labeling submitted:** 6-count carton label, 1 mg  
72-count carton label, 1 mg  
6-count carton label, 2 mg  
72-count carton label, 2 mg  
**Reviewer:** Reynold Tan  
**Review date:** July 19, 2005  
**Project manager:** Keith Olin

**Background:** The sponsor originally submitted a 505(b)(2) new drug application (NDA 21-855/N-000) on 10/1/04, which included product labeling. Since that submission, the sponsor has submitted revised draft labeling in response to FDA's recommendations for labeling changes. In this submission, the sponsor submitted draft labeling by fax and electronic formats in response to FDA's fax letter sent on July 6, 2005. In that fax letter, FDA recommended the following:

- 1) For the 2mg product, in the "**Do not use**" section, the words "***Other information***" should be in bold *italic* type, in accordance with 21 CFR 201.66(d)(3).
- 2) Position the bulleted statement "you get abdominal swelling or bulging. These may be signs of a serious condition." to conform to 21 CFR 201.66(d)(4), which requires that complete additional bulleted statement(s) shall not continue to the next line of text. Moving this statement to the second line and aligning the bullet with the first bullet in the line above conforms to the regulation.
- 3) Present the bulleted statements under the subheading "**Stop use and ask a doctor if**" in regular type, not bold type.

- 4) In the “**Directions**” section, remove the period at the end of the statement “**drink plenty of clear fluids to help prevent dehydration caused by diarrhea.**”.
- 5) Because the 2 mg product is for adults and children 12 years and over only, the directions do not need to be in table format (see 21 CFR 201.66(d)(9)).
- 6) For the 2 mg softgels, in the “**Inactive ingredients**” section, capitalize the letter “b” in “FD&C Blue”.
- 7) Please provide the actual font specifications used for text, leading, bullets, barlines, and hairlines in the Drug Facts labeling.

---

**Reviewer’s Comments:**

(The Reviewer’s comments refer to both the 1 and 2 mg products, unless otherwise noted.)

- 1) For the 2mg product, in the “**Do not use**” section, the words “*Other information*” now appear in bold italic type, in accordance with 21 CFR 201.66(d)(3).

*Comment:* This change is acceptable.

- 2) In the “**Stop use and ask a doctor if**” section, the position of the bulleted statement “you get abdominal swelling or bulging. These may be signs of a serious condition.” now conforms to 21 CFR 201.66(d)(4).

*Comment:* This change is acceptable.

- 3) The bulleted statements under the subheading “**Stop use and ask a doctor if**” now appear in regular type, not bold type.

*Comment:* This change is acceptable.

- 4) In the “**Directions**” section, the statement “**drink plenty of clear fluids to help prevent dehydration caused by diarrhea**” does not end with a period.

*Comment:* This change is acceptable.

- 5) For the 2mg product, the information under the “**Directions**” heading is presented in three bulleted statements rather than in table format.

*Comment:* This change is acceptable because the 2 mg product is for adults and children 12 years and over only, and a table format is only required when dosage directions are provided for three or more age groups (21 CFR 201.66(d)(9)).

- 6) For the 2mg softgels, in the “**Inactive ingredients**” section, the letter “b” in “FD&C Blue” is capitalized.

*Comment:* This change is acceptable.

7) The font specifications for the Drug Facts labeling are provided for all of the labels.

*Comment:* The font specifications provided for the Drug Facts labeling conform to the requirements of § 201.66(d).

8) *Comment:* A distinctive horizontal barline extending to each end of the “Drug Facts” box or similar enclosure should separate each of the headings, according to § 201.66(d)(8). The barlines in the submitted labels do not extend fully to each end of the “Drug Facts” box.

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**Reviewer’s recommendations:** The following comments can be conveyed to the sponsor:

1) Fully extend the barlines separating each of the headings in the “Drug Facts” box such that the barlines reach each end of the box, as required by § 201.66(d)(8).

This change must be made before this labeling can be approved.

---

Reynold Tan, Ph.D.  
IDS/Biologist, HFD-560

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Helen Cothran, B.S.  
Team Leader, HFD-560

N21-855 Loperamide Soft Gelatin Capsules  
Draft labeling submitted 7/11/05

4 Page(s) Withheld

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✓ Draft Labeling

       Deliberative Process

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/s/  
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Reynold Tan  
7/20/05 04:38:26 PM  
INTERDISCIPLINARY

Helen Cothran  
7/21/05 02:33:18 PM  
INTERDISCIPLINARY



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of OTC Drug Products  
Office of Drug Evaluation V**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 6, 2005**

<b>To: Shelly K. Meachum</b> Director, Regulatory Affairs	<b>From: Keith Olin</b> Regulatory Project Manager
<b>Company: Banner Pharmacaps</b>	Office of Nonprescription Products
<b>Fax number:</b> (336) 812-9091	<b>Fax number:</b> (301) 827-2315
<b>Phone number:</b> (336) 812-8700 ext. 3312	<b>Phone number:</b> (301) 827-2293
<b>Subject:</b> Labeling Comments NDA 21-855	
<b>Total no. of pages including cover:</b> 3	

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We have attached the reviewer's comments related to the labeling submitted April 20, 2005.

The labeling revisions submitted for the 1 mg and 2 mg Loperamide Hydrochloride Soft Gelatin Capsules for the 6 and 72 count cartons included in this submission are in accordance with the agency's requested revisions faxed in the March 11, 2005 correspondence, except for the following:

A. Loperamide 1 mg and 2 mg Softgels

- 1) Under the subheading "Stop us and ask doctor if", relocate the 3<sup>rd</sup> bulleted statement "you get abdominal swelling or bulging. These may be signs of a serious condition" to the next line of text to appear vertically aligned with the bulleted statements appearing on the previous line in accordance with 21 CFR 201.66(d)(4).
- 2) Under the subheading "Stop use and ask a doctor if", un-bold the bulleted statements.
- 3) Under the heading "Directions", remove the period at the end of the statement "drink plenty of clear fluids to help prevent dehydration caused by diarrhea."
- 4) Provide the graphic specifications used for *Drug Facts* (e.g. the type sizes, fonts, bullet sizes, hairline sizes, etc.) in accordance with 21 CFR 201.66(d).
- 5) Under the heading "Do not use", revise the words "*Other information*" in the 2<sup>nd</sup> bulleted statement to appear in bold *italic* type in accordance with 21 CFR 201.66(d)(3).

B. Loperamide 2 mg Softgels

- 1) This strength is only indicated for one age group, therefore it does not have to follow the requirements of 21 CFR 201.66(d)(9) and the directions do not have to appear in a table format.
- 2) Under the heading "Inactive ingredients", capitalize the letter "b" in "FD&C Blue".

In order to ensure a timely action for this new drug application, we request that you respond to the issues listed below as soon as possible. You can also fax your labeling changes to Keith Olin at (301) 827-2315.

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/s/

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Neel Patel

7/6/05 02:39:28 PM



**DISCIPLINE REVIEW LETTER**

NDA 21-855

Banner Pharmacaps, Inc.  
Attention: Shelly K. Meachum  
Director, Regulatory Affairs  
4125 Premier Drive  
High Point, North Carolina 27265

Dear Ms. Meachum:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loperamide Hydrochloride Soft Gelatin Capsules, 1 mg and 2 mg.

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

**Drug Substance:**

1. Provide the acceptance specifications (e.g. assay, identity, purity, etc., tests and test method) that will be conducted by Banner Pharmacap, Inc.

**Drug Product:**

2. Provide detailed synthesis and manufacturing process for the glyceryl caprylate (capmul). Alternatively, provide cross reference to an appropriate DMF with a letter of authorization.
3. Provide the CFR references for each of the ingredients for the ~~ink~~ ink and provide a letter of authorization to cross reference an appropriate DMF by
4. Provide detailed description for each step of the manufacturing process and explain the critical process parameters (refer to table in Vol.2 Page 564).
5. Provide specifications for the in-process control.
6. Provide stability data to support your holding times during the drug product manufacturing.

7. Provide data to demonstrate that the gelatin in the soft gelatin capsules do not covalently cross link to the drug substance. Alternatively, provide scientific rationale and test data to show why there is cross linking in your proposed formulation based on your accelerated stability data.
8. Provide stability data including dissolution at 30°C/60%RH since dissolution data at 40°C/75%RH are inconsistent at [REDACTED] minutes of dissolution even by using [REDACTED]
9. Provide intermediate dissolution data at [REDACTED] 30 minutes for the [REDACTED] month and [REDACTED] month time points in your primary stability batches.
10. Provide updated 18 month stability data for the primary stability batches when it becomes available.

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 Giuseppe Randazzo, Consumer Safety Officer, at (301) 827-1602.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Ali Al-Hakim  
6/16/05 12:20:46 PM  
Ali Al-Hakim acting team leader for Liang Zhou

N21-855

03/14/05

Page 1



Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of OTC Drug Products  
Office of Drug Evaluation V

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 11, 2005**

<b>To: Shelly Meachum</b>	Laura Shay, MS, RN, C-ANP <b>From: Regulatory Project Manager</b>
<b>Company: Banner Pharmacaps, Inc</b>	Division of Over-the-Counter Drug Products
<b>Fax number: 336-812-9091</b>	<b>Fax number: (301) 827-2315</b>
<b>Phone number: 336-812-8700 ext. 3312</b>	<b>Phone number: (301) 827-2274</b>
<b>Subject</b> Labeling comments	

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

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✓ Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative-

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/s/

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Laura Shay  
3/14/05 12:22:16 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-855

Banner Pharmacaps, Inc.  
Attention: Shelly K. Meachum,  
Director of Regulatory Affairs  
4125 Premier Drive  
High Point, NC 27265

Dear Ms. Meachum:

Please refer to your October 1, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loperamide Hydrochloride Soft Gelatin Capsules.

We also refer to your submission dated November 5, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on December 3, 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 Susan Daugherty, Regulatory Project Manager, at (301) 827-7456.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Julieann DuBeau  
11/30/04 11:19:06 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-855

Banner Pharmacaps, Inc.  
Attention: Shelly K. Meachum,  
Director of Regulatory Affairs  
4125 Premier Drive  
High Point, NC 27265

Dear Ms. Meachum:

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: Loperamide Hydrochloride Soft Gelatin Capsules, 1 mg and 2 mg

Review Priority Classification: Standard (S)

Date of Application: October 1, 2004

Date of Receipt: October 4, 2004

Our Reference Number: NDA 21-855

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 3, 2004, in accordance with 21 CFR.314.101(a). If the application is filed, the user fee goal date will be August 4, 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 requirements. We acknowledge receipt of your request for a waiver of pediatric studies in ages under two years of age for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

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

NDA 21-855

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7456.

Sincerely,

*{See appended electronic signature page}*

Susan Daugherty  
Regulatory 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/

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Susan B. Daugherty  
11/19/04 11:03:42 AM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-855

Trade Name: Loperamide Hydrochloride  
Generic Name: loperamide hydrochloride  
Strengths: 1 mg and 2 mg

Applicant: Banner Pharamcaps, Inc.

Date of Application: October 1, 2004  
Date of Receipt: October 4, 2004  
Date clock started after UN: N/A  
Date of Filing Meeting: November 19, 2004  
Filing Date: December 3, 2004  
Action Goal Date (optional): June 30, 2004

User Fee Goal Date: August 4, 2004

Indication(s) requested: control symptoms of diarrhea, including travelers diarrhea

Type of Original NDA: (b)(1) \_\_\_\_\_ (b)(2)  X   
OR  
Type of Supplement: (b)(1) \_\_\_\_\_ (b)(2) \_\_\_\_\_

**NOTE:**

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

\_\_\_\_ NDA is a (b)(1) application      OR      \_\_\_\_ NDA is a (b)(2) application

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

Form 3397 (User Fee Cover Sheet) submitted:  YES       NO

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

**NO fee due as this is a 505(b)(2) application with no clinical data.**

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

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

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? **NO**
- Does another drug have orphan drug exclusivity for the same indication? **NO**
- Is the application affected by the Application Integrity Policy (AIP)? **NO**
- Does the submission contain an accurate comprehensive index? **YES**
- Was form 356h included with an authorized signature? **YES**
- Submission complete as required under 21 CFR 314.50? **YES**

If no, explain:

- If an electronic NDA, does it follow the Guidance? **N/A**
- If in Common Technical Document format, does it follow the guidance? **N/A**
- Is it an electronic CTD? **NO**
- Patent information submitted on form FDA 3542a? **YES**
- Exclusivity requested? **NO**  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? **YES**  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

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

- Financial Disclosure forms included with authorized signature? **YES**  
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**
- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? **YES**  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. **YES**
- List referenced IND numbers: IND 68,755
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ **NO**  
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ **NO**  
 If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **NO**
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **NO**
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A**
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **N/A**

**If Rx-to-OTC Switch application:**

- 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**  
 If no, did applicant submit a complete environmental assessment? N/A  
 If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A  
 NO
- Establishment Evaluation Request (EER) submitted to DMPQ? **YES**

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: November 19, 2004

**BACKGROUND:**

NDA 21-855 for loperamide soft gelatin capsules was submitted by Banner Pharmacaps as a 505(b)(2) application on October 1, 2004, received October 4, 2004, for the control symptoms of diarrhea, including traveler's diarrhea. The Reference Listed Drug is NDA 19-860 Imodium A-D Tablet, 2 mg. Banner Pharmacaps submitted Citizen's Petitions for the 1 mg and 2 mg loperamide soft gelatin capsules on August 5, 2002, received August 22, 2002. The Office of Generic Drugs denied the 2 mg petition because it cannot conform to the dosing regimen present in the listed drug product for pediatric patients.

The regulatory history of loperamide is as follows:

- In 1976, the FDA approved the first loperamide capsule (Janssen) as a prescription under NDA 17-690 for the treatment of diarrhea.
- In 1984, the FDA approved loperamide solution (Janssen) as a prescription under NDA 19-037 for the treatment of diarrhea.
- In November 1989, the FDA approved the first OTC loperamide tablet by McNeil Consumer Healthcare (NDA 19-860.)
- In the 1990's, other OTC loperamide dosage formulations (including solutions and chewable tablets) and OTC generic loperamide tablets by different manufacturers were approved by the FDA.

This application will require joint sign off with the Division of Gastrointestinal and Coagulation Drug products and the Division of Over-the-Counter Drug Products. Since there are no clinical data, the OTC Medical Reviewer will comment on the proposed labeling. The protocol contained in the application is titled "A relative bioavailability study of 2 mg loperamide hydrochloride soft gelatin capsules versus Imodium® A-D caplets under fasting conditions."

**ATTENDEES:**

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

Joyce Korvick, M.D., M.P.H., Acting Director  
Ruyi He, M.D., Medical Team Leader  
Eric Brodsky, M.D., Medical Reviewer  
Liang Zhou, Ph.D, Chemistry Team Leader  
Ramesh Raghavachari, Ph.D, Chemistry Reviewer  
Susan Daugherty, Regulatory Health Project Manager

**Division of Pharmaceutical Evaluation, HFD-870**

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

**Division of Over-The Counter Drug Evaluation, HFD-560**

Helen Cothran, M.D, Medical Team Leader  
Reynold Tan, M.D, Medical Officer  
Laura Shay, Regulatory Project Manager

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Eric Brodsky
OTC Medical:	Reynold Tan
Statistical:	N/A
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Ramesh Raghavachari
Biopharmaceutical:	Tien-Mien Chen
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
Regulatory Project Management:	Susan Daugherty
OTC Regulatory Project Management:	Laura Shay
Other Consults:	DSI Bioequivalence

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

CLINICAL FILE   X   REFUSE TO FILE       

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

CLINICAL MICROBIOLOGY NA   X   FILE        REFUSE TO FILE       

STATISTICS NA   X   FILE        REFUSE TO FILE       

BIOPHARMACEUTICS FILE   X   REFUSE TO FILE       

- Biopharm. inspection needed: **YES**

PHARMACOLOGY NA   X   FILE        REFUSE TO FILE       

- GLP inspection needed: **NO**

CHEMISTRY FILE   X   REFUSE TO FILE       

- Establishment(s) ready for inspection? **YES**
- Microbiology **NO**

ELECTRONIC SUBMISSION: No

Any comments:

Labeling submitted electronically **Yes**

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

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

No filing issues have been identified.

\_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. Send filing letter with no filing issues identified to the sponsor by Day 74.
2. A DSI Bioequivalence Consult will be sent.

---

Susan Daugherty  
Regulatory Project Manager, HFD-180

### 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**

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

NDA 19-860 Imodium A-D Tablet, 2 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?

**NO**

*(Pharmaceutical equivalents* are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

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

(b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? **YES** **NO**  
(The approved pharmaceutical equivalent(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, Office of Regulatory Policy (ORP) (HFD-007)?

**YES** **NO**

*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? **YES**

*(Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

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

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? **YES**  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

*NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

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

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? **YES**

*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?

YES NO

*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? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

**This application provides for a change in dosage form from tablet to soft gelatin capsule.**

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)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). **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))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). **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)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- 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 has received a period of marketing exclusivity? NO
- 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)).?

**NO**

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).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # \_\_\_\_\_ 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?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

**YES**

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

/s/

-----  
Susan B. Daugherty  
12/23/04 11:43:34 AM  
CSO

## NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

Application Information		
NDA 21-855	Efficacy Supplement Type SE-	Supplement Number
Drug: <b>Loperamide Soft Gelatin Capsules, 1mg &amp; 2mg</b>		Applicant: <b>Banner Pharmacaps, Inc.</b>
RPM: <b>Giuseppe Randazzo</b>	<b>HFD-180</b>	Phone # <b>301-827-1602</b>
Application Type: <input type="radio"/> 505(b)(1) <input checked="" type="radio"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): 19-860, Imodium® A-D
❖ Application Classifications:		
• Review priority		<input checked="" type="radio"/> Standard <input type="radio"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		OTC
❖ User Fee Goal Dates		
		August 04, 2005

### Reviewers Sign Off List

Leah Christl, Supervisory Project Manager

LAC 7/26/05

Helen Cothran, ~~PhD~~

HC 7/27/05

Curtis Rosebraugh MD, Acting Division Director

CR 7/29/05

Brian Strongin, RPh, M.B.A., Supervisory Project Manager

BS 8/2/05

Liang Zhou, Ph.D., Chemistry Team Leader

LZ 8/4/05

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

SD 8/4/05

Ruyi He, M.D., Medical Team Leader

Ruyi He 8/3/05

Brian E. Harvey, M.D. Ph.D., Division Director

Brian E. Harvey 8/4/05

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA <b>21-855</b>	Efficacy Supplement Type SE-	Supplement Number
Drug: <b>Loperamide Soft Gelatin Capsules, 1mg and 2mg</b>		Applicant: <b>Banner Pharmacaps, Inc.</b>
RPM: <b>Giuseppe Randazzo (HFD-180) &amp; Keith Olin (HFD-560)</b>		<b>HFD-180</b> Phone # <b>301 827 1602</b>
<p>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.)</p> <p><b>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.</b></p> <p>(X) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p><b>NDA #19-860 Imodium® A-D Tablet, 2mg</b></p>
❖ Application Classifications:		
• Review priority		(X) Standard ( ) Priority
• Chem class (NDAs only)		<b>Type 3</b>
• Other (e.g., orphan, OTC)		<b>OTC</b>
❖ User Fee Goal Dates		
		<b>August 4, 2005</b>
❖ 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

<ul style="list-style-type: none"> <li>• This application is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Exception for review (Center Director's memo)</li> </ul>	
<ul style="list-style-type: none"> <li>• OC clearance for approval</li> </ul>	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
<ul style="list-style-type: none"> <li>• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> <li>• 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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified
	21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>• [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).</li> </ul>	
<ul style="list-style-type: none"> <li>• [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></li> <li>• [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.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><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></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No

<b>General Information</b>	
<b>❖ Actions</b>	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	<b>June 14, and July 21, 2005</b>
• Most recent applicant-proposed labeling	<b>July 22, 2005</b>
• Original applicant-proposed labeling	<b>October 04, 2004</b>
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	<b>Not applicable</b>
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	<b>NDA # 19-487</b>
<b>❖ Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	<b>Propose prior to July 11, 2005</b>
• Applicant proposed	<b>July 11, 2005</b>
• Reviews	<b>June 14, 2005 (from OTC)</b>
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	<b>Yes</b>
• Documentation of discussions and/or agreements relating to post-marketing commitments	<b>See telecon or CMC review sections: telecon or CMC review dated July 20, 2005</b>
<b>❖ Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	<input checked="" type="checkbox"/>
<b>❖ Memoranda and Telecons</b>	<input checked="" type="checkbox"/>
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	<b>Not applicable</b>
• Pre-NDA meeting (indicate date)	<b>Not applicable</b>
• Pre-Approval Safety Conference (indicate date; approvals only)	<b>Not applicable</b>
• Other	<b>Not applicable</b>
<b>❖ Advisory Committee Meeting</b>	
• Date of Meeting	<b>Not applicable</b>
• 48-hour alert	<b>Not applicable</b>
<b>❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)</b>	<b>Not applicable</b>

(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," 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)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• 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.)</li> </ul>	(X) No
<ul style="list-style-type: none"> <li>• 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.</li> </ul>	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	(X) December 23, 2004

<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	pending
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	July 22, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	Not applicable
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See medical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	Not applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	(X)
❖ Demographic Worksheet (NME approvals only)	Not applicable
❖ Statistical review(s) (indicate date for each review)	Not applicable
❖ Biopharmaceutical review(s) (indicate date for each review)	June 23, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Not applicable
• Bioequivalence studies	June 13, 2005
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	June 13, and July 20, 2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See CMC review dated 6/13/05
• Review & FONSI (indicate date of review)	See CMC review dated 6/13/05
• Review & Environmental Impact Statement (indicate date of each review)	See CMC review dated 6/13/05
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Not applicable
❖ Facilities inspection (provide EER report)	Date completed: February 25, 2005 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Not applicable
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	Not applicable
❖ CAC/ECAC report	Not applicable

### **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).