# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-892**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**Patent Information – Paragraph I Certification**

In accordance with Title 21 of the Code of Federal Regulations, Part 314, Section 50 paragraph (i) [21 CFR 314.50(i)] and Part 314, Section 53, paragraph (c) [21 CFR 314.53(c)], InKine Pharmaceutical Company, Inc (InKine) is submitting the following information for the patent described in this application. InKine certifies that this patent information has not been previously submitted to the U.S. Food and Drug Administration for the application for which approval is being sought: NDA 21-892.

(1) General requirements

(i) Patent number and the date on which the patent will expire

| | |
|---|---|
| *Patent Number:* | 5,616,346 |
| *Date of Patent:* | April 01, 1997 |
| *Date of Expiration:* | May 18, 2013 |

(ii) Type of patent

*Patent number 5,616,346 is a method of use patent.*

(iii) Name of the patent owner

*Craig A, Aronchick, M.D.*
*903 Bryn Mawr Avenue*
*Penn Valley, PA 19072*

(iv) Not Applicable

(2) Formulation, composition, or method of use patents

(i) Original declaration

*The undersigned declares that patent no. 5,616,346 covers the method of use of* [redacted]™ *(sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP), formerly INKP-102. This product is the subject of this application for which approval is being sought: NDA 21-892*

(ii) Amendment of patent information upon approval

*InKine Pharmaceutical Company, Inc shall amend the original patent declaration by letter within 30 days after the date of approval of this application.*

(3) No relevant patents – This section not applicable

(4) Authorized signature

John Cullen, J.D.
Senior Vice President & General Counsel
InKine Pharmaceutical Company, Inc.

April 11, 2005
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-892 SUPPL # N/A

Trade Name: OsmoPrep™
Generic Name: sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP

Applicant Name: Salix Pharmaceuticals, Inc. HFD # HFD-180

Approval Date If Known: March 16, 2006

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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

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

YES /_X__/ 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.

---

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

---

d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X__/ NO /__ _/

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

NDA# 21-097, Visicol Tablets

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).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

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

YES /X/ NO /___/

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 / X / 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 / X /

(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 / X /

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 / X /

If yes, explain:

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

- Investigation 1: Study INKP-102-04-01 (Phase 3 study)
- Investigation 2: Study INKP-102-03-01 (Phase 2 study)

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 / X/ |
| Investigation #2 | YES /___/ | NO /X / |

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 / X / |
| Investigation #2 | YES /___/ | NO /X / |

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

_____ _____

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

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

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

YES /X / NO /___/ Explain: _____
(Investigation 1)

YES /X / NO /___/ Explain: _____
(Investigation 2)

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

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 /X /

If yes, explain: _____

*{See appended electronic signature page}*

Tanya Clayton
Regulatory Health Project Manager

Brian E. Harvey, M.D., Ph.D.
Division Director
Division of Gastroenterology Products
Office of New Drug Evaluation III
Center for Drug Evaluation and Research

cc: Original NDA-DFS
HFD-93 Mary Ann Holovac

---

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

---

/s/

---

Tanya Clayton
3/23/2006 01:15:44 PM

Brian Harvey
3/23/2006 02:09:52 PM

# PEDIATRIC PAGE

## (Complete for all APPROVED original applications and efficacy supplements)

A # : 21-892 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: May 17, 2005 Action Date: [redacted]

DRAFT

Trade and generic names/dosage form: OsmoPrep (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)

Applicant: Salix Pharmaceuticals, Inc. Therapeutic Class: 3S

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1: cleansing of the colon as a preparation for colonoscopy in adults.

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: The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients.

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

## Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

- ☐ **Formulation needed**
- ☐ **Other:**_____

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

## Section C: Deferred Studies

**Age/weight range being deferred:**

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

**Reason(s) for deferral:**

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

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

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

## Section D: Completed Studies

**Age/weight range of completed studies:**

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

**Comments:**

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

**This page was completed by:**

*{See appended electronic signature page}*

_____
**Regulatory Project Manager**

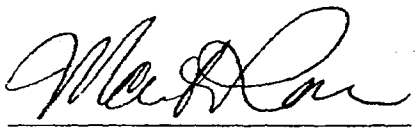
**cc: NDA**
**HFD-950/Grace Carmouze**
(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-950
301-796-7654

Debarment Certification - INKP-102 (sodium phosphate tablets)
29 Apr 2005

Item 16 – Debarment Certification

InKine Pharmaceutical Company, Inc. 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.

On behalf of InKine Pharmaceutical Company, Inc.



4/28/05

Martin Rose, M.D., J.D.
Executive Vice President,
Research and Development

Date

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

NDA # 21-892 Supplement # Efficacy Supplement Type SE-

Trade Name: /—
Established Name: sodium Phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous

Strengths: 1.5 gram, oral tablet

Applicant: Inkine Pharmaceutical
Agent for Applicant: N/A

Date of Application: April 29, 2005
Date of Receipt: April 29, 2005
Date clock started after UN: May 17, 2005
Date of Filing Meeting: July 6, 2005
Filing Date: July 30, 2005
Action Goal Date (optional): User Fee Goal Date: March 17, 2006

Indication(s) requested: Cleansing of the bowel as a preparation for colonoscopy in adults.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***

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

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

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

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

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

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

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

*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

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

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  **If an electronic NDA, all forms and certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  **If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☐ NO ☒

- Exclusivity requested? YES, _____ Years 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 ☒ NO ☐
  **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 ☒ NO ☐
  **(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**
  **NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,291

- End-of-Phase 2 Meeting(s)? Date(s) August 23, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 10, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

## Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

## If Rx-to-OTC Switch application:

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

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

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

## MEMO OF FILING MEETING

DATE: July 6, 2005

Addendum, March 21, 2006: The referenced drug for this NDA is Visicol Tablets, 21-097. Visicol is also a 505(b)(2) since they referenced published literature for their pre-clinical section.

BACKGROUND: ——— provides for cleansing of the bowel in preparation for colonoscopy in adults. This is an 505 (b)(2). The referenced drug is Visicol Tablets, NDA 21-097.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Joyce Korvick, Brian Harvey, Ruyi He, Eric Brodsky, Liang Zhou, Ali Al-Hakim, Suresh Doddapaneni, Mushifiqur Rashid, Tamal Chakraborti, Tanya Clayton

ASSIGNED REVIEWERS (including those not present at filing meeting) :

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Eric Brodsky |
| Secondary Medical: | |
| Statistical: | Mushifiqur Rashid |
| Pharmacology: | Tamal Chakraborti |
| Statistical Pharmacology: | |
| Chemistry: | Ali Al-Hakim |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Suliman Al-Fayoumi |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | Kahery Malik |
| Regulatory Project Management: | Tanya Clayton |
| Other Consults: | DMETS, DDMAC |

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

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

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

| | | | | | |
|---|---|---|---|---|---|
| BIOPHARMACEUTICS | | FILE ☒ | | REFUSE TO FILE ☐ | |
| • Biopharm. inspection needed? | | | | YES ☐ | NO ☒ |
| PHARMACOLOGY | N/A ☐ | FILE ☒ | | REFUSE TO FILE ☐ | |
| • GLP inspection needed? | | | | YES ☐ | NO ☒ |
| CHEMISTRY | | FILE ☒ | | REFUSE TO FILE ☐ | |
| • Establishment(s) ready for inspection? | | | | YES ☐ | NO ☐ |
| • Microbiology | | | | YES ☐ | NO ☒ |

ELECTRONIC SUBMISSION:
Any comments: Fully Electronic

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ 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. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Stats will provide Information Request regarding the location of SAS files.
Clinical will provide Information Request regarding Safety Follow-up.

Tanya Clayton, B.S.
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 ☒ NO ☐

   *If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 21-097

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

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☒ 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 ☐ NO ☐

   (***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 ☐ NO ☐
   (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 ☐ NO ☐

*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 new dosage regimen, based on comparability studies.

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)). YES ☐ 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)). YES ☐ 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). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

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)
Patent number(s): 5,616,346

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

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

☐ 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)
Patent number(s):

**NOTE:** *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)
Patent number(s):

☐ 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).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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 ☐ NO ☒

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A ☒ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☒ YES ☐ 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):

- 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 ☒ NO ☐

---

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

---

/s/

---

Tanya Clayton
3/21/2006 06:16:19 PM
CSO

# NDA ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|---|---|
| NDA 21-892 | | |
| Drug: Osmoprep(sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) | Applicant: Salix Pharmaceuticals, Inc. | |
| RPM: Tanya Clayton | HFD-180 | Phone 301-796-0871 |
| Application Type: () 505(b)(1) (X) 505(b)(2) | Reference Listed Drug (NDA #, Drug name): Visicol Tablets, NDA 21-097 | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (X) Standard ( ) Priority |
| • Chem class (NDAs only) | 3 |
| • Other (e.g., orphan, OTC) | N/A |
| ❖ User Fee Goal Date | March 17, 2006 |
| ❖ Special programs (indicate all that apply) | ( X) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information | |
| • User Fee | (X ) Paid - |
| • User Fee waiver | () Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2)<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes (X) No |
| • This application is on the AIP | ( ) Yes (X) No |
| • Exception for review (Center Director's memo) | N/A |
| • OC clearance for approval | N/A |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | (X) Verified |
| ❖ Patent | |
| • Information: Verify that patent information was submitted | (X) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>(X ) I ( ) II ( ) III ( ) IV<br>21 CFR 314.50(i)(1)<br>() (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of | ( ) Verified |

| | |
|---|---|
| notice). | |
| ❖ Exclusivity (approvals only) | |
| • Exclusivity summary | X |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | ( ) Yes, Application #_____<br>**(X)** No |
| ❖ Administrative Reviews (Project Manager, July 11, 2005, amended March 21, 2006) | X |
| **General Information** | |
| ❖ Actions | |
| • Proposed action | **(X )** AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | N/A |
| • Status of advertising (approvals only) | **(X)** Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | **(X)**Yes () Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | **(X)** None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | X (March 16, 2006 Final) |
| • Most recent applicant-proposed labeling *(February, 2006)* | X |
| • Original applicant-proposed labeling *(April 29, 2005)* | X |
| • Labeling reviews ( Office of Drug Safety trade name review)<br>• *ODS DMETS*- February 22, 2006, August 24, 2005<br>• *ODS DDMAC* – November 29, 2005 | X |
| • Other relevant labeling (e.g., most recent 3 in class) | N/A |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | N/A |
| • Applicant proposed (April, 2005 and February, 2006) | X |
| • Reviews DMETS (February 22, 2006, August 24, 2005); DDMAC (November 29, 2005) | X |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | X |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | X |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | X |
| ❖ Memoranda and Telecons | X |
| ❖ Minutes of Meetings | |
| • Pre-NDA meeting (March 10, 2005)<br>• | X |
| • Filing meeting (July 6, 2005) | X |
| • Pre-Approval Safety Conference | N/A |

| | |
|---|---|
| ❖ Advisory Committee Meeting | N/A |
| • Date of Meeting | N/A |
| • 48-hour alert | N/A |
| ❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)-Tentative Final Monograph | N/A |
| **Summary Application Review** | X |
| Summary Review (e.g., Office Director, Division Director, Medical Team Leader) ❖ 2006 | Division Director- March 16, 2006 Medical Team Leader- March 6, |
| **Clinical Information** | |
| ❖ Clinical review ( March 3, 2006) | X |
| ❖ Microbiology (efficacy) review | N/A |
| ❖ Safety Update review (included in March 3, 2006 Clinical review) | X |
| ❖ Pediatric Page (separate page for each indication addressing status of all age groups) | X |
| ❖ Demographic Worksheet *(NME approvals only)* | N/A |
| ❖ Statistical review (February 1, 2006) | X |
| ❖ Biopharmaceutical (February 13, 2006) | X |
| ❖ Controlled Substance Staff review and recommendation for scheduling | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | X |
| • Clinical studies (February 22, 2006) | X |
| • Bioequivalence studies | N/A |
| **CMC Information** | |
| ❖ CMC review | X |
| ❖ Environmental Assessment | |
| • Categorical Exclusion | X |
| • Review & FONSI | N/A |
| • Review & Environmental Impact Statement | N/A |
| ❖ Micro (validation of sterilization & product sterility | N/A |
| ❖ Facilities inspection (provide EER report) | X |
| ❖ Methods validation | N/A |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review, including referenced IND reviews (February 3, 2006) | X |
| ❖ Nonclinical inspection review summary | X |
| ❖ Statistical review of carcinogenicity studies | N/A |
| ❖ CAC/ECAC report | N/A |

---

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

---

/s/

---

Tanya Clayton
3/21/2006 05:57:31 PM

Salix®
PHARMACEUTICALS, INC.

March 15, 2006

**NDA Amendment – Phase IV Commitments**
**Osmoprep™**

Brian Harvey, MD, PhD
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Subject:** **NDA 21-892**
**Sodium Phosphate Monobasic Monohydrate, USP, and sodium phosphate dibasic anhydrous, USP Tablets**
**NDA Amendment – Phase IV Commitments**

Dear Dr. Harvey:

Please note the above referenced pending New Drug Application (NDA) submitted 29 April 2005 in accord with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age and older.

Salix Pharmaceuticals has received the Agency's proposed Phase IV commitment and agrees to perform the following:

1. Conduct a pharmacokinetic (pK) and safety study of OsmoPrep in patients with renal impairment.

Salix agrees to perform the Phase IV study in accord with the following timelines:

| | |
|---|---|
| 1) submission of the protocol; | 1 year after approval |
| 2) start of study enrollment; | 21 months after approval |
| 3) completion of the study; and | |
| 4) submission of the final study report | 33 months after approval |

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 862-1047, facsimile (919) 862-1095, or email, Jill.Kompa@salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Jill Kompa

Jill Kompa, M.S., RAC
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Salix Pharmaceuticals, Inc. | 15 March 2006 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE** *(FAX)* **Number** *(Include Area Code)* |
| (919) 862-1000 | (919) 862-1095 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued).* | **AUTHORIZED U.S AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE** |
| 1700 Perimeter Park Drive<br>Morrisville, NC 27560 | Not Applicable |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-892

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| See Chemical | OsmoPrep™ |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)* |
|---|---|
| Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP | INKP-102 |

| DOSAGE FORM. | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Tablet | 1.5 grams | Oral |

(PROPOSED) INDICATION(S) FOR USE

Cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older

## APPLICATION DESCRIPTION

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

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Visicol ® Tablets Holder of Approved Application Salix Pharmaceuticals, Inc.

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

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

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

REASON FOR SUBMISSION

Phase IV Commitments

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

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

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

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

NDA 21-097, IND 56,291, DMF# _____ DMF# _____

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| ☐ | 1. Index |
| ☐ | 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3. Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6 Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| ☐ | 7. Clinical Microbiology (e g., 21 CFR 314.50(d)(4)) |
| ☐ | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5), 21 CFR 601.2) |
| ☐ | 9. Safety update report (e.g , 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| ☐ | 10. Statistical section (e.g , 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g , 21 CFR 314.50 (f)(2); 21 CFR 601 2) |
| ☐ | 13. Patent Information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☐ | 14. A patent certification with respect to any patent which claims the drug (21 U S C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☒ | 20. OTHER *(Specify)* Phase IV Commitments |

**ERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following.

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Jill Kompa | Jill Kompa, M.S., RAC<br>Director, Regulatory Affairs | 3/15/06 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 1700 Perimeter Park Drive<br>Morrisville, NC 27560 | (919) 862-1047 |

**Public reporting burden for this collection of information** is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

********** -COMM. JOURNAL- ********** DATE MAR-16-2006 ***** TIME 15:32 ********

MODE = MEMORY TRANSMISSION START=MAR-16 15:29 END=MAR-16 15:32

FILE NO.=012

| STN NO. | COMM. | ONE-TOUCH/ ABBR NO. | STATION NAME/EMAIL ADDRESS/TELEPHONE NO. | PAGES | DURATION |
|---|---|---|---|---|---|
| 001 | OK | a | 919198621095 | 014/014 | 00:03:08 |

-FDA/CDER/DDDDP/HFD540 -

********** -301 827 2075 - ***** - 301 827 2075- **********

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

# FACSIMILE TRANSMITTAL SHEET

DATE: March 16, 2006

| | |
|---|---|
| **To:** Jill Kompa, Director, Regulatory Affairs | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Action Letter

**Total no. of pages including cover:** __14__

**Comments:**

Please find attached the Action Letter for NDA 21-892, OsmoPrep Tablets.

Best regards.

**Document to be mailed:** ☑YES NO

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

# FACSIMILE TRANSMITTAL SHEET

DATE: March 16, 2006

| | |
|---|---|
| **To:** Jill Kompa, Director, Regulatory Affairs | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Action Letter

**Total no. of pages including cover:** __14__

**Comments:**

Please find attached the Action Letter for NDA 21-892, OsmoPrep Tablets.

Best regards.

**Document to be mailed:** ☑YES NO

Salix
PHARMACEUTICALS, INC.

March 14, 2006

**NDA Amendment – Revised Label Mock-up**
**Osmoprep™**

Brian Harvey, MD, PhD
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Subject:** **NDA 21-892**
**Sodium Phosphate Monobasic Monohydrate, USP, and sodium phosphate dibasic anhydrous, USP Tablets**
**NDA Amendment – Revised Label Mock-up**

Dear Dr. Harvey:

Please note the above referenced pending New Drug Application (NDA) submitted 29 April 2005 in accord with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age and older.

Enclosed please find the revised final printed labeling mock-up for the OsmoPrep container label. Changes were made to the label in accord with the Agency's requested changes sent via email on March 9, 2006.

If there are any questions concerning this submission, please do not hesitate to contact me at (919) 862-1047, facsimile (919) 862-1095, or email, Jill.Kompa@salix.com.

Sincerely,
Salix Pharmaceuticals, Inc.

Jill Kompa, M.S., RAC
Director, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Salix Pharmaceuticals, Inc. | 14 March 2006 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE** *(FAX)* **Number** *(Include Area Code)* |
| (919) 862-1000 | (919) 862-1095 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U S. License number if previously issued)* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE** |
| 1700 Perimeter Park Drive<br>Morrisville, NC 27560 | Not Applicable |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-892

| ESTABLISHED NAME *(e g , Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY | |
|---|---|---|
| See Chemical | OsmoPrep™ | |
| **CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME** *(If any)* | | **CODE NAME** *(If any)* |
| Sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP | | INKP-102 |
| **DOSAGE FORM** | **STRENGTHS:** | **ROUTE OF ADMINISTRATION:** |
| Tablet | 1.5 grams | Oral |

(PROPOSED) INDICATION(S) FOR USE

Cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older

## APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314 94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Visicol ® Tablets Holder of Approved Application Salix Pharmaceuticals, Inc.

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

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

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

REASON FOR SUBMISSION

Revised Container Label Mock-up

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

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

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

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

NDA 21-097, IND 56,291, DMF# [redacted] c., DMF# _____

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| ☐ | 1. Index |
| ☐ | 2 Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3 Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314 50(d)(3); 21 CFR 601 2) |
| ☐ | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| ☐ | 8 Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| ☐ | 9 Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601 2) |
| ☐ | 10 Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1), 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| ☐ | 13 Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☐ | 14 A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16 Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☒ | 20. OTHER *(Specify)* Revised Container Label Mock-up |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314 80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE: |
|---|---|---|
| Jill Kompa | Jill Kompa, M.S., RAC<br>Director, Regulatory Affairs | 3/14/06 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 1700 Perimeter Park Drive<br>Morrisville, NC 27560 | (919) 862-1047 |

**Public reporting burden for this collection of information** is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

1 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

**Clayton, Tanya**

**From:** Peat, Raquel [raquel.peat@fda.hhs.gov]
**Sent:** Monday, March 13, 2006 2:16 PM
**To:** Clayton, Tanya
**Cc:** Strongin, Brian K; Colangelo, Kim M; Harvey, Brian; Korvick, Joyce A; He, Ruyi; Brodsky, Eric
**Subject:** CLEARED: 505(b)(2)- NDA 21-892, —— with a goal date of March 17, 2006

Hi Tanya:

Thanks so very much for the detailed responses to our questions. You are cleared to act on NDA 21-892 by IO, ORP and OCC. It should be noted that the applicant should submit a new Form 3542 (Patent Information Submitted Upon and After Approval of an NDA or Supplement) to list their patents within 30 days after approval.

Happy Action!

Raquel

*LT Raquel Peat, MS, MPH, USPHS*

Regulatory Project Officer
FDA/CDER/OND, Immediate Office
301-796-0700 (OND IO main)
301-796-0517 (direct)
Fax: 301-796-9858

Address:
10903 New Hampshire Ave.
Bldg #22, Room 6469
Silver Spring, MD 20993
Email address has changed as of February 1, 2006: Raquel.Peat@fda.hhs.gov

**M E M O R A N D U M**

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

---

CLINICAL INSPECTION SUMMARY

DATE: January 27, 2006

TO: Tanya Clayton, B.S., Regulatory Health Project Manager
Eric Brodsky, M.D., Medical Officer

FROM: Khairy W. Malek, M.D., Ph.D.
Medical Officer

THROUGH: Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: # 21-892

APPLICANT: InKine Pharmaceutical, Inc.

DRUG: ———

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Cleansing of the bowel in preparation for Colonoscopy in adults.

CONSULTATION REQUEST DATE: Date: July 7, 2005

DIVISION ACTION GOAL DATE: December 6, 2005

PDUFA DATE: March 17, 2006

I. BACKGROUND:

Visicol tablets [INKP-100] (sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous) was approved for its use in colon cleansing before colonoscopy in 2001. There were post-marketing reports of whitish flocculent or hazy residue which obscured mucosal visualization in some cases. It was found to be microcrystalline cellulose (MCC) which was used as excipient in the original formula (23%). The sponsor has introduced another form of tablets which contain the same active ingredients plus 13% of the excipient MCC [INKP-101].

In this NDA, the sponsor included results from study INKP-102-04-01 using a new formulation which contain the same active ingredient without MCC to get a better visualization of the mucosa. Each tablet contains 1.102 gm of sodium phosphate monobasic monohydrate USP and 0.398 gm of sodium phosphate dibasic anhydrous USP for a total of 1.5gm of sodium phosphate.

Eligible subjects will be randomized to receive one of the following 3 regimens:

1. Visicol tablets (INKP-101), 60 g of sodium phosphate.
2. 40 INKP-102 tablets (60 g sodium phosphate)
3. 32 INKP-102 tablets (48 g sodium phosphate)

Primary Efficacy Endpoint:

The primary efficacy endpoint evaluation would be performed by a blinded investigator (endoscopist) directly viewing the colon at Visit 1. Assessment of the effectiveness of the study medication was measured by the investigator using a 4-point scale as stated in Appendix 4 of the protocol (1 = Excellent, 2 = Good, 3 = Fair, 4 = inadequate). The Investigator would assign a score for the overall quality of colonic cleansing and a score for the quality of cleansing of the ascending colon based on the amount of retained colonic content observed during the endoscopic procedure.

Secondary endpoints:

- Frequency of inadequate preparation, assessed by the physician questionnaire
- Length of procedure time
- Amount of irrigation fluid used
- Assessment of laboratory parameter changes from baseline.
- Assessment of safety, assessed by frequency and severity of clinical adverse events.
- Assessment of patient acceptance of dosing regimen taken.

required by the protocol. The CI did not do a complete physical examination at the screening for six subjects: 1201, 1202, 1203, 1204, 1205 and 1206. The systems not done for these subjects at the screening physical examination were: HEENT (except for 1202), Endocrine/Metabolic, Neurologic, Hematologic/Lymphatic and Musculoskeletal.

There was no limitation to the inspection.

These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.

3. Site # 3: Nav Grandhi, M.D., Gastrointestinal Research Consultants of Greater Cincinnati, 10600 Montgomery Road, Suite 100, Cincinnati, Ohio, 45242

   The field investigator reviewed the records of 19 subjects out of 47 enrolled. There were no violations observed at this site.

   There was no limitation to the inspection.

   The data from this site can be used in support of the NDA.

## III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The violations observed in the first two sites (# 31 & 12) do not adversely affect data acceptability and the results of the inspection at these two sites support use of the data for this NDA. The third site (# 3) had no violations observed during the inspection, and the data from that site are acceptable for use in support of this NDA.

No follow-up inspections are needed in this case.

Khairy W. Malek
Medical Officer

CONCURRENCE:

Constance Lewin, M.D., MPH
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

---

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

---

/s/

---

Khairy Malek
2/22/2006 03:01:44 PM
MEDICAL OFFICER

Constance Lewin
2/22/2006 03:06:58 PM
MEDICAL OFFICER

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

# REQUEST FOR CONSULTATION

| (Division/Office): | FROM: |
|---|---|
| Scott Dallas and Diane Smith, White Oak Rm 4421 | Tanya Clayton, Regulatory Health Project Manager White Oak, Rm 5103 |

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| February 22, 2006 | 56,291 | 21-892 | Tradename Review | February 16, 2006 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| INKP-102 (Sodium Phosphate Monobasic Monohydrate, USP, sodium Phosphate dibasic anhydrous, USP tablets | High | Laxative | April 16, 2006 |

NAME OF FIRM: Salix Pharmaceuticals, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

**COMMENTS/SPECIAL INSTRUCTIONS:**

This is a 505 (b)(2) New Drug Application that is indicated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age and older. The sponsor is previously proposed [redacted] and [redacted] as the tradename. Your August 24, 2005 review denied both names as the tradename. Consequently, the firm then proposed [redacted] Osmoprep, or [redacted] as the proposed tradenames, as you are currently reviewing. However, as of Feb. 16, 2006 (see attached e-mail), the firm has changed their order of proposed trade names. The firm is now proposing [redacted] Osmoprep and [redacted] The firm is aware that a decision on these proposals will not take place prior the PDUFA goal date, 03/17/06. Please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21892/29April2005 . I will forward the official submission once it arrives. Please let me know if you require additional information. Thank you in advance.
Tanya Clayton – 301-796-0871.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☒ MAIL (e-mail) ☐HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

Hi Tanya,

I relayed the information you provided yesterday to our marketing group regarding the proposed trade names. They have actually decided that they would ask the Agency reviewers to reprioritize the trade names we submitted yesterday, even if it means you them to stop reviewing the names previously submitted in Dec 05 (Osmoprep, [redacted] They understand that you cannot rantee approval of a trade name by the NDA action date of March 17, however, they would prefer these names enough to reshuffle those in the queue. Again, they would like those we submitted yesterday, in that order [redacted] OsmoPrep, and [redacted].

I would like to discuss with you by phone – would you kindly give me a call when you get this. My main concern is that once we obtain the Agency's agreement on a trade name post-approval, do we need to resubmit the mock-up labeling with the approved trade name, even if it is after approval.

Also, I am working to get you the labeling mock-ups in the Salix tradedress format by next week.

Kind regards, Jill

Jill Kompa, M.S., RAC
Director, Regulatory
Salix Pharmaceuticals
1700 Perimeter Park Drive
Morrisville, NC 27560
Phone: 919-862-1047
Cell: 919-360-3314
Fax: 919-862-1095
Email: jill.kompa@salix.com

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

/s/

Tanya Clayton
2/22/2006 01:27:28 PM

**********
*** TX REPORT ***
**********

TRANSMISSION OK

| | |
|---|---|
| TX/RX NO | 0672 |
| RECIPIENT ADDRESS | 919198621095 |
| DESTINATION ID | |
| ST. TIME | 02/21 16:23 |
| TIME USE | 00'19 |
| PAGES SENT | 2 |
| RESULT | OK |

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** February 21, 2006

| | |
|---|---|
| **To:** **Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastroenterology Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Clinical Information Request

**Total no. of pages including cover:** __2__

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** February 21, 2006

| | |
|---|---|
| **To: Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastroenterology Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Clinical Information Request

**Total no. of pages including cover:** __2__

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

**The clinical Information Request is as follows:**

Please submit the efficacy results for the co-primary efficacy endpoints for the seven treatment groups for the following three subgroups in Study NKP-102-03-01 (your phase 2, dose ranging study): patients between ages of 18 and 64 years old, patients between the ages of 65 and 74, and patients 75 years or older.

**********
*** TX REPORT ***
**********

TRANSMISSION OK

| | |
|---|---|
| TX/RX NO | 0654 |
| RECIPIENT ADDRESS | 919198621095 |
| DESTINATION ID | |
| ST. TIME | 02/14 17:21 |
| TIME USE | 00'18 |
| PAGES SENT | 2 |
| RESULT | OK |

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** February 14, 2006

| | |
|---|---|
| **To: Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Clinical Information Request

**Total no. of pages including cover:** __2__

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** February 14, 2006

| | |
|---|---|
| **To:** **Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Clinical Information Request

**Total no. of pages including cover:** __2__

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

**The Statistical Information Request is as follows:**

- Please send the *Glimmix* Sas macro that was used to analyze the primary endpoint in Study INKP-102-04-01.

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

# REQUEST FOR CONSULTATION

| (Division/Office): | | | FROM: | |
|---|---|---|---|---|
| Scott Dallas and Diane Smith, White Oak Rm 4421 | | | Tanya Clayton, Regulatory Health Project Manager White Oak, Rm 5103 | |
| DATE: January 5, 2006 | IND NO.: 56,291 | NDA NO.: 21-892 | TYPE OF DOCUMENT: Tradename Review | DATE OF DOCUMENT: December 19, 2005 |
| NAME OF DRUG: INKP-102 (Sodium Phosphate Monobasic Monohydrate, USP, sodium Phosphate dibasic anhydrous, USP tablets | PRIORITY CONSIDERATION: High | | CLASSIFICATION OF DRUG: Laxative | DESIRED COMPLETION DATE: February 1, 2006 |

NAME OF FIRM: Salix Pharmaceuticals, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

**COMMENTS/SPECIAL INSTRUCTIONS:**

This is a 505 (b)(2) New Drug Application that is indicated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age and older. The sponsor is previously proposed [redacted] and [redacted] as the tradename. Your August 24, 2005 review denied both names as the tradename. Consequently, the firm is now proposing [redacted] Osmoprep, or [redacted] as the proposed tradenames. The PDUFA goal date is 03/17/06. Please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21892/29April2005 . Please let me know if you require additional information. Thank you in advance.
Tanya Clayton – 301-796-0871.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☒ MAIL (e-mail) ☐HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

---

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

---

/s/

---

Tanya Clayton
1/5/2006 12:54:42 PM

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | **REQUEST FOR CONSULTATION** |
|---|---|

| (Division/Office): | FROM: |
|---|---|
| Scott Dallas and Diane Smith, White Oak Rm 4421 | Tanya Clayton, Regulatory Health Project Manager<br>White Oak, Rm 5103 |

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| January 5, 2006 | 56,291 | 21-892 | Tradename Review | December 19, 2005 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| INKP-102 (Sodium Phosphate Monobasic Monohydrate, USP, sodium Phosphate dibasic anhydrous, USP tablets | High | Laxative | February 1, 2006 |

NAME OF FIRM: Salix Pharmaceuticals, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

**COMMENTS/SPECIAL INSTRUCTIONS:**

This is a 505 (b)(2) New Drug Application that is indicated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age and older. The sponsor is previously proposed ——— and ——— as the tradename. Your August 24, 2005 review denied both names as the tradename. Subsequently, the firm is now proposing ——— Osmoprep, or ——— as the proposed tradenames. The PDUFA goal date is 03/17/06. Please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21892/29April2005 . Please let me know if you require additional information. Thank you in advance.
Tanya Clayton – 301-796-0871.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one)<br>☒ MAIL (e-mail) ☐HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

turn down

---

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

---

/s/

---

Tanya Clayton
1/5/2006 12:54:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-892

Salix Pharmaceuticals, Inc.
Attention: Jill Kompa, Director, Regulatory Affairs
1700 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Kompa:

We acknowledge receipt on October 11, 2005, of your October 7, 2005, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

| | |
|---|---|
| Name of Drug Product: | Sodium Phosphate Monobasic Monohydrate, USP & Sodium Phosphate Dibasic Anhydrous, USP, Tablets |
| NDA Number: | 21-892 |
| Name of New Applicant: | Salix Pharmaceuticals, Inc. |

Name of Previous Applicant: InKine Pharmaceutical Company, Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Salix Pharmaceuticals, Inc. as the sponsor of record for this application

We remind you that you must comply with the requirements for an NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-0871.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastroenterology Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc: InKine Pharmaceutical Company, Inc.
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

---

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

---

/s/

---

Tanya Clayton
11/16/2005 02:50:53 PM

# MEMORANDUM

**To:** Tanya Clayton, B.S.
Div. of Gastroenterology Products

**From:** Iris Masucci, PharmD, BCPS
Debi Tran, PharmD
DDMAC

**Date:** November 23, 2005

**Re:** Comments on draft labeling for ——— tablets
(sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous)
NDA 21-892

---

DDMAC has reviewed the proposed package insert, carton, and container for ——— and offers the following comments.

**Package Insert**

**Description**

" ™ *is manufactured with a highly soluble tablet binder and does not contain microcrystalline cellulose (MCC).*"

———

**Clinical Studies**

[

]

We recommend that the mention of the brand name "Visicol" be deleted from this sentence. In general, comparator drugs are identified only by generic names in labels, regardless of whether or not they are produces by the same manufacturer.

*"Response was defined as a rating of "excellent" or "good" on a 4 point cleansing scale, as determined by the physician performing the colonoscopy, who was blinded to the treatment assignment."*

Is this rating scale a validated instrument? We note that the Visicol label specifically mentions that its scale is in fact validated. We recommend you consult Laurie Burke of the OND IO for evaluation of the adequacy and validity of this scale for use in labeling.

---

Is the inclusion of the dose ranging study appropriate for labeling? In general, dose ranging studies are not included in labeling because they are inadequately designed to allow clinical conclusion (as this label in fact notes) and because they include a range of off-label dosing regimens. Unless this study is particularly helpful to the clinician for understanding the proper use of the drug, we recommend its deletion.

Table 2: Phase 3 Study – Overall Colon Cleansing Response Rates

In this table, we suggest that results for all possible scores on the rating scale be included, not just the "overall response rate," a combination of "excellent" and "good" scores. This revised presentation would be consistent with the results presentation in the Visicol clinical studies section.

In addition, we recommend deletion of the p-values from this table. Despite the explanation of the p-values in the table footnote and in the paragraph that immediately follows the table, the overall impression from these data with p-values is that —— is statistically better than Visicol.

Are the data on results in the ascending colon supported by substantial evidence? If not, we recommend they be deleted entirely from the label. We also note that the claim of " —— " mentioned above is most likely inappropriate for labeling because it appears to be a secondary endpoint and the findings have not been replicated in another study.

These final three paragraphs of the clinical studies section describe results for amount of irrigation fluid needed, compliance rates, and patient preferences. We recommend these findings all be deleted from the label unless they are adequate supported.

**Precautions – Preparative Diet**

We suggest the section on preparative diet be moved to the Dosage and Administration section so that it is included in the description of the overall bowel prep regimen. In its current placement, it can be easily overlooked.

**Adverse Reactions**

We recommend that all mention of ' differences in adverse event rates be deleted from the label. This includes removal of the p-values from Table 6. In general, adverse events are not presented with statistics unless particular events were the primary endpoints of prospectively designed safety studies.

Table 6

We recommend that the results for the 32 tablet dose of not appear on bolded type as is currently proposed.

**Carton and Container Labeling**

DDMAC has no comment on the proposed carton or container labeling.

---

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

---

/s/

---

Michelle Safarik
11/29/2005 01:41:43 PM
DDMAC REVIEWER
Signed for Iris Masucci.

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** November 1, 2005

| | |
|---|---|
| **To: Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Statistical Information Request

**Total no. of pages including cover:** __2__

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

**********
*** TX REPORT ***
**********

TRANSMISSION OK

| | |
|---|---|
| TX/RX NO | 0304 |
| RECIPIENT ADDRESS | 919198621095 |
| DESTINATION ID | |
| ST. TIME | 11/01 15:19 |
| TIME USE | 00'18 |
| PAGES SENT | 2 |
| RESULT | OK |

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

# FACSIMILE TRANSMITTAL SHEET

**DATE:** November 1, 2005

| | |
|---|---|
| **To:** **Jill Kompa, Director, Regulatory Affairs** | **From:** Tanya D. Clayton, BS<br>Regulatory Health Project Manager |
| **Company:** Salix Pharmaceuticals, Inc. | Division of Gastrointestinal and Coagulation Drug Products |
| **Fax number:** 919-862-1095 | **Fax number:** 301-796-9905 |
| **Phone number:** 919-862-1047 | **Phone number:** 301-796-0871 |

**Subject:** NDA 21-892 Statistical Information Request

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

**Comments:**

Please find attached an Information request for NDA 21-892. Please submit the request as an amendment to the NDA.

Best regards.

**Document to be mailed:** YES ☑ NO

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

# REQUEST FOR CONSULTATION

*(Division/Office)*:

Guirag Poochikian,
Acting Chair of the CDER Nomenclature Committee,
White Oak, 2618 (building #21)

FROM:

Tanya Clayton, Project Manager
Division of Gastroenterology
White Oak, 5103 (building #22)

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| November 2, 2005 | | 21-892 | Tradename Review | February 25,2005 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| [redacted] (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) | Standard | Laxative | December 17, 2006 |

NAME OF FIRM: Salix Pharmaceuticals, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

**COMMENTS/SPECIAL INSTRUCTIONS:**

This is an New Drug Application that is being investigated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older. The proposed tradenames are [redacted]™ and [redacted]™. The original consult was sent to DDMAC and DMETS prior to the submission of the NDA. Both divisions have completed their reviews and DMETS recommended further review by the CDER Labeling and Nomenclature Committeee. The NDA review is now in progress with a PDUFA date of March 17, 2006. The Divisional Goal date is January 17, 2006, in which I'm asking for your completed review by December 17, 2006, if possible. I'm attaching the supportive documents provided by the sponsor as well as the DDMAC/DMETS review. Please let me know if you require additional information. Thank you in advance. Tanya Clayton – 301-796-0871.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

---

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

---

/s/

---

Tanya Clayton
11/2/2005 06:06:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-892

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Executive Vice President, Research and Development
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to your May 17, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 16, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have identified the following potential filing review issues.

1. Please provide the location of the SAS datasets that contain the primary and secondary variables.
2. Please provide the names of the variables within the SAS datasets.

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 Tanya Clayton, B.S., Regulatory Health Project Manager, at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Brian K. Strongin, R.Ph., M.B.A
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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

---

/s/

---

Brian Strongin
7/25/05 01:57:39 PM

# MEMORANDUM OF TELECON

DATE: June 15, 2005

APPLICATION NUMBER: NDA 21-892

BETWEEN:

Name: Ronald Carnal, Compliance Manager
Martin Rose, M.D., J.D., Executive Vice President, Research and Development
John Cullen, General Counsel
Phone: 215-283-6861
Representing: Inkine Pharmaceuticals

AND

Name: Tanya Clayton, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Michael Jones, Special Assistant
Office of Regulatory Policy, HFD-005

SUBJECT: **User Fee Goal Date**

**Background**

The purpose of this teleconference was to discuss InKine's request to have their use fee date adjusted to April 29, 2005, their original submission date. Upon arrival on April 29, 2005, it was determined that the NDA was not exempt from user fees and a fee was not paid. As a result, the sponsor was notified and an Unacceptable for Filing-No User fee Received letter, dated May 11, 2005, was sent to the sponsor. On May 17, 2005, the Agency was notified of the receipt of payment of user fees. The agency followed up with a May 24, 2005, acknowledgment letter acknowledging receipt of the user fees.

Following the sponsors receipt of the May 24, 2005, acknowledgment letter, the sponsor responded by submitting a General Correspondence letter, dated May 24, 2005. Their May 24, 2005, letter outlined Inkine's reasons as to why the PDUFA goal date should start as of April 29, 2005. Consequently, the Agency scheduled a teleconference to discuss their concerns.

**Discussion**

Dr. Rose led the discussion on InKine's behalf. Mr. Jones led the discussion on the Agency's behalf. Dr. Rose explained that InKine's failure to submit a user fee was based, in part, on their misinterpretation of the user fee cover sheet (FDA Form 3397). He also stated that experienced FDA counsel (counsel were not FDA employees, rather they were outside counsel with FDA experience) was consulted in which they concluded that a user fee would not be required.

InKine's rationale for adjusting the PDUFA goal date back to the original submission date is because InKine acted in "good faith" as shown by sending the fee on May 13, 2005. Mr. Jones responded:

- The statute (see section 736(e) of the FDC Act) is clear in that if an application is subject to a fee, and the fee is not paid then the application is not accepted for filing. It does not matter if you believed that you did not need to pay a fee.

InKine then suggested that instead of returning the goal date to April 29, 2005, it should start as of May 13, 2005, the date they state that they have documentation to show that the bank received their check. Mr. Jones responded:

- MaPP 6050.1 states that FDA's longstanding, consistent policy, is that the goal date starts when FDA's Office of Financial Managment has been notified of payment. The goal date does not start when the check is delivered to the bank.

Therefore, the goal date remains as March 16, 2006.

The sponsor closed by asking the project manager to provide information concerning the procedures required to discuss this topic further.

Tanya Clayton, B.S.
Regulatory Health Project Manager

---

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

---

/s/
---
Tanya Clayton
7/20/05 09:45:52 AM
CSO

Michael Jones
7/20/05 11:17:51 AM
MEDICAL OFFICER

ATTACHMENT

## MEMO OF FILING MEETING

DATE: July 6, 2005

BACKGROUND: ——— provides for cleansing of the bowel in preparation for colonoscopy in adults. This is an 505 (b)(2). The referenced drug is Visicol Tablets, NDA 21-097.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Joyce Korvick, Brian Harvey, Ruyi He, Eric Brodsky, Liang Zhou, Ali Al-Hakim, Suresh Doddapaneni, Mushifiqur Rashid, Tamal Chakraborti, Tanya Clayton

ASSIGNED REVIEWERS (including those not present at filing meeting) :

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Eric Brodsky |
| Secondary Medical: | |
| Statistical: | Mushifiqur Rashid |
| Pharmacology: | Tamal Chakraborti |
| Statistical Pharmacology: | |
| Chemistry: | Ali Al-Hakim |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Suliman Al-Fayoumi |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | Kahery Malik |
| Regulatory Project Management: | Tanya Clayton |
| Other Consults: | DMETS, DDMAC |

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

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

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

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

ELECTRONIC SUBMISSION:
Any comments: Fully Electronic

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ 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. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Stats will provide Information Request regarding the location of SAS files.
Clinical will provide Information Request regarding Safety Follow-up.

Tanya Clayton, B.S.
Regulatory Project Manager, HFD-180

---

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

---

/s/

---

Tanya Clayton
7/11/05 01:18:15 PM
CSO

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

NDA # 21-892 Supplement # Efficacy Supplement Type SE-

Trade Name: ———
Established Name: sodium Phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous

Strengths: 1.5 gram, oral tablet

Applicant: Inkine Pharmaceutical
Agent for Applicant: N/A

Date of Application: April 29, 2005
Date of Receipt: April 29, 2005
Date clock started after UN: May 17, 2005
Date of Filing Meeting: July 6, 2005
Filing Date: July 30, 2005
Action Goal Date (optional): User Fee Goal Date: March 17, 2006

Indication(s) requested: Cleansing of the bowel as a preparation for colonoscopy in adults.

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

***NOTE:***

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

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

☐ NDA is a (b)(1) application OR ☒ NDA is a (b)(2) application

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

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

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

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

*product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

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

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  **If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  **If an electronic NDA, all forms and certifications must be in paper and require a signature.**
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  **If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☐ NO ☒

- Exclusivity requested? YES, _____ Years 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 ☒ NO ☐
  **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 ☒ NO ☐
  **(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**
  **NOTE:** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,291

- End-of-Phase 2 Meeting(s)? Date(s) August 23, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 10, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

## Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

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

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

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

## Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

## Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

## MEMO OF FILING MEETING

DATE: July 6, 2005

BACKGROUND: ——— provides for cleansing of the bowel in preparation for colonoscopy in adults. This is an 505 (b)(2). The referenced drug is Visicol Tablets, NDA 21-097.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Joyce Korvick, Brian Harvey, Ruyi He, Eric Brodsky, Liang Zhou, Ali Al-Hakim, Suresh Doddapaneni, Mushifiqur Rashid, Tamal Chakraborti, Tanya Clayton

ASSIGNED REVIEWERS (including those not present at filing meeting) :

| **Discipline** | **Reviewer** |
|---|---|
| Medical: | Eric Brodsky |
| Secondary Medical: | |
| Statistical: | Mushifiqur Rashid |
| Pharmacology: | Tamal Chakraborti |
| Statistical Pharmacology: | |
| Chemistry: | Ali Al-Hakim |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Suliman Al-Fayoumi |
| Microbiology, sterility: | |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | Kahery Malik |
| Regulatory Project Management: | Tanya Clayton |
| Other Consults: | DMETS, DDMAC |

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

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

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

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

ELECTRONIC SUBMISSION:
Any comments: Fully Electronic

REGULATORY CONCLUSIONS/DEFICIENCIES:
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

☐ 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. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Stats will provide Information Request regarding the location of SAS files.
Clinical will provide Information Request regarding Safety Follow-up.

Tanya Clayton, B.S.
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 ☒ NO ☐

   *If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 21-097

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

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☒ 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 ☐ NO ☐

   (***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 ☐ NO ☐
   (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 ☐ NO ☐

*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 new dosage regimen, based on comparability studies.

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)). YES ☐ 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)). YES ☐ 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). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

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)
Patent number(s): 5,616,346

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

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

☐ 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)
Patent number(s):

**NOTE:** *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)
Patent number(s):

☐ 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).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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 ☐ NO ☒

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☒ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☒ YES ☐ 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):

- 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 ☒ NO ☐

---

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

---

/s/

---

Tanya Clayton
7/11/05 01:18:15 PM
CSO

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

## Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **December 6, 2005**. We intend to issue an action letter on this application by (action goal date) **March 17, 2006**.

Should you require any additional information, please contact Tanya Clayton at 301-827-4005.

Concurrence: (if necessary)

N/A

---

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

---

/s/

---

Tanya Clayton
7/11/05 10:51:56 AM

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

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Shannon Benedetto and Elaine Hu,
HFD-42, Parklawn Building, Room 17B-17

FROM:
Tanya Clayton (Regulatory Health Project Manager)
GI and Coagulation Drug Products, HFD-180,
PKLN 6B-45

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| June 24, 2005 | | 21-892 | New Drug Application | April 29, 2005 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| [redacted] (sodium phosphate monobasic monohydrate, USP & sodium phosphate dibasic anhydrous, USP | Standard | Laxative | November 30, 2005 |

NAME OF FIRM: InKine Pharmaceutical Company

**REASON FOR REQUEST**

**I. GENERAL**

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling Review

**COMMENTS/SPECIAL INSTRUCTIONS:**

This is a 505 (b)(2) New Drug Application that is indicated for cleansing of the bowel as a preparation for colonoscopy in adults 18 years of age or older. The reference drug for this application is Visicol Tablets, NDA 21097, which is also owned by InKine Pharmaceutical Company. The PDUFA goal date is 10/17/06. I'm attaching a copy of the proposed package and PI labeling. Also, please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21892/29 Apr2005 . Please let me know if you require additional information. Thank you in advance.
Tanya Clayton – 827-4005.

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

12 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

---

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

---

/s/

---

Tanya Clayton
6/24/05 03:46:17 PM

# PDUFA Clock Restart

(This form must be completed upon applicant removal from the arrears list.)

**Applicant: InKine Pharmaceutical Company, Inc.**

**Date Firm Removed From Arrears List (Payment Date): May 17, 2005**

| NDA # | Supplement (S) or Reviewable Unit (RU) # |
|---|---|
| 21-892 | Original NDA |
| | |
| | |
| | |
| | |

PROJECT MANAGER: Tanya Clayton

HFD-180

**NOTES:**

1. The user fee clock restarts on the date the firm was removed from arrears list. This date is from the daily "User Fee Payment & Arrears List" e-mail.
2. In DFS, link the form only to the initial submission of the NDA (original N document) or the supplement (base document) or the Reviewable Unit (RU).
3. This form performs different functions depending on how it is checked into DFS.
   a. If checked in as:
      Document type: "FORMS"
      Form group: "ADMINISTRATIVE"
      Form name: "PDUFA Clock Restart"
      then it informs the DDR to create an AR document, which restarts the clock as of the payment date.
   b. If checked in as:
      Document type: "FORMS"
      Form group: "ADMINISTRATIVE"
      Form name: "Establishment UN & PDUFA Clock Restart"
      then it informs the DDR to stop the clock with an UN decision as of the submission receipt date and also create an AR document, which restarts the clock as of the payment date.
   c. If checked in as:
      Document type: "FORMS"
      Form group: "ADMINISTRATIVE"
      Form name: "Application UN & PDUFA Clock Restart"
      then it informs the DDR to stop the clock with an UN decision as of the submission receipt date plus 5 calendar days and also create an AR document, which restarts the clock as of the payment date.
4. The document room will create a document with amendment type "AR" for each listed application/supplement/reviewable unit on the form. The payment date will be used as the letter date, stamp date, and decision date. After this document has been created, prepare an "Acknowledge Receipt of Owed User Fee" letter and link it to the "AR" document in DFS.

---

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

---

/s/

---

Tanya Clayton
5/24/05 04:15:42 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-892

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Executive Vice President, Research and Development
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for —— (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP).

You were notified in our letter dated May 11, 2005, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of May 17, 2005.

The review priority classification for this application is standard(S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 16, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 17, 2006 and the ~~secondary user fee goal date will be May 17, 2006~~ obsolete

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

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

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Tanya Clayton
5/24/05 12:12:31 PM

This letter was faxed to the sponsor May 23, 2005. Following receipt, the sponsor noticed that the Un letter date (April 29, 2005) in the second paragraph was incorrect. The correct date is May 11, 2005. As a result, the project manager sent another letter with the correct date. Please refer to the May 24, 2005 User Fee Letter as the correct letter for acknowledgment of receipt for owed user fees.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-892

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Executive Vice President, Research and Development
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for [redacted] (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP).

You were notified in our letter dated April 29, 2005, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of May 17, 2005.

The review priority classification for this application is standard(S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 16, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 17, 2006 and the secondary user fee goal date will be May 17, 2006.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

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

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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

---

/s/

---

Tanya Clayton
5/23/05 01:48:57 PM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-892

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Executive Vice President, Research and Development
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for ——. (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP).

You were notified in our letter dated ~~April 29,~~ May 11 2005, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of May 17, 2005.

The review priority classification for this application is standard(S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 16, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 17, 2006 and the secondary user fee goal date will be May 17, 2006.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

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

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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

---

/s/

---

Tanya Clayton
5/23/05 01:48:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-892

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Executive Vice President, Research and Development
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

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: [redacted] (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP)

Date of Application: April 29, 2005

Date of Receipt: April 29, 2005

Our Reference Number: NDA 21-892

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

**NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.**

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

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

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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

---

/s/

---

Tanya Clayton
5/11/05 11:23:06 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,291

InKine Pharmaceutical Company
Attention: Martin Rose, M.D., J.D.
1787 Sentry Parkway West
Building 18, Suite 440
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Visicol Tablets, INKP-102 (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anyhydrous, USP).

We also refer to the meeting between representatives of your firm and the FDA on March 10, 2005. The purpose of the meeting was to discuss the future submission of your original NDA for the new formulation product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

*{See appended electronic signature page}*

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** March 10, 2005

**Time:** 10:30-12:00 PM

**Location:** Parklawn Building, Conference Room C

**Application:** IND 56,291

**Type of Meeting:** Type B, pre-NDA meeting

**Meeting Chair:** Ruyi He, M.D.

**Meeting Recorder:** Tanya Clayton, B.S.

**FDA Attendees, Titles, and Office/Division:**

Division of Gastrointestinal and Coagulation Drug Products

| | |
|---|---|
| Julie Beitz, M.D. | Deputy Director, Office of Drug Evaluation III |
| Joyce Korvick, M.D., M.P.H | Acting Division Director |
| Kathy Robie-Suh, M.D., Ph.D. | Acting Deputy Director |
| Ruyi He, M.D. | Medical Team Leader |
| Fathia Gibril, M.D. | Medical Reviewer |
| Jasti Choudary, Ph.D., B.V.Sc. | Supervisory Pharmacologist |
| Sushanta Chakder, Ph.D. | Pharmacology Reviewer |
| Stella Grosser, Ph.D. | Biometrics Team Leader |
| Liang Zhou, Ph.D. | Chemistry Team Leader |
| Ali Al-Hakim, Ph.D. | Chemistry Reviewer |
| Tanya Clayton, B.S. | Regulatory Health Project Manager |

**External Constituent Attendees and Titles:**

InKine Pharmaceutical Company, Inc.

| | |
|---|---|
| Martin Rose, M.D, J.D. | Executive Vice President, R&D |
| Robyn Karlstadt, M.D. | Vice President, Clinical Operations |
| Nancy Ettinger | Senior Director, Clinical Operations |
| Ronald Carnal | Compliance Manager |
| Stephen Skiendzielewski | Vice President, Manufacturing |
| Eddie Carter | Vice President, Kentucky Clinical Research |

**Background:**

On January 10, 2005 the sponsor, InKine Pharmaceuticals, requested a type B, pre-NDA meeting for the purpose of discussing the upcoming submission of their original NDA for the new formulation product.

A subsequent February 9, 2005 background package was submitted, which contained 4 questions for discussion.

Following introductions, the Sponsor provided a brief presentation in response to the pre-meeting responses that were sent February 25, 2005 via facsimile. After the presentation, the Sponsor agreed to proceed directly to the questions for discussion.

***Discussion Points: (bullet format):***

**List of specific questions, grouped by discipline:**

*General*

1. By the time of the requested meeting, InKine should have the efficacy and safety data from the completed Phase 3 study comparing INKP-102 with marketed Visicol® Tablets. InKine believes that there is a reasonable likelihood that INKP-102 will show superiority to Visicol® in efficacy, safety and patient preference.

   If INKP-102 is demonstrated to be more effective than Visicol® in the phase 3 study, InKine believes that Priority Review would be appropriate for the INKP-102 NDA. To our knowledge, all approved colon-cleansing agents have been approved on the basis of data showing comparability or non-inferiority of efficacy to marketed products. This is certainly true for NuLYTELY® (which was compared to GoLYTELY®), HalfLytely® with bisacodyl (compared to NuLYTELY®), and Visicol® (compared to NuLYTELY®). INKP-102 may be the first NDA colon-cleansing agent with data from a large, well-controlled trial showing statistically significant superiority in efficacy over an approved product along with improved safety and patient preference. Our smaller, completed phase 2 study would be supportive of a superiority claim.

   Our question is: how and when should InKine request Priority Review for INKP-102 if we believe that the data support this request?

   (Although InKine acknowledges that our phase 3 trial was set up as a non-inferiority trial, we cite the EMEA document CPMP/EWP/482/99 entitled "Points to Consider on Switching Between Superiority and Non-Inferiority" (attached Tab 2). This document indicates that a superiority claim may be appropriate when a study planned to demonstrate non-inferiority does indeed demonstrate superiority.)

**Response**

**A priority designation will be determined by the Division at the 45-day meeting after the application is filed.**

**The request for priority review should be requested at the time of NDA submission. You should provide rationale for priority review.**

2. Does FDA agree with the presentation and formatting of the data as represented in the attachments listed in item 9 of this package?

**Response**

**The presentation and formatting of ISS and ISE tables appear reasonable.**

**CMC**

3. In the meeting between InKine and FDA on January 7, 2004, FDA agreed with InKine's stated plan to submit for approval CMC data from 3 batches with 6-month stability data under stressed (40° C, 75% RH) and ambient (25° C, 60% RH) conditions, with updates during the review period at 9 and 12 months (ambient conditions only). Since that discussion, InKine's project timelines have accelerated. At this time, InKine is proposing to submit to the FDA for approval of the new formulation, CMC data from 3 batches with **3-month** stability data under stressed (40° C, 75% RH) and ambient (25° C, 60% RH) conditions, with updates during the review period at **6 and 9 months** (ambient conditions only). Does FDA agree with this revised plan?

**Response**

**No, you should provide 3-month accelerated (40° C, 75% RH) and 6-month ambient conditions (25° C, 60% RH) stability data at submission. You can submit 9-month data during the review cycle, prior to 3 months of the action date. However, the assignment of expiration dating period will be a review issue.**

4. The 12-month stability data will be available in mid November 2005; which would be during the review period, albeit not in the first 6 months of the review period. Would the Agency be willing to accept and consider the 12-month stability at that point of the review cycle without penalty regarding the user fee goal date?

**Response**

**The submission of 12-month stability data would not be considered a major amendment and would not affect the user fee goal date of the application.**

**Additional Comments**

- **We remind you of the meeting minutes dated August 31, 2004 for IND 56, 291 and your correspondence dated November 19, 2004. The need for recommended 4-week toxicology studies in a rodent and non-rodent species would depend on your submission of the NDA under 505 (b)(1) application. It is our understanding that you are going to submit your NDA as a 505 (b)(2) application. You have not submitted data to the IND to support that PEG 8000 in your formulation is not an active ingredient. If PEG 8000 shows activity as an active ingredient in the clinical subjects, toxicology studies would still be needed.**
- **If PEG 8000 is an active ingredient, the manufacturing site(s) for PEG 8000 should be ready for inspection at the time of NDA submission and CMC information for PEG 8000 would need to be submitted or cross-referenced to a DMF.**

---

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

---

/s/

---

Tanya Clayton
4/1/05 11:46:39 AM

Ruyi He
4/1/05 04:20:24 PM