CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

CORRESPONDENCE

NDA 21-097

DEC - 7 1999

InKine Pharmaceutical Company, Inc.
Attention: Kevin Malobisky, RAC
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

Dear Mr. Malobisky:

Reference is made to your correspondence dated November 22, 1999, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Diacol™ (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets for colonic purgation prior to colonoscopy for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Alice Kacuba, Regulatory Health Project Manager, at 301-827-7450.

Sincerely,

/S/ 12-7-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-097

DEC - 7 1999

InKine Pharmaceutical Company, Inc.
Attention: Kevin Malobisky, RAC
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

Dear Mr. Malobisky:

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: Diacol™ (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets

Therapeutic Classification: Standard (S)

Date of Application: November 22, 1999

Date of Receipt: November 23, 1999

Our Reference Number: NDA 21-097

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 22, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 23, 2000 and the secondary user fee goal date will be November 23, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you

within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

U.S. Postal/Courier/Overnight Mail:

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

If you have any questions, contact me at (301) 827-7450.

Sincerely,

/S/ 12-7-99

Alice Kacuba
Regulatory Health Project Manager
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-097

INFORMATION REQUEST LETTER

InKine Pharmaceutical Company, Inc.
Attention: Kevin P. Malobisky, RAC
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

FEB 17 2000

Dear Mr. Malobisky:

Please refer to your November 22, 1999 new drug application for Diacol™ (sodium phosphate dibasic monohydrate and sodium phosphate monobasic anhydrous) Tablets.

We are reviewing your submission and have the following information requests. Your prompt written response is needed to continue our evaluation of your NDA.

Clinical

A. Regarding colon cleansing and the appearance of mucosal aphtous ulcerations observed in the INKP-100 clinical studies, please provide:

   1. Copies of original colonoscopy reports for all subjects enrolled in Phase I, Phase II, and Phase III trials.

   2. A tabular list of all patients who presented with mucosal aphtous ulcerations, including the treatment group assignment and center.

   3. Case Report Forms for all subjects who were found to have mucosal aphtous ulcerations.

B. Regarding the patients who had QTc changes on EKG, please provide a tabular list of patients, treatment assignment, center, and comments, if any, on all patients who had QTc prolongation, referenced in Tables 34, 35, and 36, on pages 96, 97, and 99, respectively, in the Integrated Summary of Safety (ISS). Alternatively, if this information has already been submitted, please provide the section and page number where this information is located.

C. Regarding the All-Randomized Patients (ARP) analysis, please provide baseline characteristics not provided in Table 6, page 26, in the Integrated Summary of Efficacy (ISE). Alternatively, if this information has already been submitted, please provide the section and page number where this information is located.

D. Regarding Study INKP-100-302, please provide:

1. A detailed explanation for the imbalance between the number of subjects in the two treatment groups in the All-Randomized Patients (ARP) and All-Treated Patients (ATP) groups, referred to in Table 7, page 27, in the ISE, i.e., a rationale for why each subject that was randomized was not treated/assessed.

2. The reason(s) for the imbalance between the number of subjects randomized and treated between the Diacol and NuLYTELY study groups.

E. Regarding the secondary efficacy analysis for Study INKP-100-301 and INKP-100-302 (Table 9, page 31, in the ISE), please provide:

1. An efficacy analysis of the ATP for Study 301 and Study 302, which compares each individual category (for Excellent, Good, Fair, and Inadequate) between treatment groups.

2. A tabular list, by study, of each patient and outcome.

Biopharmaceutics

Regarding Study INKP-100-101, please provide individual subject demographics (weight, height, and age) and creatinine clearance values for all subjects.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/

Kati Johnson
Chief, Project Management Staff
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-097

INFORMATION REQUEST LETTER

InKine Pharmaceutical Company, Inc.
Attention: Kevin P. Malobisky, RAC
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

MAR - 9 2000

Dear Mr. Malobisky:

Please refer to your November 22, 1999 new drug application for Diacol™ (sodium phosphate dibasic monohydrate and sodium phosphate monobasic anhydrous) Tablets.

We also refer to our Information Request letter dated February 17, 2000, in which we requested, among other things:

1. Copies of original colonoscopy reports for all subjects enrolled in Phase I, Phase II, and Phase III trials.

2. A tabular list of patients, treatment assignment, center, and comments, if any, on all patients who had QTc prolongation, referenced in Tables 34, 35, and 36, on pages 96, 97, and 99, respectively, in the Integrated Summary of Safety (ISS).

We are amending our request as follows:

A. Regarding the colonoscopy reports, please submit:

   1. Copies of the original colonoscopy reports for all subjects, with mucosal lesions, irrespective of study site or clinical trial.

   2. Copies of original colonoscopy reports for all subjects from the following six sites for Study INKP-100-301:

      a. Site 01. Charles Barish, M.D.
      b. Site 04. Michael Fedotin, M.D.
      c. Site 07. David Mangles, M.D.
      d. Site 09. Robert Morton, M.D.
      e. Site 12. John Turse, M.D.
      f. Site 14. Donald Walters, M.D.

B. Regarding the patients with QTc changes, please submit a tabular list of patients whose QTc interval on ECG changed from baseline and exceeded a value of 450 milliseconds on treatment. The tabular listing should include patient number, center, treatment assignment, and comments, if any.

Your prompt written response to these requests and to the remainder of the requests in the February 17, 2000 Information Request letter are needed to continue our evaluation of your NDA.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/ 3/9/00

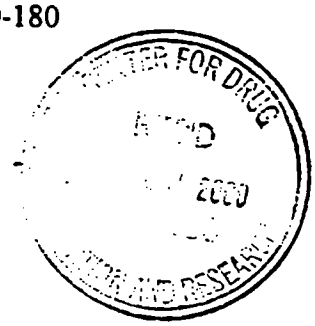
Kati Johnson
Chief, Project Management Staff
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

InKine Pharmaceutical Company, Inc.

SU

March 31, 2000

Lilia Talarico, M.D.
Division Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
United States Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA Number 21-097 (Diacol™ Tablets); Amendment 11
Safety Update Report

Dear Dr. Talarico:

In accordance with 21 CFR 314.50 (vi)(b), InKine Pharmaceutical Company, Inc (InKine) is submitting the following Safety Update Report in reference to the New Drug Application for Diacol Tablets, number 21-097. The original NDA for Diacol was submitted to the Agency on November 23, 1999. Since that time, no additional human clinical safety or efficacy studies or animal studies have been conducted with Diacol. Therefore, the safety information presented in the Integrated Summary of Safety in the original NDA for Diacol represents the most current safety information for the Diacol Tablets. InKine is unaware of any additional new safety information that may reasonably affect the statements of contraindications, warnings, precautions, or adverse events in the draft labeling presented in the NDA.

Please do not hesitate to contact me directly if you have any questions regarding this safety update or the Diacol NDA. I look forward to working with you during the review of this very exciting and much anticipated product.

InKine formally requests that all information presented in this letter and NDA Amendment is held in strict confidence at the Agency. The material presented in this letter and amendment may not be disseminated to the public through the Freedom of Information Act or any other means without the prior written authorization of InKine.

Sincerely,

Kevin P. Malobisky, R.A.C.
Assistant Director, Regulatory Affairs

Sentry Park East • 1720 Walton Road • Blue Bell, Pennsylvania 19422
Tel: (610) 260-9350 • Fax: (610) 260-9355

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-097

DISCIPLINE REVIEW LETTER

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

MAY 24 2000

Dear Dr. Rose:

Please refer to your November 23, 1999 new drug application for Diacol (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets.

We also refer to your submissions dated December 28, 1999, January 6, February 10, March 14, and March 29, 2000.

Our review of the chemistry section of your submissions is complete, and we have identified the following deficiencies. Please provide:

1. A description of the proposed acceptance specifications used for the drug product components when received from the supplier.

2. Information on the holding time and storage conditions used for the blend before moving into the final compressing stage of the tablets.

3. A detailed description of the titration test method used for content uniformity.

4. The manufacturing date for the stability batches. Please note that expiration dating for the drug product will be determined from real time stability data obtained from the production batches.

5.

6.

7. Complete method validation packages as described in the "Guideline for Submitting Samples and Analytical Data for Methods Validation, February 1987". This document is available on the Agency's website.

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

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/

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

-Kamba

NDA 21-097

DISCIPLINE REVIEW LETTER

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

JUN 19 2000

Dear Dr. Rose:

Please refer to your November 22, 1999 new drug application for Diacol™ (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets.

Our review of the proposed tradename, Diacol™, is complete, and we have the following comments and recommendations.

1. "Diacol", when scripted, appears similar to "Dical" and "Dilacor".

2. "Diacol" is similar to sound-alike names of "Dical" and "Dilacor".

3. If a medication error were to occur between Diacol and another agent, a gross overdose would occur due to the numerous tablets ingested.

Due to these potential safety concerns, we do not recommend the use of the proposed tradename of "Diacol". Please submit a new proposed tradename for review and evaluation.

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

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-7450.

Sincerely,

/S/ 6/15/00

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Kacuba

NDA 21-097

AUG - 8 2000

InKine Pharmaceutical Company, Inc.
Attention: Martin Rose, M.D., J.D.
Sentry Park East
1720 Walton Road
Blue Bell, PA 19422

Dear Dr. Rose:

Please refer to the meeting between representatives of your firm and FDA on July 18, 2000. The purpose of the meeting was to discuss the data regarding the ECG changes seen in the clinical trials.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7450.

Sincerely,

/S/ 8-8-00

Alice Kacuba
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

InKine Pharmaceutical Company, Inc.

MARTIN ROSE, M.D., J.D.
Senior Vice President
Clinical Research & Regulatory Affairs

fax received 8.31.00

August 31, 2000

Lilia Talarico, M.D.
Division Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
United States Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA Number 21-097 (Visicol™ Tablets); Amendment 28
Response to FDA's Communications of August 30, 2000

Dear Dr. Talarico:

InKine Pharmaceutical Company, Inc (InKine) is submitting the following amendment to the Visicol™ New Drug Application submitted to the Agency on November 23, 1999. This amendment contains responses to FDA's fax communications to InKine of August 30, 2000 regarding the Division's recommendation to approve the NDA provided InKine and FDA reach agreement on several outstanding issues, which are discussed below. The table of contents for this submission is on page 8.

We also hereby formally notify FDA that "Visicol" will be the trade name in the US for the product covered by NDA 21-097.

We greatly appreciate FDA's efforts to complete the review of our NDA by the user fee target date of September 23, 2000. Throughout the review, FDA's communications with InKine have been excellent. The Agency consistently has been responsive to InKine's requests for information. We also commend the Agency for its willingness to arrange for teleconferences or meetings when we have requested them. These actions are consistent with the letter and spirit of FDAMA and FDA's important role in promoting public health.

With respect to FDA's communications of August 30, 2000:

NDA Number 21-097 (Visicol™ Tablets); Amendment 28
Response to FDA's Communications of August 30, 2000

1. Biopharmaceutics Phase IV Commitment

InKine fully agrees to the Phase IV commitment to collect additional dissolution data described in the first fax sent to us by Alice Kacuba, R.N., MSN, CCRN on August 30, 2000. The requested data will be submitted within 3 months of approval as specified by FDA.

2. FDA's Revisions to the Visicol Bottle Label

InKine accepts all of FDA's revisions to the Visicol bottle label that were included in the second fax to us from Alice Kacuba, R.N., MSN, CCRN on August 30, 2000.

Although we are prepared to implement all of FDA's revisions, we would at this time additionally propose that the label be enlarged to completely circle the bottle and that dosing instructions be moved from the front of the bottle to the back of the bottle. The label wording be exactly as FDA has suggested – only the location of the dosing information would change. (See page 9.)

3. FDA's Revisions to the Visicol Package Insert

We have reviewed and accepted most of FDA's proposed revisions to the package insert that were in Ms. Kacuba's second fax to us of August 30, 2000 in a document captioned "FDA Revised Labeling." InKine's proposed revisions to this document captioned are attached as hard copy, and a disk with a WORD computer file with these revisions is enclosed.

The following comments deal with two of InKine's proposed revisions that we believe are especially important:

QT Interval Information

On page 6 of the faxed revisions that we received, FDA has proposed a new precaution regarding QT prolongation following use of Visicol. We have proposed modest changes to this precaution tnat would present a more balanced view of the data in our NDA. We believe that precaution is primarily based on information from InKine's controlled trials, which showed that Visicol and the comparator agent, a PEG-salt solution, both induced transient QT prolongation. If the data for Visicol are reliable (and we have no reason to doubt them) and relevant, then the data for the comparator must be just as reliable and relevant.

However, the labeling for the comparator agent does not mention QT prolongation. If the medical community is informed of transient QT prolongation with Visicol, it should be

informed that the comparator agent also produced QT prolongation. Otherwise, medical decision-making about choice of colon cleansing agent will be distorted. In this vein, we are quite concerned that our competitors will unfairly take advantage of any disparity in labeling regarding the QT interval.

In reality, the differences between Visicol and PEG salt solution in cardiovascular risk are nil, as elucidated by Dr. Arthur Moss, InKine's expert on cardiac electrophysiology who has consulted for FDA on other occasions, at our recent meeting with the Division on the issue of QT prolongation. If the labeling for Visicol contains a balanced description of the findings of our trials regarding changes in the QT interval that includes information about the comparator agent, rational medical decision-making will be enhanced.

Display of Adverse Event Information

On page 8 of the faxed revisions that we received from FDA, the Agency has deleted the table of adverse event information from InKine's two pivotal trials, in which 859 patients received either Visicol or the comparator agent, a PEG-salt solution. Instead, FDA proposes that Visicol adverse event information be communicated in a brief paragraph without any numerical information on the incidence of adverse events and without any information regarding adverse events in patients taking the comparator.

We believe that the best way to convey information about the frequency of adverse events in large, identical, and well-conducted randomized studies is to provide a simple frequency table of the results of those trials for the NDA drug and comparator agents, which we originally proposed. This approach will enhance medical decision-making by providing physicians with additional, reliable information about adverse events that is not included in FDA's proposed revisions.

InKine's labeling approach is clearly contemplated by FDA's own regulations at 21 CFR § 201.57(g)(1), which states that the labeling shall "list the adverse reactions that occur with the drug *and with drugs in the same pharmacologically active and chemically related class*, if applicable." (Emphasis added). Paragraphs (2) and (4) indicate that data for comparator agents may be displayed in labeling if the studies performed were well-controlled, as InKine's were.

We note that two NMEs recently approved by your division, Colazal® (balsalazide, approved 7/18/00) and Lotronex® (alosetron, approved 2/9/00), have labeling which includes a table of adverse events for both the drug and the comparator agent in the pivotal trials (see attached). Indeed, this sort of table occurs in the labeling for many drugs approved throughout CDER. Notably, the comparator group for balsalazide included only 35 patients (just 13.5% of the balsalazide treated group, which included 259 patients). On the other hand, the comparator group in InKine's studies included 432

patients, essentially equal to the Visicol group (427 patients). If the balsalazide comparator data are appropriate for labeling, certainly the Visicol comparator data must be appropriate for labeling.

InKine's approach to the presentation of adverse event information is consistent with FDA's recent draft guidance on the "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics", issued in May 2000. Section II.B.3. indicates that a tabular display in the preferred method of displaying the common adverse events and "is intended to present the best available quantitative display of the relatively common adverse reactions." This provision goes on to state that the table should preferably be based on placebo-controlled or dose-response studies if they are adequate in size. **Otherwise, the table should be based on active control studies.**

In the development of Visicol, no placebo-controlled studies were done because they were not ethical or feasible. The one dose response study was quite small, and included about 30 patients in each of 3 dosing groups. In contrast, the two identical well-controlled pivotal trials included a total of 427 patients who received Visicol at our recommended dose and another 432 patients who received a marketed PEG-salt solution at the dose recommended in its labeling. These two large active-controlled studies, which were highly consistent in their safety findings, are by far the best source of adverse event information for a tabular display, and are source of the data in the table proposed by InKine.

The guidance goes on to describe the organization and presentation of data in the tabular display in Section III. The guidance there states that,

> "**Comparator Adverse Reaction Data:** Adverse reaction rates from placebo or other comparator arms (e.g., active control, different dosage groups) should be included in the table unless inclusion of such rates would be misleading (for example, if a suboptimal or excessive dose of an active comparator was used) or would constitute or imply an unfair or unsubstantiated comparative safety claim."

Because none of the listed exceptions apply here, it is wholly appropriate and consistent with FDA's own guidance and practice over the years to present information on common adverse events in a table which includes data for Visicol and the comparator arm in InKine's pivotal trials. Thus, InKine's approach to the display of comparative adverse event information is supported by FDA's regulations, the Agency's new draft guidance, and the practice within CDER, including your Division.

We also note that the CDER website indicates that recently approved labeling for Prevacid® (lansoprazole, labeling approved 7/6/99, but not yet available online) includes a superiority claim over ranitidine in the clinical studies section. Accordingly, we have

inserted a safety superiority claim over PEG-salt solution into our clinical studies section, based on our study data.

Thank you for your consideration. Please do not hesitate to contact me directly if you have any questions regarding this letter. We look forward to working with your Division to finalize our labeling.

InKine formally requests that all information presented in this letter and NDA Amendment is held in strict confidence at the Agency. The material presented in this letter and amendment may not be disseminated to the public through the Freedom of Information Act or any other means without the prior written authorization of InKine.

Sincerely yours,

Martin Rose, M.D., J.D.
Senior Vice President
Clinical Research and Regulatory Affairs

Enclosures