CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-903

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

N-000 C

NEW CORRESP

DUPLICATE

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

RECEIVED
MAR 24 2006
CDER/CDR

March 16, 2006

Norman Stockbridge, M.D., Ph.D., Director
Food and Drug Administration
Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

RECEIVED
MAR 27 2006
CDER White Oak DR1

RE: NDA 21-903

Dear Dr. Stockbridge:

NDA 21-903

21 CFR 314.50(i)(1)(ii): No Relevant Patents

In the opinion and to the best knowledge of Farmacon-IL, LLC, there are no patents that claim the drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drugs.

Respectfully submitted,

Laszlo L. Darko

Laszlo L. Darko, Ph.D.
Managing Partner

Department of Health and Human Services
Food and Drug Administration

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

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

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-903

NAME OF APPLICANT / NDA HOLDER
Farmacon-IL, LLC

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

TRADE NAME (OR PROPOSED TRADE NAME)
NeoProfen

ACTIVE INGREDIENT(S)
R,S-Ibuprofen

STRENGTH(S)
10 mg/mL

RECEIVED
SEP 01 2005
CDR / CDER

DOSAGE FORM
intravenous (iv)

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

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

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

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

1. GENERAL

a. United States Patent Number
6,342,530

b. Issue Date of Patent
January 29, 2002

c. Expiration Date of Patent
11/14/2020

d. Name of Patent Owner
Farmacon-IL, LLC

Address *(of Patent Owner)*
1071 Post Road East

City/State
Westport, Connecticut

ZIP Code
06880

FAX Number *(if available)*
203/222-8820

Telephone Number
203/222-8801

E-Mail Address *(if available)*
ldarko@FarmaconInc.com

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

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

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

1-067

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 1, 8, 9, 10, 11, 18, 19, 20	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* [redacted]	

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Laura L Darko	July 20, 2005

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

Check applicable box and provide information below.

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

Name Farmacon-IL, LLC	
Address 1071 Post Road East	City/State Westport, Connecticut
ZIP Code 06880-5361	Telephone Number 203/222-8801
FAX Number *(if available)* 203/222-8820	E-Mail Address *(if available)* ldarko@FarmaconInc.com

Department of Health and Human Services
Food and Drug Administration

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

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

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-903

NAME OF APPLICANT / NDA HOLDER
Farmacon-IL, LLC

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

TRADE NAME (OR PROPOSED TRADE NAME)
NeoProfen

ACTIVE INGREDIENT(S)
R,S-Ibuprofen

STRENGTH(S)
10 mg/ml

RECEIVED
SEP 0 1 2005
CDR / CDER

DOSAGE FORM
Intravenous (iv)

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

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

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

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

1. GENERAL

a. United States Patent Number
5,895,789

b. Issue Date of Patent
4/20/1999

c. Expiration Date of Patent
8/27/2015

d. Name of Patent Owner
Dompe' SpA

Address *(of Patent Owner)*

City/State
L'Aquila, ITALY

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

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

Address *(of agent or representative named in 1.e.)*
Armstrong, Westerman Hattori, McLeland & Naughton

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1-056

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

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☒ No

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

NA

2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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

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

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1. Composition 10. Process	☐ Yes	☒ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Patent claims pharmaceutical, composition and preparation of ibuprofen lysine and other NSAIDs salt by a much more circumvent method.

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Laurko I Darko	July 20, 2005

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

Check applicable box and provide information below.

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

Name Farmacon-IL, LLC	
Address 1071 Post Road East	City/State Westport, Connecticut
ZIP Code 06880-5361	Telephone Number 203/222-8801
FAX Number *(if available)* 203/222-8820	E-Mail Address *(if available)* ldarko@FarmaconInc.com

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

NDA 21-903
Paragraph IV Certification

I, Laszlo L. Darko, certify that Patent 6,342,530 will not be infringed by the manufacture, use or sale of NeoProfen for which this application is submitted as it is the Applicant's patent.

Laszlo L Darko July 29, 2005

Laszlo L. Darko, Ph.D. Date
Managing Partner
Farmacon-IL, LLC

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

NDA 21-903
Patent Certification Statement

The applicant of NDA 21-903, Farmacon-IL, LLC, will comply with the requirements under 314.52(a) with respect to providing a notice to the patent owner representative, Armstrong and Partners, Washington, DC, that Farmacon-IL, LLC has certified to the FDA that US Patent 5,895,789 will not be infringed by the manufacture, use or sale of ibuprofen-l-lysine iv for the early treatment of patent ductus arteriosus.

Laszlo L Darko July 21, 2005

Laszlo L. Darko, Ph.D. Date
Managing Partner
Farmacon-IL, LLC

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

July 21, 2005

James E. Armstrong, III, Esq.
Armstrong, Kratz, Quintos, Hanson & Brooks, LLP
Suite 1000
1725 K Street, N.W.
Washington, DC 2006

Re: U.S. Patent 5,895,789
"Parenteral pharmaceutical compositions containing ammoniomalkyl salts of 2-arylpropionic acids"
Dompe' SpA, L'Aquila, Italy

Dear Sir:

By this letter, I would like to serve notice that Farmacon-IL, LLC will submit a New Drug Application (NDA) to the U.S. Food and Drug Administration and as part of the process, we will attach a Paragraph IV Certification which certifies that the above referenced patent will not be infringed by the manufacture, use or sale of ibuprofen-l-lysine iv for [redacted] patent ductus arteriosus (PDA). The composition, manufacture and use of this product is covered in Farmacon-IL, LLC's patent No. 6,342,530, issued January 29, 2002. Further, we have an Orphan Drug Designation for this product use for said indication.

If you have any comments or questions, please feel free to reach me at 203/222-8801 or email at ldarko@FarmaconInc.com.

Respectfully yours,

Laszlo L Darko

Laszlo L. Darko, Ph.D.
Managing Partner

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

NDA 21-903
Paragraph IV Certification

I, Laszlo L. Darko, certify that Patent 5,895,789 will not be infringed by the manufacture, use or sale of NeoProfen for which this application is submitted.

Laszlo L Darko July 21, 2005

Laszlo L. Darko, Ph.D. Date
Managing Partner
Farmacon-IL, LLC

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

The undersigned declares that Patent No. 6,342,530 covers the formulation, composition, and/or method of use of NeoProfen. The Product is the subject of this application for which approval is being sought.

Laszlo L Darko July 20, 2005

Laszlo L. Darko, Ph.D. Date
Managing Partner
Farmacon-IL, LLC

EXCLUSIVITY SUMMARY

NDA # 21-903 SUPPL # HFD # 110

Trade Name NeoProfen 10/mg/mL IV Injection

Generic Name ibuprofen lysine

Applicant Name Farmacon-IL, LLC

Approval Date, If Known April 13, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

The applicant requested Pediatric Exclusivity; however, the Division did not issue a Pediatric Written Request.

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

YES ☐ NO ☒

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

N/A; a Pediatric Written Request was not issued.

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 17-463 Motrin (ibuprofen) Tablet; reference listed drug

NDA# 19-842 Motrin (ibuprofen) Suspension; reference listed drug

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

FCR-00-01/CB88; "A Randomized, Double-Blind Study of Ibuprofen Lysine Intravenous Solution in Premature Infants for the Early Treatment of PDA"

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	FCR-00-01/CB88	YES ☐	NO ☒
Investigation #2		YES ☐	NO ☐

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

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

Investigation #1	FCR-00-01/CB88	YES ☐	NO ☒
Investigation #2		YES ☐	NO ☐

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

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

FCR-00-01/CB88; "A Randomized, Double-Blind Study of Ibuprofen Lysine Intravenous Solution in Premature Infants for the Early Treatment of PDA"

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

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

Investigation #1		!
		!
IND # 58,997	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Daryl Allis
Title: Regulatory Health Project Manager
Date: April 5, 2006

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

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

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

/s/

Norman Stockbridge
4/13/2006 11:01:16 AM

Farmacon-IL, LLC
1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

August 4, 2005

Norman Stockbridge, MD, Director
CDER/Cardio Renal Drug Products Division
Food and Drug Administration
Attn: Document Control Room, HFD-110
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA #21-903 – Pediatric Exclusivity

Dear Doctor Stockbridge:

We are in the process of submitting an application (NDA# 21-903), under Section 505(b)(2), for marketing approval of ibuprofen lysine iv solution for [redacted] patent ductus arteriosus (PDA). We did not receive a Written Request from the Agency to study the drug for this indication in pediatric population, under Section 505(a) of the Food, Drug & Cosmetic Act, although the drug would be eligible to receive it. The applicant respectfully requests the Cardio Renal Drug Products Division to issue a written request, prior to our submission of the NDA (end of August, 2005), so the Pediatric Exclusivity could be claimed by Farmacon-IL, LLC.

Sincerely,

Laszlo L. Darko

Laszlo L. Darko, Ph.D.
Managing Partner

AMENDED PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-903 **Supplement Type (e.g. SE5):** N/A **Supplement Number:**

Stamp Date: September 1, 2005 **Action Date:** April 13, 2006

HFD -110 **Trade and generic names/dosage form:** NeoProfen (ibuprofen lysine) 10 mg/mL IV Injection

Applicant: Farmacon-IL, LLC **Therapeutic Class:** 2 & 3/P

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: Closure of patent ductus arteriosus [redacted]

Note: NeoProfen (ibuprofen lysine) has been granted orphan drug designation, and therefore, is exempt from all requirements set forth under the Pediatric Research Equity Act of 2003. This NDA, however, includes the data from a clinical trial in premature neonates weighing from 500 to 1500 g, who were no more than 32 weeks gestational age.

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

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: **NDA 21-903**
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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

/s/

Daryl L. Allis
4/13/2006 11:18:12 AM
Amended Pediatric Page on 4/13/06: Orphan Drug designation

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-903 **Supplement Type (e.g. SE5):** N/A **Supplement Number:**

Stamp Date: September 1, 2005 **Action Date:** March 1, 2006

HFD-110 **Trade and generic names/dosage form:** NeoProfen (ibuprofen-L-lysinate) 10mg/mL IV Injection

Applicant: Farmacon-IL, LLC **Therapeutic Class:** 3/P

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: [redacted] patent ductus arteriosus [redacted]

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

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

X **No: Please check all that apply:** X **Partial Waiver** ____ **Deferred** ____ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.** >1	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.** 16	**Tanner Stage**	

Reason(s) for partial waiver:

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

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg 0.5 mo._____ yr._____ Tanner Stage_____
Max_____ kg 1 mo._____ yr._____ Tanner Stage_____

Comments: Study included premature neonates ≤ 30-weeks gestation weighing from 500 to 1000 gm.

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}

Daryl Allis, RN, MSN, FNP
Regulatory Project Manager

cc: NDA 21-903
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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

/s/

Daryl L. Allis
11/8/2005 10:46:38 AM

Farmacon-IL, LLC
1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

Debarment Certification

I, Laszlo L. Darko, certify that I did not and will not use the services, in any capacity, of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 21-903).

Laszlo L Darko — August 30, 2005

Laszlo L. Darko, PhD
Managing Partner

Date

1-094

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted], who participated as a clinical investigator in the submitted study [redacted], is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☒ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Laszlo L. Darko, PhD	Managing Partner
FIRM / ORGANIZATION Farmacon-IL, LLC	
SIGNATURE Laszlo L Darko	DATE 8/1/05

Paperwork Reduction Act Statement

1-108

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

1-109

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	- PLEASE SEE ATTACHED LIST OF INVESTIGATORS	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Laszlo L. Darko, PhD	Managing Partner
FIRM / ORGANIZATION: Farmacon-IL, LLC	
SIGNATURE: Laszlo L Darko	DATE: 8/1/05

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1-105

Created by: PSC Media Arts Branch (301) 443-1090 EF

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	[redacted]	[redacted]
	SAME:	[redacted]

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Laszlo L. Darko, PhD	Managing Partner
FIRM / ORGANIZATION: Farmacon-IL, LLC	
SIGNATURE: Laszlo L Darko	DATE: 7/27/05

Paperwork Reduction Act Statement

1-103

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
[redacted]	[redacted]
[redacted]	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Laszlo L. Darko, PhD	Managing Partner
FIRM / ORGANIZATION: Farmacon-IL, LLC	
SIGNATURE: Laszlo L Darko	DATE: 7/27/05

Paperwork Reduction Act Statement

1-100

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

Allis, Daryl

From: Peat, Raquel
Sent: Wednesday, March 15, 2006 12:12 PM
To: Allis, Daryl; Colangelo, Kim M
Cc: Fromm, Edward J
Subject: RE: 505(b)(2) applications

Hi Daryl:
Thank you so very much for the update. Based on the information that you have provided in regards to the ibuprofen referenced in the published literature, we are requesting that you notify the applicant to submit a no relevant patent certification statement. Basically, the statement states that to the best of their knowledge, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted. Once the applicant has submitted this information, you are cleared to act on this application by the IO, ORP and OCC.

Also, please let us know the action date once the division has decided on this.

Many thanks!
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

---

From: Allis, Daryl
Sent: Monday, March 13, 2006 8:39 AM
To: Peat, Raquel; Colangelo, Kim M
Cc: Fromm, Edward J
Subject: FW: 505(b)(2) applications

Raquel and Kim,

NDA 21-903 NeoProfen (ibuprofen lysine) 10 mg/mL Injection

The Division issued an approvable (AE) letter on 3/1/06 for this 505b2 NDA. We have completed all reviews and are nearing final labeling negotiations. I expect that the Division will issue an approval (AP) letter within 1-3 weeks.

As you recall, I have entered the amended 505b2 checklist in DFS, as you requested.

Please advise me when you have cleared this application.

Thanks,
Daryl

RHPM Overview for NDA 21-903 Resubmission
NeoProfen® (ibuprofen lysine) 10 mg/mL Injection
April 13, 2006

Sponsor:	Farmacon-IL, LLC
Type:	505(b)(2)/2 (new salt) & 3 (new formulation)/P
Receipt Date:	September 1, 2005
Resubmission Date:	Letter date April 7, 2006, received April 12, 2006
User Fee Goal Date:	June 12, 2006

Letter Issued:	Approval: April 13, 2006
Final Draft Labeling:	Carton and Vial Labels submitted March 14, 2006 Electronic content of labeling received April 12, 2006

Background
This new drug application (NDA # 21-903) was submitted by Farmacon-IL, LLC (Farmacon) in order to obtain marketing approval for NeoProfen® (ibuprofen lysine) 10 mg/mL Injection for the indication of [redacted]. The Agency granted both Orphan Drug status and Fast Track designation for NeoProfen®. The sponsor received User Fee exception based on their Orphan Drug designation. This NDA was granted Priority Review status.

The Division issued an approvable letter for this NDA on March 1, 2006 based on our request that Farmacon provide additional information to show what clinical events accompanied investigators' decisions to institute rescue therapy when they did not check off specific criteria (bounding pulses, hyperdynamic precordium, pulmonary edema, increased cardiac silhouette, systolic murmur), and the need to reach final labeling agreements.

Project Management Overview: Resubmission following an approvable action

Secondary Medical Review
Farmacon's submission of February 23, 2006 (not reviewed fully during the first review cycle) provided sufficient clinical information indicating the need for rescue therapy. Dr. Karkowsky's review of March 1, 2006 stated the signs that necessitated rescue therapy were largely driven by the assessment of the neonatologist, who deemed the shunting significant. Approximately 30% of those infants who were contemplated for rescue did not subsequently receive rescue therapy. Of those contemplated for rescue, 80% had significant shunting. There was no assessment of growth, development, and more importantly, a neuro-cognitive assessment at 18-months adjusted gestational-age.

Labeling
The Division and Farmacon agreed upon the electronic final content of labeling that was received on April 12, 2006. The final carton and vial labels were submitted electronically on March 14, 2006. Dr. Cooper's memo of April 10, 2006 stated that the carton and vial labels are acceptable. Farmacon agreed to revise the established name and formulation [(ibuprofen lysine) Injection] on the carton and vial labels, at the time of printing the final printed labeling, to be consistent with the package insert.

Patent Information
The Immediate Office, Office of Regulatory Policy [redacted] notified the Division that they cleared this 505(b)(2) for an approval regulatory action providing that Farmacon submit a "No Relevant Patent" certification statement per 21 CFR 314.50(i)(1)(ii): No Relevant Patents. Farmacon submitted their statement on March 16, 2006.

Pediatric Rule
NeoProfen (ibuprofen lysine) Injection has been granted orphan drug designation; therefore, the sponsor is exempt from all requirements set forth under the Pediatric research Equity Act of 2003. An amended Pediatric Page has been filed in the Division Filing System.

Project Management Overview of the Original NDA

Secondary Medical Review
Dr. Karkowsky's memo of March 1, 2006, supports the approval recommendation for NeoProfen at a regimen of 10 mg/kg first dose, followed at 24 and 48 hours by doses of 5 mg/kg. Its use should be [redacted]. Approval is based on a prospective, randomized, clinical trial in which NeoProfen, at the above regimen was administered as a prophylaxis to premature infants with echocardiographic evidence of a PDA, but who were asymptomatic at the time of enrollment. There is convincing evidence that the use of NeoProfen facilitates closure of the ductus. There is also suggestive evidence that the closure is associated with a decrease in signs associated with a hemodynamically significant shunting.

There is insufficient information as to long-term outcomes after NeoProfen treatment to recommend its use as a prophylactic treatment for severely premature neonates. There is no indication that mortality, irreversible morbidity or the hospital course of the premature infants was altered by the prophylactic use of NeoProfen. Given the uncertainty of the long-term risk and benefit, the use of NeoProfen as a prophylactic treatment exposes a large number of premature infants, perhaps unnecessarily to the risks attendant to its use. It is more prudent to limit NeoProfen's use to the treatment of symptomatic premature neonates.

Medical Review
In her review dated January 20, 2006, Dr. Gordon recommended approval for the use of ibuprofen lysine for the closure of symptomatic patent ductus arteriosus in premature infants weighing between 500 and 1000 kg, inclusive, up to 30 weeks gestational-age, and less than 72 hours of age based on one pivotal study and two supportive studies that have demonstrated ibuprofen lysine to be effective in closing asymptomatic as well as symptomatic patent ductus arteriosus (PDA) in premature infants. Similar to indomethacin, the only drug currently approved for the treatment of symptomatic PDA, ibuprofen induces oliguria with concomitant increases in BUN and serum creatinine. This effect on the kidney appears to be transient. Minor anemia is also associated with the use of ibuprofen. The relationship between the use of ibuprofen in premature infants and the occurrence of intraventricular hemorrhage remains unknown. Overall, there are no convincing data showing the benefit of using ibuprofen prior to the development of symptomatic PDA.

Deficiencies (to be obtained from mandatory post marketing studies): long term (one year or longer) outcome data evaluating long term mortality as well as growth and development in infants who received ibuprofen because of a symptomatic PDA. Dose response studies are recommended, but may not be possible with limited sample sizes.

Conclusions about the superiority or inferiority of ibuprofen in safety and efficacy compared to indomethacin are not possible [redacted] Long term outcome data regarding the kidney as well as other organs such as the brain are unknown and should be pursued by the sponsor. Considering the adverse events associated with ibuprofen, the lack of long term outcome data, the high spontaneous closure rates, the lack of obvious harm when treatment is delayed

until the onset of symptoms, and the satisfactory results with closing symptomatic PDA with treatment, prophylactic use is not recommended.

The 120-day safety update for the open-label, uncontrolled trial (treatment protocol) was integrated into the Medical Review (page 3). This treatment protocol permitted investigators who were not part of the clinical development program to treat premature infants with ibuprofen l-lysine IV. The information provided in this safety update does not alter the overall conclusions of the NDA review.
In a memo dated February 22, 2006, Dr. Gordon stated that the financial disclosure statement provided by the sponsor indicated no unusual activity.

Statistical Review
In his review dated December 7, 2005, Dr. Bai stated that the primary analysis in the study is statistically significant. The statistically significant lower proportion of infants who received ibuprofen lysine IV required rescue treatment for PDA through Study Day 14 compared to infants in the placebo group (25.0% versus 48.5%). The logistic regression with factors of treatment group and site provided a significant p-value of 0.0028. The results of this study demonstrated that ibuprofen lysine IV therapy initiated within the first 72 hours of life is significantly more effective than placebo for treatment of PDA in very low birth weight infants (<1000g) with non-symptomatic PDA.

Clinical Pharmacology/Biopharmaceutical Review
In her review dated January 26, 2006, Dr. Mishina stated that the Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-903 and finds the clinical pharmacology section and biopharmaceutics sections acceptable provided labeling comments are adequately addressed.

Ibuprofen lysine was administered as an IV 10 mg/kg dose followed with two doses of 5 mg/kg per day to premature newborn infants with non-symptomatic PDA (mean age at receipt of first dose was 37.5 hours and the mean birth weight was 791 g). The mean (SD) ibuprofen concentrations achieved at nominal sampling times of 1, 24, 48 and 120 hours after the start of the first 10 mg/kg infusion were 34.7 (9.0), 24.7 (7.5), 27.5 (14.0), and 13.5 (11.5) pg/mL, respectively. The population average ibuprofen clearance and volume of distribution values for premature infants on day of birth were 2.96 mL/kg/h (CV 60%) and 320 mL/kg (CV 14%), respectively. Ibuprofen clearance in premature infants significantly correlated with post-natal age; it increased rapidly over time by 0.5 mL/kg/h per day, probably reflecting the maturation of metabolic capacity. The ibuprofen elimination in neonates was markedly slower than in adults.

In her review dated February 21, 2006, Dr. Mishina stated that the Office of Clinical Pharmacology and Biopharmaceutics finds the assay validation is acceptable.

Non-Clinical Review
In his review dated March 1, 2006, Dr. Resnick stated that this NDA contains numerous publications bearing on the pharmacokinetics, pharmacodynamics and toxicity of ibuprofen administered orally to various species, including summaries of carcinogenicity, reproductive toxicity and genetic toxicity studies. Few, if any, of the toxicology studies include sufficient detail regarding results and methodology to permit independent review. However, considering that the Agency has previously found this drug to be safe and effective for chronic oral use as an analgesic and anti-inflammatory agent, such information is not needed to support the safety of the short-term IV treatment of premature neonates.

Dr. Resnick recommended that the sponsor should monitor the growth and development of the drug-treated infants that had been entered into their clinical trials or agree to a prospective evaluation as a long-term phase 4 commitment. Because of the expected difficulty in successfully following up the human neonate beyond the first few years of life, it is suggested that the sponsor attempt to identify or develop an

animal model that will allow exploration of the long-term effects of short-term exposure of the premature neonate to NeoProfen. We do not consider the latter recommendation to constitute an approvability issue.

Chemistry Review
In the reviews dated February 8 and 24, 2006, Dr. Cooper recommended approval for this NDA. There are no outstanding issues with regard to chemistry, manufacturing and controls. She recommended that the approval letter request a retest date of [redacted] for the drug substance when stored at controlled room temperature and an expiration date of 24 months is granted for the drug product when stored at controlled room temperature (20 — 25°C with excursions permitted to 15 — 30°C), protected from light. There are no Phase 4 commitments, agreements or risk management steps.

In addition, Dr. Cooper recommended the following revisions for the carton and container labels:

- The current storage statement on the Carton and Vial labels should be replaced with the following:

  Store at 20 – 25°C (68 – 77°F); excursions permitted 15 – 30°C (59 – 86°F).
  Store vials in carton until use.

- If the drug was further diluted in the clinical studies, please put a dilution statement on the carton and vial labels.

The overall evaluation from the Office of Compliance for cGMP compliance is acceptable.

Microbiology Review
In his reviews dated February 14 and 28, 2006, Dr. Mello stated that the NDA for NeoProfen (ibuprofen lysine) is recommended for approval from a microbiology product quality standpoint.

DSI
In their report dated February 9, 2006, Drs. Gershon and Ball stated that, in general, all three sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. One site was issued an FDA Form 483 for not maintaining informed consent documents for three subjects who were screen failures for the study. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent. Data submitted in support of this NDA for the PDA indication appear acceptable. If conclusions changes after receipt and review of full inspection results for Dr. VanOvermier's site, an inspection summary addendum will be generated.

Pediatric Rule
In our letter of December 5, 2005, the Division granted a partial waiver for pediatric studies in patients from 1-month to 16-years of age for NeoProfen (ibuprofen lysine) for the early treatment of PDA in premature neonates because this condition exists predominately in premature infants. In addition, we noted that Farmacon-Il, LLC fulfilled the pediatric study requirement for this NDA for pediatric patients ≤30-weeks gestation weighing 500 to 1000 grams.

In our letter of August 19, 2005, the Division stated that we did not plan to issue a Written Request compatible with Farmacon's development program that they have undertaken.

Labeling
Final draft labeling agreements were not reached during this regulatory review cycle for this NDA.

Advisory Committee Meeting
This data provided in this NDA were not presented before an Advisory Committee.

Project Manager's Summary: Resubmission following an approvable action
To my knowledge, there are no issues that might prevent taking regulatory action for this NDA.

Daryl Allis, R.N., M.S., F.N.P.
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/

Daryl L. Allis
4/13/2006 10:50:35 AM
CSO

RPM overview for the NDA: resubmission following the approvable action of March 1, 2006.

Deficiencies (to be obtained from mandatory post marketing studies): long term (one year or longer) outcome data evaluating long term mortality as well as growth and development in infants who received ibuprofen because of a symptomatic PDA. Dose response studies are recommended, but may not be possible with limited sample sizes.

Conclusions about the superiority or inferiority of ibuprofen in safety and efficacy compared to indomethacin are not possible [redacted] Long term outcome data regarding the kidney as well as other organs such as the brain are unknown and should be pursued by the sponsor. Considering the adverse events associated with ibuprofen, the lack of long term outcome data, the high spontaneous closure rates, the lack of obvious harm when treatment is delayed until the onset of symptoms, and the satisfactory results with closing symptomatic PDA with treatment, prophylactic use is not recommended.

The 120-day safety update for the open-label, uncontrolled trial (treatment protocol) was integrated into the Medical Review (page 3). This treatment protocol permitted investigators who were not part of the clinical development program to treat premature infants with ibuprofen l-lysine IV. The information provided in this safety update does not alter the overall conclusions of the NDA review.

In a memo dated February 22, 2006, Dr. Gordon stated that the financial disclosure statement provided by the sponsor indicated no unusual activity.

Statistical Review
In his review dated December 7, 2005, Dr. Bai stated that the primary analysis in the study is statistically significant. The statistically significant lower proportion of infants who received ibuprofen lysine IV required rescue treatment for PDA through Study Day 14 compared to infants in the placebo group (25.0% versus 48.5%). The logistic regression with factors of treatment group and site provided a significant p-value of 0.0028. The results of this study demonstrated that ibuprofen lysine IV therapy initiated within the first 72 hours of life is significantly more effective than placebo for treatment of PDA in very low birth weight infants (<1000g) with non-symptomatic PDA.

Clinical Pharmacology/Biopharmaceutical Review
In her review dated January 26, 2006, Dr. Mishina stated that the Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-903 and finds the clinical pharmacology section and biopharmaceutics sections acceptable provided labeling comments are adequately addressed.

Ibuprofen lysine was administered as an IV 10 mg/kg dose followed with two doses of 5 mg/kg per day to premature newborn infants with non-symptomatic PDA (mean age at receipt of first dose was 37.5 hours and the mean birth weight was 791 g). The mean (SD) ibuprofen concentrations achieved at nominal sampling times of 1, 24, 48 and 120 hours after the start of the first 10 mg/kg infusion were 34.7 (9.0), 24.7 (7.5), 27.5 (14.0), and 13.5 (11.5) pg/mL, respectively. The population average ibuprofen clearance and volume of distribution values for premature infants on day of birth were 2.96 mL/kg/h (CV 60%) and 320 mL/kg (CV 14%), respectively. Ibuprofen clearance in premature infants significantly correlated with post-natal age; it increased rapidly over time by 0.5 mL/kg/h per day, probably reflecting the maturation of metabolic capacity. The ibuprofen elimination in neonates was markedly slower than in adults.

In her review dated February 21, 2006, Dr. Mishina stated that the Office of Clinical Pharmacology and Biopharmaceutics finds the assay validation is acceptable.

Non-Clinical Review
In his review dated March 1, 2006, Dr. Resnick stated that this NDA contains numerous publications bearing on the pharmacokinetics, pharmacodynamics and toxicity of ibuprofen administered orally to various species, including summaries of carcinogenicity, reproductive toxicity and genetic toxicity studies. Few, if any, of the toxicology studies include sufficient detail regarding results and methodology to permit independent review. However, considering that the Agency has previously found this drug to be safe and effective for chronic oral use as an analgesic and anti-inflammatory agent, such information is not needed to support the safety of the short-term IV treatment of premature neonates.

Dr. Resnick recommended that the sponsor should monitor the growth and development of the drug-treated infants that had been entered into their clinical trials or agree to a prospective evaluation as a long-term phase 4 commitment. Because of the expected difficulty in successfully following up the human neonate beyond the first few years of life, it is suggested that the sponsor attempt to identify or develop an animal model that will allow exploration of the long-term effects of short-term exposure of the premature neonate to NeoProfen. We do not consider the latter recommendation to constitute an approvability issue.

Chemistry Review
In the reviews dated February 8 and 24, 2006, Dr. Cooper recommended approval for this NDA. There are no outstanding issues with regard to chemistry, manufacturing and controls. She recommended that the approval letter request a retest date of [redacted] for the drug substance when stored at controlled room temperature and an expiration date of 24 months is granted for the drug product when stored at controlled room temperature (20 — 25°C with excursions permitted to 15 — 30°C), protected from light. There are no Phase 4 commitments, agreements or risk management steps.

In addition, Dr. Cooper recommended the following revisions for the carton and container labels:

- The current storage statement on the Carton and Vial labels should be replaced with the following:

  Store at 20 – 25°C (68 – 77°F); excursions permitted 15 – 30°C (59 – 86°F).
  Store vials in carton until use.

- If the drug was further diluted in the clinical studies, please put a dilution statement on the carton and vial labels.

The overall evaluation from the Office of Compliance for cGMP compliance is acceptable.

Microbiology Review
In his reviews dated February 14 and 28, 2006, Dr. Mello stated that the NDA for NeoProfen (ibuprofen lysine) is recommended for approval from a microbiology product quality standpoint.

DSI
In their report dated February 9, 2006, Drs. Gershon and Ball stated that, in general, all three sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. One site was issued an FDA Form 483 for not maintaining informed consent documents for three subjects who were screen failures for the study. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent. Data submitted in support of this NDA for the PDA indication appear acceptable. If conclusions changes after receipt and review of full inspection results for Dr. VanOvermier's site, an inspection summary addendum will be generated.

Pediatric Rule
In our letter of December 5, 2005, the Division granted a partial waiver for pediatric studies in patients from 1-month to 16-years of age for NeoProfen (ibuprofen lysine) for the early treatment of PDA in premature neonates because this condition exists predominately in premature infants. In addition, we noted that Farmacon-II, LLC fulfilled the pediatric study requirement for this NDA for pediatric patients ≤30-weeks gestation weighing 500 to 1000 grams.

In our letter of August 19, 2005, the Division stated that we did not plan to issue a Written Request compatible with Farmacon's development program that they have undertaken.

Labeling
Final draft labeling agreements were not reached during this regulatory review cycle for this NDA.

Advisory Committee Meeting
This data provided in this NDA were not presented before an Advisory Committee.

Project Manager's Summary
To my knowledge, there are no issues that might prevent taking regulatory action for this NDA. Before this application may be approved, the sponsor will need to supply information to show what clinical events accompanied investigator's decisions to institute rescue therapy when they did not check off specific criteria; the sponsor's submission of February 23, 2006, may address this deficiency. In addition, final labeling agreements need to be reached.

Daryl Allis, R.N., M.S., F.N.P.
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/

Daryl L. Allis
3/2/2006 07:57:16 AM
CSO

Amended 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): N/A

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 an injectable foumulation for ibuprofen lysine indicated for the early treatment of patent ductus arteriosus in preterm infants who weigh between 500 and 1750 g and are less than 32 weeks gestational age.

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.)

N/A; The patents provided with the NDA are not listed in the Orange Book.

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

(Paragraph I certification)
Patent number(s):

☐ 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# 59,778 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/

Daryl L. Allis
2/28/2006 09:38:05 AM
CSO

Appendix B for the 505b2 regulatory review was amended as requested.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 01/24/2006

TO: Daryl Allis, Regulatory Project Manager
Maryann Gordon, M.D. Clinical Reviewer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Sharon K. Gershon, Pharm.D., GCP 2 Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-903

APPLICANT: Farmacon IL, LLC

DRUG: Neoprofen (Ibuprofen-L-lysine) 10mg/ml IV solution

THERAPEUTIC CLASSIFICATION: Priority Review, Orphan designation

INDICATION: [redacted] Patent Ductus Arteriosus (PDA) [redacted]

CONSULTATION REQUEST DATE: 10/24/2005

DIVISION ACTION GOAL DATE: 03/01/2006

PDUFA DATE: 03/01/2006

I. BACKGROUND:

Patent ductus arteriosus (PDA) is a condition where the ductus arteriosus, a blood vessel that allows blood to bypass the baby's lungs before birth, fails to close after birth. Prior to birth, bloodflow in the fetus bypasses its lungs because the fetus gets oxygen through the placenta. After birth, the ductus arteriosus and foramen ovale close because blood must then go to the infant's lungs. PDA occurs in about 1 in 2,000 infants. Premature infants (any infant born before 37 weeks gestation) and those with respiratory distress syndrome are at higher risk. Patients with PDA have a characteristic heart murmur that can be heard with a stethoscope. The diagnosis is confirmed with an echocardiogram. If the patent dutus is not closed, the infant has a risk of developing heart failure or infective endocarditis.

The ductus arteriosus remains patent (open) in about 40% to 80% of very low birth weight infants. Early treatment by intravenous ibuprofen L-lysine (IV Neoprofen) has been suggested in preliminary studies to

close the ductus and shorten hospital stay. This study aimed to determine the effect of early treatment with IV ibuprofen given to the very low birth weight infant with a non-symptomatic patent ductus arteriosus (PDA) at less than 72 hours of life to accelerate and maintain ductal closure, thereby reducing the need for rescue therapy (indomethacin or surgical ligation). The study design was an intent to treat, multicenter, randomized, double blind study with a 3-day treatment course of 10mg/kg, 5mg/kg and 5mg/kg of IV ibuprofen vs. placebo (an approximate n=60/group, total 120 infants) stratified in 2 birth weight categories (500-750 g; 751-1000 g). The primary efficacy outcome was symptomatic PDA treated with indomethacin or by surgery. The presence of a PDA requiring intervention or closure was determined by three or more clinical and physical findings of symptomatic ductus and confirmed by an ECHO.

The protocol audited for this study was: FRC 00-01/CB88 "A Randomized, Double-Blind Study of Ibuprofen L-Lysine Intravenous Solution in Premature Infants for the Early Treatment of PDA."

Drs. Blair Cox (Dallas) and Paul Wozniak (San Diego) were selected as U.S. sites to inspect because they enrolled a large number of U.S. subjects for these studies. Neither clinical investigator had been inspected previously. Dr. Blair Cox died after the last subject was enrolled; Dr. Charles R. Rosenfeld, sub-investigator on the Form 1572, assumed responsibility for this study. Dr Bart Van Overmeire, M.D. PhD, University Hospital Antwerp, Belgium was identified for foreign inspection because he conducted both non-IND supportive studies.

II. RESULTS (by CI Site):

Name of CI	City, State*	County	Protocol No.	Insp. Date	EIR Received Date	Final Classification
Bart Van Overmeire, MD, PhD		Edgegem, Belgium	FRC 00-01/CB88	11/28-12/2/2005	Pending	NAI, pending DSI review
Blair E. Cox/Charles R. Rosenfeld, M.D.	Dallas, Texas		FRC 00-01/CB88	11/28/2005 - 12/02/2005	01/02/2006	NAI
Paul Wozniak, MD	San Diego, CA		FRC 00-01/CB88	12/12/ - 12/16/2005	01/06/2006	VAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # FRC 00-01/CB88

1. **Blair Cox, MD, University of Texas, Southwestern Medical Center, Department of Pediatrics, Dallas, Texas 75390**

a. **What was inspected**: 67 subjects were screened, 27 subjects were randomized and 25 subjects completed the study. An audit of 14 randomized subjects' records and all 17 screen failure records was conducted. Information was verified against source data for the 14 subjects reviewed. Study records were reviewed for informed consent, inclusion/exclusion criteria, questionnaires, and adverse events.

b. **Limitations of inspection**: Blair Cox, M.D., principal investigator for this study passed away on Nov 30, 2004, following completion of the last subject. Charles Rosenfeld, sub-investigator on the FDA 1572, retained duties of the clinical investigator for this investigation.

c. **General observations/commentary**: No Form FDA 483 was issued for this inspection. The information recorded on CRFs was found to be supported by source data. All subject records were found to be compliant with regards to informed consent.

d. **Assessment of data integrity**: Data appear acceptable for consideration in the NDA review process.

2. **Paul Wozniak, MD, University of California, San Diego, 4094 Fourth Avenue, San Diego, CA 92103**

a. **What was inspected**: There were 21 subjects treated in the study at this site. Records for 14 subjects were reviewed in detail. Review included comparison of source records with CRF data and data tables with the assignment. Source records included study team progress notes, study-specific data sheets, and hospital records. Types of data reviewed included 100% informed consent forms, inclusion/exclusion criteria, adverse events and echocardiogram reports.

b. **Limitations to the inspection**: there were no limitations to this inspection

c. **General Observations/commentary**: signed informed consent documents were not observed for three subjects. These 3 subjects were screen failures. Some of the informed consent forms appeared to have parents signature dated by staff.

d. **Assessment of data integrity:** data appear acceptable for consideration in the NDA review decision.

3. **Bart Van Overmeire, M.D., PhD, University Hospital Antwerp, Edgegem, B, 2650, Belgium**

a. **What was inspected**: The site enrolled 25 subjects. Record review of 7 of the 25 subjects was done. Review included looking within the hospital computer system, Case report Forms, hospital records of the subject and mother. Informed consent forms were reviewed for all 25 subjects.

b. **Limitations of inspection**: There were no limitations to this inspection. The receipt of the written EIR from the field investigator is pending. Observations noted here are based on communications and an inspection summary from the field investigator. If conclusion change upon receipt and review of EIR, an inspection summary addendum will be generated.

c. **General Observations**: No FDA Form 483 was issued during this inspection. A review of inclusion criteria was done for the 7 subject charts reviewed, and all appeared adequate. The dosing regimen appeared appropriately done. A review of the CRFs appeared adequate.

d. **Assessment of data integrity**: data appear acceptable in support of the NDA review decision.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general all 3 sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. One site (Wozniak) was issued an FDA Form 483 for not maintaining informed consent documents for 3 subjects who were screen failures for the study. The inspection of documents support that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent. Data submitted in support of this NDA for the PDA indication appear acceptable. If conclusion changes after receipt and review of full inspection results for Dr. Van Overmiere's site, an inspection summary addendum will be generated.

(See appended electronic signature page)

Sharon K. Gershon, Pharm.D.
GCP II Reviewer

CONCURRENCE:

Supervisory comments

(See appended electronic signature page)
Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
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/

Sharon Gershon
2/1/2006 03:23:23 PM
CSO

Leslie Ball
2/9/2006 09:44:51 PM
MEDICAL OFFICER

Minutes of a Meeting

Date of Meeting:	January 6, 2006
NDA Application:	21-903
Drug:	NeoProfen (ibuprofen L lysinate) 10 mg/mL IV Injection
Meeting Type:	Internal
Sponsor:	Farmacon-IL, LLC
Request Date:	N/A; Internal meeting
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Daryl Allis

FDA Attendees:

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Edward Fromm, R.Ph.	Chief, Project Management Staff
Daryl Allis, M.S.N., F.N.P.	Regulatory Health Project Manager
Carol Holquist, R.Ph.	Director, Division of Medication Errors and Technical Support
Tina Tezky, Pharm.D.	Safety Evaluator, DMETS

Background

Farmacon-IL, LLC submitted a trade name review request dated August 4, 2004 for "NeoProfen" or [redacted] for the compound ibuprofen L lysinate 10 mg/mL Injection. The Division of Medication Errors and Technical Support (DMETS) did not recommend the use of either of the proposed trade names because their potential to look and sound similar to Naprosyn, Naproxen and Ibuprofen. The purpose for this internal meeting was to discuss further the proposed trade name NeoProfen.

Discussion Points

The greatest concern expressed by DMETS is the potential for medication errors related to the look-alike similarities between NeoProfen, Naprosyn and Naproxen. They all start with "N", have "pro" in the middle and end with "n." They believe that the similar placement for these overlapping letters increase the risk for medication errors, especially hand written orders. It was noted, on the other hand, that NeoProfen would be available as an IV formulation only, while liquid forms of Naprosyn and Naproxen would be available only as a suspension, and would not resemble an IV formulation. DMETS is also concerned with an increased potential for errors if an alternative dosage form of ibuprofen L lysinate is developed in the future (e.g., a tablet) and marketed with the trade name NeoProfen. DMETS is concerned about an increased potential for errors should the medication be used in off-label indications and different patient populations.

Recommendations/Conclusions

1. This drug would be indicated for use in a high-knowledge environment, and the likelihood for inadvertently giving an oral suspension instead of the intended intravenous formulation to a neonate seemed remote.

2. The Office of Drug Evaluation I and Division of Cardiovascular and Renal Products agreed that the proposed trade name NeoProfen for ibuprofen L lysinate 10 mg/mL IV Injection was acceptable.
3. The Division would notify Farmacon-IL, LLC that the trade name NeoProfen was acceptable.

Meeting Recorder: *(See appended electronic signature page)*
Daryl Allis, M.S.N., F.N.P.

Concurrence Chair: *(See appended electronic signature page)*
Robert Temple, M.D.

Draft	01/10/06	**Final**	01/18/06
RD:			
Tezky	01/11/06		
Holquist	01/11/06		
Fromm	01/12/06		
Unger	01/13/06		
Stockbridge	01/15/06		
Temple	01/18/06		

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

/s/

Daryl L. Allis
1/18/2006 03:59:18 PM

Robert Temple
1/24/2006 08:42:02 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PREA PARTIAL WAIVER GRANTED

NDA 21-903

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, Connecticut 06880-5361

Dear Dr. Darko:

Please refer to your submission dated November 15, 2005, requesting a partial waiver under 505B(a) of the Federal Food, Drug, and Cosmetic Act (the Act) for pediatric studies for NeoProfen (ibuprofen-L-lysinate) 10 mg/mL IV Injection.

We have reviewed your submission and agree that a waiver is justified for pediatric studies in patients from 1-month to 16-years of age for NeoProfen (ibuprofen-L-lysinate) for [redacted] patent ductus arteriosus [redacted] The reason for granting the waiver is because this condition exists predominantly in premature infants.

We note that you have fulfilled the pediatric study requirement for pediatric patients ≤30-weeks gestation weighing 500 to 1000-grams for this application.

If you have questions, please call Mr. Daryl Allis, Regulatory Project Manager, at 301-796-1034.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

Norman Stockbridge
12/5/2005 08:05:29 AM

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

FILING COMMUNICATION

NDA 21-903

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, Connecticut 06880-5361

Dear Dr. Darko:

Please refer to your August 30, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NeoProfen (ibuprofen-L-lysinate) 10 mg/mL Intravenous Injection.

We also refer to your submissions dated August 30, September 19, October 26 and November 1, 2005.

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 October 31, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Additional microbiology data are needed, and portions of the microbiology data are not legible.
2. The Bacteriostasis/Fungistasis test report was for "Ibuprofen" and not for the final drug product ibuprofen-L-lysine (NeoProfen). The latter will be required in the submission.
3. Some of the [redacted] validation studies are nearly three years old. More recent studies, if available, would better support your application.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Microbiological specifications (sterility and bacterial endotoxin) for the final drug product
2. Microbiological methods for routine sterility, bacterial endotoxin testing
3. Environmental monitoring program
4. Bacteriostasis/Fungistasis test report for the final drug product ibuprofen- L-lysine (NeoProfen)
5. Additional recent [redacted] validation studies, if available
6. Resubmit legible copies of the product specific validation verification study for the LAL test and the Bacteriostasis/Fungistasis (B/F) test report

We strongly recommend that you review the following 1994 guidance document (**"Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"**) prior to submitting microbiological information in support of your NDA. In addition, you should be aware that product specific information should be provided in the application and not in the master file of the contract manufacturer [redacted]

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Mr. Daryl Allis, Regulatory Project Manager, at (301) 796-1034.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

Norman Stockbridge
11/10/2005 08:27:55 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-903 Supplement # NA Efficacy Supplement Type SE- N/A

Trade Name: NeoProfen
Established Name: ibuprofen-L-lysinate
Strengths: 10mg/mL Injection

Applicant: Farmacon-IL LLC
Agent for Applicant: Laszlo L. Darko, Ph.D.

Date of Application: August 30, 2005
Date of Receipt: September 1, 2005
Date clock started after UN: N/A
Date of Filing Meeting: October 24, 2005
Filing Date: October 31, 2005
Action Goal Date (optional): User Fee Goal Date: March 1, 2006

Indication(s) requested: [redacted] patent ductus arteriosus [redacted]

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.) 3
Other (orphan, OTC, etc.) Orphan Drug

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: Data sets and labeling were submitted electronically.

- 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, Peds Years NO ☐
  The Division is unable to issue a Written Request based on the submission.

  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 X 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: 59,778

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

- Pre-NDA Meeting(s)? Date(s) Sponsor declined the meeting. 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 ☐
  Trade name not accepted; DMETS comments sent to the sponsor.

- 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?
  NA 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: October 24, 2005

BACKGROUND:

This new drug application (NDA #21-903) was submitted by Farmacon-IL, LLC (Farmacon) to obtain marketing approval for ibuprofen-l-lysine 10mg/mL IV solution for the indication of [redacted] patent ductus arteriosus [redacted] The Agency has granted Orphan Drug status and Fast Track determination for this drug. The Chemistry, Manufacturing and Controls information were presubmitted to the Agency on April 15, 2005.

ATTENDEES:
Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Ellis Unger, M.D., Deputy Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical Officer, HFD-110
Thomas Marciniak, M.D., Team Leader, Medical Officer, HFD-110
Shari, Targum, M.D., Acting Team Leader, Medical Officer, HFD-110
Maryann Gordon, M.D., Medical Officer, HFD-110
Charles Resnick, Ph.D., Team Leader, Pharmacology, HFD-110
Albert DeFelice, Ph.D., Team Leader, Pharmacology, HFD-110
Elena Mishina, Ph.D., Clinical Pharmacologist/Biopharmaceutist, HFD-860
John Lawrence, Ph.D., Acting Team Leader, Statistics, HFD-710
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, HFD-810
Raj Misra, Ph.D., Chemist, HFD-810
Monica Cooper, Ph.D., Chemist, HFD-810
Robert Mello, Ph.D., Microbiologist
Edward Fromm, R.Ph., Chief, Project Management Staff
Daryl Allis, R.N., M.S., F.N.P., Regulatory Health Project Manager, HFD-110

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

Discipline	Reviewer	Expected Date
Medical:	Dr. Gordon	February 01, 2006
Secondary Medical:	Dr. Karkowsky	February 15, 2006
Statistical:	Dr. Bai	January 15, 2006
Pharmacology:	Dr. Resnick	February 01, 2006
Statistical Pharmacology:	N/A	
Chemistry:	Drs. Misra and Cooper	February 01, 2006
Environmental Assessment (if needed):	N/A	
Biopharmaceutical:	Dr. Mishina	January 15, 2006
Microbiology, sterility:	Dr. Mello	February 1, 2006
Microbiology, clinical (for antimicrobial products only):	N/A	
DSI:	Dr. Gershon	January 15, 2006
Regulatory Project Management:	Mr. Allis	
Other Consults:	DDMAC (labeling); ODS (trade name review)	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site inspection needed? YES X NO ☐
  DSI consult sent.
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- 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 X YES ☐ NO ☐

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

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO X

PHARMACOLOGY N/A ☐ FILE X REFUSE TO FILE ☐
Some of the published articles submitted in the NDA are too small to read; the sponsor resubmitted articles that are acceptable.

- GLP inspection needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
  Inspections are completed.
- Microbiology YES X NO ☐
  Additional microbiology data will be listed in the 74-day letter.

ELECTRONIC SUBMISSION:
Any comments: NA

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

☐ The application is unsuitable for filing. Explain why:

X 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.
- X 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. X Convey document filing issues/no filing issues to applicant by Day 74.

Mr. Daryl Allis
Regulatory Project Manager, HFD-110

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):

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 an injectable formulation for ibuprofen-l-lysinate indicated [redacted]

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):

☐ 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): 5,895,789

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): 6,344,479 B1 This patent is held jointly with Farmacon-IL, LLC and Bart Van Overmire [redacted]

☐ 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# 59,778 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/

Daryl L. Allis
11/8/2005 10:25:01 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-903

NDA ACKNOWLEDGMENT

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, Connecticut 06880-5461

Dear Dr. Darko:

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: NeoProfen (ibuprofen lysine) 10 mg/mL Injection

Review Priority Classification: Priority (P)

Date of Application: August 30, 2005

Date of Receipt: September 1, 2005

Our Reference Number: NDA 21-903

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 31, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be March 1, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
Attention: Division of Cardio-Renal Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Edward Fromm
11/7/2005 01:24:26 PM

Farmacon-IL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

Field Copy Certification

Farmacon-IL, LLC, the applicant for NDA 21-903 hereby states that the field copy is a true copy of the technical section of the application as described in Paragraph 314.50(d)(1) contained in the archival and review copies of the application.

Laszlo L Darko August 30, 2005

Laszlo L. Darko, PhD
Managing Partner

Date

1-095

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-903

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, CT 06880-5361

Dear Dr. Darko:

We refer to your correspondence dated 4 August 2005, requesting that FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for Neoprofen (ibuprofen lysine) 10 mg/mL Injectable.

We have reviewed your request and are unable to issue a Written Request based on your submission.

FDA is allowed to issue a Written Request for pediatric studies underway or completed provided that the results have not been submitted and that the trials are what we would have requested prospectively. We have reviewed our various communications with Farmacon-IL, LLC (Farmacon) to determine what the Division would have put into a prospective Written Request. The reviewed documents include minutes of an internal 30-day safety meeting (23 February 2000), minutes of a meeting with Farmacon (12 April 2000), minutes of a teleconference with Farmacon (6 March 2001), the medical and statistical review of a study protocol (13 June 2001), a digest of the medical and statistical comments sent to Farmacon (14 June 2001), a medical and statistical review of a protocol (7 December 2001), a digest of the medical and statistical comments send to Farmacon (10 December 2001), the Division's response to your letter of 25 January 2002 (5 September 2002), minutes of a meeting with Farmacon (28 April 2004), and minutes of a meeting with Farmacon (11 August 2004).

[redacted] have been discussed with you, but the trial you have done is basically a "prevention" trial in premature infants with an uncertain need for surgical correction of a patent ductus. The Division has said that a single trial with $p<0.01$ on a primary measure of clinical benefit (such as time on ventilator, duration of hospitalization, prevention of surgery, or mortality) would be adequate. Your study was sized to achieve $p<0.01$, and the end point--need for rescue--was similar to what we proposed.

However, your study compares one dosing regimen with placebo, and the Division quite clearly requested evaluation of more than one dosing regimen. In addition, I note that the Division repeatedly recommended a comprehensive statistical analysis plan prior to collection of the data.

Written Requests for studies originating in this Division also routinely include provision for long-term evaluation of growth and development. We would normally require assessment of cognitive and neuromotor development at approximately 18 months, corrected post-natal age. It is doubtful that your 36-week follow-up would have been what we would have requested.

Because of these discrepancies, the Division does not plan to issue a Written Request compatible with the development program you have undertaken.

This determination should not be construed as being prejudicial with regard to the adequacy of your development program to support the indication you seek.

We recommend that you resubmit your proposed pediatric study request addressing all of the issues outlined above.

Clearly mark your submission, **"PROPOSED PEDIATRIC STUDY REQUEST"** in large font, bolded type at the beginning of the cover letter of the submission.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Mr. Daryl Allis, Regulatory Project Manager, at 301-594-5332.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

Norman Stockbridge
8/19/2005 09:00:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 29, 1996

Farmacon, Inc.
Attention: Laszlo L. Darko, Ph.D.
President and CEO
90 Grove Street, Suite 109
Ridgefield, CT 06877-4118

Dear Dr. Darko:

Reference is made to your orphan drug application of August 9, 1996 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of ibuprofen intravenous (i.v.) solution as an orphan drug (application #96-1014).

We have completed the review of this application and have determined that ibuprofen i.v. solution qualifies for orphan designation for [redacted] patent ductus arteriosus.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if ibuprofen i.v. solution were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of ibuprofen i.v. solution as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Ms. Erica McNeilly at (301)827-0989.

1-098

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

1-099

Farmacon-JL, LLC

1071 Post Road East • Westport, CT 06880-5361 • Phone: 203/222-8801 • Fax: 203/222-8820

Laszlo L. Darko, Ph.D.
Managing Partner
ldarko@farmaconinc.com

Ibuprofen-l-lysine has been designated as an Orphan Drug for [redacted] patent ductus arteriosus for which NDA 021-903 (present application) is submitted. (Letter from FDA Office of Orphan Product Development, October 29, 1996 is attached.)

Laszlo L Darko August 1, 2005

Laszlo L. Darko, Ph.D. Date
Managing Partner

1-097

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-029
Expiration Date: December 31, 2006

See Instructions on Reverse Side Before Completing This Form

completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on th everse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rate can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Farmacon-IL, LLC
1071 Post Road East
Westport, Connecticut 06880-5361

2. TELEPHONE NUMBER *(Include Area Code)*
(203) 222-8801

3. PRODUCT NAME
NeoProfen

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 021-903

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 021-903
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

NOTE: PLEASE SEE ATTACHMENT.

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Paulo L Darko	Managing Partner	8/1/2005

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

1-096

IND 59778

Memorandum of Telephone Conversation

Between: Laszlo Darko, Ph.D.
Managing Partner
Farmacon-II, LLC

and

CA. Resnick, Ph.D.
Supervisory Pharmacologist
DCRDP (HFD-110), CDER

Date: 29 June 2004 (2:30pm)

Subject: Ibuprofen L-Lysine iv

Synopsis of Conversation: I called Dr. Darko regarding the intravenous neonatal dog study conducted for Farmacon-II, LLC [redacted] I pointed out that this was a failed study in that most of the animals in both drug-treatment groups died (no effect dose for lethality not demonstrated; nor was cause of death identified for most of the nonsurviving pups), and interpretation of the study was compromised by hemorrhage, inflammation and/or necrosis at the injection site, effects that might have been related to the poor survival (some of these animals had developed sepsis and peritonitis and/or pulmonary emboli). Dr. Darko noted that deaths had *not* been associated with iv ibuprofen in human neonates with patent ductus arteriosis (the indication being sought). I told him that the Division was interested in knowing why the neonatal dogs were dying at a dose as low as 5 times the clinical dose (on a mg/m^2 basis) and that we would like to see a no effect dose, not only for lethality but also for clinical and histopathology in the neonatal dog. I asked Dr. Darko about the blood samples taken for plasma drug level measurements in the neonatal dog study as I wondered whether there might be a PK based explanation for the apparently better toleration of the drug by human vs canine neonates. His response was that those samples were never analyzed and have been destroyed. I advised Dr. Darko that we might accept data from neonatal dogs (or other species) from studies conducted by routes other than iv if the company could document that systemic exposure from the alternate route exceeded, by a reasonable margin, the systemic exposure that occurs in the human infant.

I told Dr. Darko that in earlier contacts with the company regarding this IND, it had been our recommendation that a developmental toxicity, rather than a general toxicity study, be done in neonatal animals. Whereas human experience trumps animal data is many instances, that is seldom the case when it comes to effects on post-natal development. (Because of the much longer time required for follow-up of the human relative to the laboratory animal, adequate human data is seldom available.) I noted that I still considered it important to have information on post-natal development. I further noted that if iv dosing in neonatal animals proved impractical, a different route could be utilized, provided that there is PK data to support the adequacy of systemic exposure. In view of the apparent misinterpretation of our earlier recommendations, I advised Dr. Darko to submit to the division protocols for any nonclinical studies that are likely to be considered essential to approvability of a new drug application before initiating those studies.

C.A. Resnick

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

/s/

Charles Resnick
7/22/05 04:26:28 PM
PHARMACOLOGIST

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: ONDC/Microbiology

FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Raj N. Misra
ONDC/DNDCI (Cardiorenal), 301-594-5351

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06-Jul-2005	59,778	21-903/003	M	23-Jun-2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ibuprofen lysinate	Yes	NSAID	30-Sep-2005

NAME OF FIRM: Farmacon-IL, LLC

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 2a MEETING
- ☐ END-OF-PHASE 2 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)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Request for microbiology review of NDA 21-903; sterile solution drug product

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Raj N. Misra	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND 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/

Raj Misra
7/6/05 04:52:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-903

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, CT 06880-5361

Dear Dr. Darko:

We have received your presubmission of the Chemistry, Manufacture and Controls information for the following:

Name of Drug Product: Neoprofen (ibuprofen lysine) 10 mg/ml Injection

Date of Submission: April 13, 2005

Date of Receipt: April 15, 2005

Our Reference Number: NDA 21-903

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete. Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send the submission that completes this application and is intended to start the review clock as well as all electronic or mixed (both electronic and paper) submissions 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

Send all other submissions that are paper only to one of the following addresses:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110Attention: Document Room
1451 Rockville Pike
Rockville, Maryland 80502

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Edward Fromm
7/1/05 12:48:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,778

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, CT 06880-5361

Dear Dr. Darko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R,S-Ibuprofen L-Lysinate.

We also refer to your amendment dated April 27, 2005 (serial # 043), requesting a waiver for the requirement [21 CFR 314.50(f)(1)] for Case Report Tabulations for your pending NDA for R,S-Ibuprofen L-Lysinate.

We have reviewed your request and have the following comments and recommendations.

1. The Division recommends that you submit electronic data sets for your clinical trial(s) in SAS transport files with documentation for interpreting them. Separate paper or PDF files would not be required. Guidance is available at www.fda.gov/cder/guidance under Electronic Submissions.

2. Please provide Case Report Forms (CRFs) for all deaths, serious adverse events and withdrawals from the trial due to medical reasons. In addition, commit to providing CRFs for other subjects in a timely manner upon request during the review cycle.

3. We strongly recommend that you have a pre-NDA meeting with the Division to discuss additional questions that you might have regarding the formatting and submission of your NDA.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Norman Stockbridge
5/13/05 04:39:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,778

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1071 Post Road East
Westport, CT 06880-5361

Dear Dr. Darko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R,S-Ibuprofen L-Lysinate.

We also refer to your amendment dated February 25, 2005 (serial # 041), requesting a waiver of animal studies.

We have completed our review of your submission. Animal studies to evaluate effects of ibuprofen on growth and development of the neonate, although recommended by the Division, are not required for approval of a new drug application for ibuprofen. Long-term follow-up of patients in your clinical trials would provide more useful data than would be generated by animal studies.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Norman Stockbridge
4/29/05 08:14:48 AM

Minutes of a Tele-Conference between Farmacon-IL, LLC and the FDA Division of Cardio-Renal Drug Products

Sponsor:	Farmacon-IL, LLC
Drug:	Ibuprofen L-Lysine IV
IND:	59,778
Date of request:	August 9, 2004
Date request received:	August 10, 2004
Date of confirmation:	August 10, 2004
Date of meeting:	August 11, 2004
Time:	2:00-3:00 PM
Type/Classification:	C/Guidance Meeting
Meeting Chairs:	Norman Stockbridge, M.D., Ph.D.
Meeting recorders:	John David Alisea Sermon

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Maryann Gordan, M.D.	Medical Officer, HFD-110
John David	Regulatory Health Project Manager, HFD-110
Alisea Sermon, Pharm.D.	Regulatory Health Project Manager, HFD-110

Farmacon-IL Attendees:

Laszlo L. Darko, Ph.D.	Managing Partner
Hannon Seth, Ph.D.	Statistician

Background:
Farmacon-IL, LLC requested a teleconference to precisely understand the wording ***"that you do not stop this study early"*** as stated in the August 2, 2004 FDA letter. Farmacon-IL, LLC indicated that understanding is needed in context to the July 16, 2004 letter, in which Farmacon planned to stop the ongoing US study when approximately 130 infants completed the study, ensuring an alpha of 0.05 and a power of 90%, assuming a rescue rate of 30% (presently at 32% in the study) and a discontinuation rate of 10% (presently at 9.1% in the study). Farmacon is still committed to completing the approximately 130 subjects as planned at the beginning of the US clinical study.

Introductions

Discussion:

Dr. Stockbridge began the teleconference by stating that the sponsor had originally targeted a p value of 0.01 for the US study; however the Division received a letter dated July 16, 2004 stating that the sponsor is contemplating unblinding and possibly stopping the ongoing US study based on a target alpha of 0.05. Dr. Darko explained that he expected the rest of the evidence to come from the Overmeire studies. Dr. Stockbridge replied that the US study is far more valuable than the Overmeire studies and it would be extremely difficult for the sponsor to make a case that the European studies should weigh as heavily as the US study. He also stated that the value of the study would be significantly decreased if the sponsor discontinued the U.S. study early with fewer than half of the agreed upon subjects, since the program has so few subjects with good safety follow-up and using the sponsor's drug product. [redacted] stated that he understood Dr. Stockbridge's position and responded that recruitment for the study is difficult because of the type of study population (premature neonates). In addition, the rate of need for rescue therapy, the primary efficacy endpoint, is approximately 30%, less than what was predicted when sample size was calculated.

Dr. Stockbridge noted that the Division would not refuse to file or review the NDA, but the sponsor would be taking a huge risk with a p value of 0.05. Dr. Darko stated that the length of the study could be endless and the cost is exorbitant. He also admitted that the quality of the studies is different, but wanted to know if the FDA would consider this product as an orphan drug. Dr. Stockbridge replied that orphan drug status does not reduce the evidence needed to show effectiveness. [redacted] mentioned that there were previous discussions that referenced the value and importance of the Overmeire studies and they worked hard to provide the Division with the data. Dr. Stockbridge acknowledged that the Overmeire studies were more valuable for having the data available.

The sponsor stated that they will have internal discussions and consider the Division's recommendations.

Meeting recorder: _____
John David

Meeting concurrence: _____
Norman Stockbridge, M.D.

Draft: 11Aug04
Final: 25Aug04

RD:
Sermon 8/12/04
Gordon 8-13-04
Stockbridge 8/13/04

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

/s/

John David
8/26/04 02:22:50 PM

Norman Stockbridge
8/26/04 03:29:06 PM

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

REQUEST FOR CONSULTATION

TO (Division/Office):			FROM:	
DMETS, HFD-420			LCDR John David	
DATE 8/5/04	IND NO. 59,788	NDA NO.	TYPE OF DOCUMENT DMETS Consult	DATE OF DOCUMENT 8/4/04
NAME OF DRUG Ibuprofen L-Lysine IV	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Drugs for Patent Ductus Arteriosus (PDA)	DESIRED COMPLETION DATE 10/4/04

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proposed trade names for IND 59,778 Ibuprofen L-Lysine IV and provide comments.
The trade names are listed below in order of preference:

1. **NeoProfen**
2. [redacted]

The application is currently in a Phase 3 clinical trial for [redacted] **patent ductus arteriosus (PDA)** [redacted]

Thank you!

SIGNATURE OF REQUESTER CDR John David	METHOD OF DELIVERY (Check one) X 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/

John David
8/5/04 10:28:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,778

Farmacon- IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1720 Post Road East
Suite 213
Westport, CT 06880-5643

Dear Dr. Darko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen L-Lysine Injection.

We also refer to your letter dated July 16, 2004, containing information regarding previous discussions of studies for Ibuprofen L-Lysine Injection and your request for recommendations related to breaking the code of the U.S. study and the demonstration of efficacy if the p value is 0.05 or less for each study.

We have completed the review of your submission and have the following comments and recommendations.

> Our understanding is that the supporting publications are based on studies not conducted using your drug product and that some of the key information was obtained retrospectively. These properties will make these studies much less persuasive than they otherwise might be. Therefore, you should expect that the study you have in progress will need to shoulder most of the evidentiary burden. Consequently, we recommend that you do not stop this study early. If, however, you chose to do so, we recommend that you make the decision based on your expected effect size and the aggregate event rate, rather than simply on enrollment.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please call Mr. John David, Regulatory Health Program Manager at (301) 594-5368.

Sincerely,
{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
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/

Norman Stockbridge
8/2/04 04:02:18 PM

Minutes of a Meeting between Farmacon and the FDA

Date: April 28, 2004

Application: IND 59,778
Ibuprofen Lysine Injection

Indication: [redacted] PDA (Patent Ductus Arteriosus)

Applicant: Farmacon-Il, LLC

Subject: Clinical Guidance on NDA Submission

FDA participants

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Thomas Marciniak, M.D., HFD-110, Medical Team Leader
Peter Hinderling, M.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Maryann Gordon, M.D., HFD-110, Medical Officer
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Ramsharan Mittal, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Regulatory Health Project Manager

Farmacon

Laszlo Darko, Ph.D., Managing Partner

Bart Van Overmeire, M.D., Ph.D., Consultant Neonatologist, PI for European trials, University of Antwerp

Background

Farmacon is currently conducting a trial that is entitled "A Randomized, Double-Blind Study of Ibuprofen L-Lysine Intravenous Solution in Premature Infants for the Early Treatment of PDA". Enrollment is progressing at a good rate and it is anticipated that the results of the study will be finalized in early 2005. The sponsor has also acquired right of reference to data from 2 European studies that involve the comparison of ibuprofen, indomethacin, and placebo. These studies conducted by Dr. Bart Van Overmeire at the University Hospital, Antwerp, Belgium, were entitled CB88A-"*Pharmacologic Closure of Patent Ductus Arteriosus in Preterm Infants: Comparison Between Ibuprofen, Indomethacin, and No Treatment*", and CB88B-"*Prophlactic Administration of Ibuprofen in Premature Infants: Effect on Patent Ductus Arteriosus and Intracranial Hemorrhage*".

Farmacon believes that these studies show that ibuprofen is just as effective as indomethacin in closing an open ductus but with fewer adverse effects, particularly those that affect the renal system. They requested the meeting today to discuss the possibility of submitting an NDA based on Van Overmeire data with results from their own trial being sent in at a later date.

Meeting

CMC

Formulation

Farmacon noted that the difference between the ibuprofen lysinate formulation used in the Van Overmeire trials and the current trial in the United States was that the lysine salt was l-lysine, whereas the European (Imbon) formulation was d,l-lysine. [redacted] They also mentioned that the formulation in Europe had a small amount of mannitol added to help solubilize the lyophilized powder into solution, whereas the U.S. drug product was supplied as a solution. Farmacon noted however, that the amount of mannitol added would not contribute any pharmacologic activity (e.g., as a diuretic). Dr. Throckmorton replied that high doses of mannitol had some potential effects of interest (e.g., as a diuretic), and the sponsor would need to be say why the doses used in this product would not have be expected to have such effects. In addition, the sponsor will need to characterize the pharmacologic activity, if any, of the lysine component of the formulation.

Container Closure

Farmacon noted that a lot of drug product made by [redacted] had problems with the presence of some particulate matter thought to originate from leaching of the rubber stopper. They replaced the stopper with a rubber stopper manufactured by [redacted] and have not experienced any particulate matter in subsequent batches of drug product.

Stability Studies

Farmacon presented a slide outlining the stability data they would have for the drug at the time of filing of the NDA. They noted that [redacted] had been the supplier of drug substance for the last 3 batches of drug substance and that these batches were uniform in content (i.e., for excipients). Two of these lots have been designated validation lots (VAL-1 and VAL-2). The sponsor anticipates to have 6 months accelerated (40°/75%RH) and 6-12 months room temperature (25°/60%RH) data for the drug substance at the time of NDA filing. Dr. Srinivasachar said the 3 batches of drug substance made by [redacted] would be considered primary stability batches for retest date purposes while the other previous studies [redacted] would be considered supportive data. For the drug product, data from the 3 batches using the [redacted] closure would be considered primary stability data and would be used for assigning an expiration date.

Dr. Srinivasachar noted that stability data seemed to indicate a yellowing of the drug product at accelerated conditions and he suggested that the sponsor follow ICH guidelines for this type of situation by studying the affected lot under intermediate conditions. Farmacon agreed with this suggestion and said they have already placed this lot under intermediate conditions.

Dr. Srinivasachar encouraged the sponsor to follow ICH guidelines for specifications for drug substance and drug product. He noted that a more specific identity test (i.e., HPLC retention time

combined with UV or IR) would be needed for the drug product. This test should also be specific for the lysine component of the drug substance.

Dr. Mittal asked if the sponsor had clarified the grade of lysine used in the manufacturer of drug substance. Farmacon replied that the drug substance supplier, [redacted], uses the highest grade possible (medical) of lysine for making the drug substance.

Clinical

Dr. Throckmorton said that it appeared from the sponsor's briefing package that they were considering two potential paths to obtaining approval for the drug:

1. The 2 Van Overmeire studies, one in prevention and one in treatment of PDA, are sufficient to establish safety and efficacy for the drug.
2. Ad Hoc Rolling Review-the 2 Van Overmeire studies would be submitted at the time of NDA filing with the U.S. trial submitted later in the review cycle.

Farmacon said their preference would be option #1 as indicated above as they believe that the Van Overmeire data, which they have complete right of reference to, establishes at a statistical significance level of $p<0.05$ the endpoint of reduction of rescue treatment when patients are treated with ibuprofen compared to indomethacin. They believe that these studies also show that ibuprofen injection is at least as safe as indomethacin, if not safer. The U.S. trial when completed would, in essence, confirm the results of the 2 European trials and would also be a bridge between the 2 patient populations of the Van Overmeire studies. They emphasized, however, that they believe the European data are robust enough by themselves to support approval.

Dr. Throckmorton asked if approval were granted for this drug, in which patient population would it be indicated. The sponsor replied that it could be indicated, for example, in pre-term infants who have PDA and are symptomatic (i.e., have respiratory distress). Dr. Throckmorton noted that a treatment indication would be more plausible given the sponsor's desire to submit only the Van Overmeire data. A prevention claim based on the evidence of single trial seemed very unlikely, as the safety and efficacy data standard is much higher for this claim, since many children would receive the drug that would not benefit from its use.

Dr. Throckmorton stated that if the sponsor submitted an NDA for ibuprofen for a treatment indication based solely on the Van Overmeire data, the Division would probably not Refuse-to-File the application. He noted, however, that there were several issues that would make an approval difficult based on those data alone:

- The prevention trial, although placebo-controlled, was in a different patient population than the comparator, treatment protocol with indomethacin. Thus the prevention trial would not be considered a second, 'confirmatory' trial for this drug, although it would be supportive.
- There is already an approved product, indomethacin, for the treatment of PDA.
- The treatment, comparator study with indomethacin was open-label. Since a placebo control was not present, the sponsor would need to provide assurance that both treatment groups in the trial had a clinical benefit that the Agency could understand and describe.
- There does not seem to be an abundance of data (i.e., in the literature) to suggest that the use of indomethacin in PDA is linked to clear clinical outcomes.
- The sponsor's initial analyses of the treatment and prevention trial data are, in fact, post-hoc analyses and ones not necessarily pre-specified when the trials were initiated.

Dr. Throckmorton stated that because of the potential, confounding issues noted above, it is our clear preference to have the results of the U.S. trial included in the NDA submission. In this circumstance, the U.S. trial would be 'pivotal' and the Van Overmeire data supportive. Farmacon replied that they believe that the prevention trial data is robust and is, in fact, a second confirmatory trial demonstrating the safety and efficacy of ibuprofen in neonates with PDA. They mentioned that they started the U.S. trial a few years ago because the quality of the Van Overmeire data were not known. Nevertheless, they expect that the trial will be completed next year and will confirm the results of the European studies.

Datasets

Dr. Throckmorton asked for an explanation of how the data from the Van Overmeire trials were formatted as well as how the data were source verified before being reanalyzed by the sponsor. Farmacon replied that the data are in SAS format and that [redacted] sent trained nurses to Belgium to source verify the original data and then transfer these data to new CRFs developed by [redacted] They noted they have exclusive rights to all original data and CRFs of the European studies. Dr. Gordon expressed concern that although the source verification was likely done in a thorough manner, it nevertheless was being done on one trial that was unblinded and thus could further compromise the integrity of the data.

Pharmacology/Toxicology

Dr. Throckmorton asked what pharmacology/toxicology studies the sponsor had conducted to date. Farmacon replied that they had attempted a 14 day toxicology study in neonatal dogs at doses of 80 and 200 mg/kg/day but that the study was compromised by a large number of deaths at these dosage levels. The kidney was identified as a target organ. Dr. Resnick expressed a desire to see effects on growth and development evaluated in neonates and that this would, in the case of dogs, require a follow-up period much longer than that provided by the study described by the sponsor.

Dr. Throckmorton said that, in general, a prevention claim would entail more pharmacology/toxicology studies than a treatment indication. He said that since the sponsor is pursuing a treatment claim, additional pharmacology/toxicology studies may be minimal, but asked that a report of such studies conducted so far and other supportive literature be submitted to the Division for our assessment. A follow-up conversation with the Pharm-Tox reviewers was recommended.

Conclusion

Farmacon believes that data from the two Van Overmeire studies are robust and would support approval of ibuprofen injection in the treatment of PDA in preterm infants. They also note that a US trial using ibuprofen in the early treatment will likely be completed late this year or early next year. Dr. Throckmorton stated that although he very much appreciated the work by the sponsor and Dr. Overmeire in this disease and patient population, the approval of ibuprofen injection for the treatment of PDA would be problematic for a variety of reasons. These include that the treatment trial was open-label, the second 'confirmatory' trial was in a different population than the treatment trial, and there is already an approved drug, indomethacin, for the treatment of PDA. Dr. Throckmorton stated that it is our strong preference that the U.S. trial be considered the pivotal trial for this application with the European data being supportive.

Dr. Throckmorton encouraged the sponsor to include in their CMC section of their NDA submission, arguments detailing the lack of pharmacologic activity of lysine and mannitol in the

formulation to-be-marketed. In addition, we would like a report of all pharmacology/toxicology studies conducted to date by the sponsor with ibuprofen injection to be submitted as soon as possible.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair: _____
Douglas C. Throckmorton, M.D.

drafted/ef: 5/3/04-5/24/04

Rd: DThrockmorton 5/24/04
TMarciniak-5/21/04
PHinderling-5/20/04
MGordon-5/19/04
CResnick-5/18/04
KSrinivasachar-5/13/04
RMittal-5/6/04

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

/s/

Doug Throckmorton
5/25/04 12:36:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,778

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1720 Post Road East
Suite 213
Westport, Conneticut 06880-5643

Dear Dr. Darko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R,S-Ibuprofen-l-lysine Intravenous Solution.

We also refer to your treatment protocol, dated August 10, 2000, and to your amendment dated April 25, 2003, serial number 024, received April 29, 2003, titled "In-Use Open Study of Ibuprofen Lysine Intravenous Solution in Premature Infants for Treatment of PDA", which provided a complete response to our September 11, 2000 letter that cited the reasons for placing this treatment protocol on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submission and have concluded that the treatment use may proceed as proposed. However, we request that you submit progress reports on enrollment of your controlled, clinical trial (Protocol FCR-00-01/Ross CB88, entitled "A Randomized, Double-blind Study of Ibuprofen-l-lysine Intravenous Solution in Premature Infants for the early Treatment of PDA") in your next Annual Report (October 2003) and also in December 2003.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of New Drugs
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/

Kim Colangelo
5/29/03 01:14:12 PM
For Dr. John Jenkins

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,778

Farmacon-IL, LLC
Attention: Laszlo L. Darko, Ph.D.
1720 Post Road East
Suite 213
Westport, Connecticut 06880-5643

Dear Dr. Darko:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R,S-Ibuprofen-l-Lysine IV Solution and to your correspondence dated January 25, 2002 (serial #10).

As you requested, we are stating in writing that we acknowledge your responses, dated January 25, 2002, to the comments made by our medical and statistical reviewers concerning IND 59,778 (please refer to our fax of December 10, 2001). We, however, still consider infants who die during the 14-day trial period to be treatment failures (we expect that there will be no difference in mortality rate between patients on ibuprofen and those on placebo). We also recommend adding additional doses of study drug as it will be difficult to write dosing information based only on one dosing regimen.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation ODE I
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/

Doug Throckmorton
9/5/02 09:19:41 AM

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

/s/

Doug Throckmorton
5/28/02 09:38:51 AM

Comments from the medical reviewer:

1) The primary efficacy endpoint is the need for medical or surgical intervention of a symptomatic PDA (rescue treatment). Therefore, for each infant who receives rescue treatment, the reason for this intervention must be defined unambiguously. There must be a clear separation in the efficacy analysis between those infants treated for a PDA and those infants treated for a symptomatic PDA.

2) Recommend adding additional doses of ibuprofen.

Comments from the statistical reviewer:

Sample size calculation is adequate given the assumptions.

The primary efficacy parameter is the proportion of infants requiring rescue treatment. The ITT analysis includes all randomized infants. Thus, the 50% dropout rate is a serious concern in that it is not clear whether each dropout should be assigned a success (not requiring rescue) or a failure (requiring rescue) in the ITT analysis. The protocol needs to have a detailed plan for how to handling dropouts.

The protocol states that no interim analyses are planned. But DSMB will perform mandatory reviews of adverse event data based on blinded data grouped by treatment code after 25%, 50%, and 75% of infants have been enrolled. Will DSMB receive the efficacy data?

If yes, grouping by treatment code may give a clue of treatment difference in either direction. Unless it is made clear that there is no possibility of stopping the trial early because of observing a large treatment difference on efficacy, the false positive (or type I) error rate can be substantially inflated without a proper adjustment of alpha level. The protocol needs to be clear on this issue. I strongly recommend that the DSMB have a statistician to deal with statistical issues during data monitoring.

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

/s/

Edward Fromm
12/10/01 03:45:46 PM
CSO

Comments from the medical reviewer:

1) The primary efficacy endpoint is the need for medical or surgical intervention of a symptomatic PDA (rescue treatment). Therefore, for each infant who receives rescue treatment, the reason for this intervention must be defined unambiguously. There must be a clear separation in the efficacy analysis between those infants treated for a PDA and those infants treated for a symptomatic PDA.

2) Recommend adding additional doses of ibuprofen.

Comments from the statistical reviewer:

Sample size of 60 completers per arm is powered to detect a 50% increase in success rate (i.e., from the rate of 0.35 to 0.70). I'm not sure of whether 50% is an optimistic estimate. I'd suggest that the sponsor take a look at treatment difference in success rate at some interim time of the trial (e.g., half of the patients have contributed to the efficacy data) and increase sample size if the observed treatment difference in success rate is far below 50%. In this case, an adaptive test procedure might be needed (e.g., Cui, Hung and Wang (1999, Biometrics, p. 854-857), Lan and Trost (1997, Proceedings of Biopharmaceutical Section), or Proschan and Hunsburger (1995, Biometrics, cited in CHW's paper)).

I strongly recommend that the DSMB have a statistician to deal with statistical issues during data monitoring.

Conclusions: there are no reasons for this study not to proceed as written.

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

/s/

Edward Fromm
6/14/01 07:34:43 AM
CSO

Minutes of a Telecon between Farmacon and the FDA

Date: March 6, 2001

Sponsor: Farmacon-IL, LLC.

Subject: IND 59,778 (Ibuprofen Lysinate Injectable)

Type of Meeting: Guidance

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Project Manager

Farmacon

Laszlo Darko, Ph.D., President and CEO

Background

Ibuprofen lysinate injectable is being studied for facilitating the closure of Patent Ductus Arteriosus (PDA) [redacted] in very low birth weight premature infants after administering within the first three hours after birth. The proposed use of ibuprofen injection is for [redacted] indomethacin injection, an approved product, is only indicated for the treatment of PDA.

The firm submitted this IND to the Division on January 27, 2000.

The sponsor requested a telecon with the Division to discuss comments on a proposed Phase 3 study in neonates. The study's proposed primary endpoint is closure of the patent ductus.

Telecon

Clinical Protocol

Dr. Darko opened the teleconference by noting that batches of Ibuprofen Lysinate were being made for the proposed clinical trial due to start in late April, 2001. He said that the proposed primary endpoint of the trial would be the closure of PDA by cardiac ECHO performed at the following timepoints: Baseline, Study Day 4, and Study Day 14. Dr. Darko said that ibuprofen would be compared with placebo in at least 72 non-symptomatic neonates and that these patients would be stratified into 3 birth weight categories (500-750g; 751-1000g; 1001-1250g).

Dr. Darko said a major study had been completed in Europe showing that ibuprofen was more successful than placebo and indomethacin in closing the ductus. He also said that ibuprofen appeared to have less adverse effects

on the kidney than indomethacin in the study. Dr. Lipicky asked the sponsor if he had right of reference to the study data. Dr. Darko said he did.
Dr. Lipicky said that closure of the ductus was not sufficient by itself as a primary endpoint. The Division strongly urged the sponsor to use a clinical event; for example, prevention of surgeries to close the ductus would be an acceptable endpoint. Dr. Darko said that he agreed that prevention of surgeries would be a good clinical endpoint, but noted that, with the increased use of indomethacin, the need for surgical intervention was decreasing. Thus indomethacin rescue might be an endpoint. Dr. Lipicky concurred and said it could be part of a composite endpoint.

Dr. Lipicky said that a major reservation the Division had with the [redacted] ibuprofen is that a sizeable number of patients will receive the drug even though their ductus would have closed spontaneously. Such patients will not benefit from the drug, but still will be exposed to its potential harmful effects. Therefore, this will be considered when the risk/benefit analysis of the drug is undertaken.

Dr. Darko said they are measuring a number of secondary clinical endpoints in the proposed trial and asked the Division if these could be used to demonstrate the clinical benefit of the drug. Dr. Lipicky replied, not for efficacy, but that the firm could do a trial comparing the differences in renal parameters (e.g., BUN, creatinine) between ibuprofen and indomethacin for safety. Such a trial as this, if successful, would support approval of ibuprofen.

The sponsor asked the Division what other parameters could serve as primary endpoints for the study. Dr. Lipicky replied that showing a reduction in mortality and/or less need for hospitalization would strongly support an approval of the drug.

Statistical Significance of Trial

Dr. Lipicky said that the proposed trial should achieve statistical significance as much below $p< 0.01$ as possible. He added that when the sponsor revises the primary endpoint of the trial, sample size must be re-evaluated.

Handling of Dropouts

Dr. Lipicky said the protocol does not address the problem of study patient withdrawals. A prospective statistical plan will need to outline the assignment of dropouts (e.g., as treatment failures, LOCF, to placebo, drug) and how they would be handled in the primary statistical analysis.

Lysinate salt

Dr. Lipicky asked the sponsor if there are data showing that the lysinate salt of ibuprofen has an effect of its own. Dr. Darko said that the lysinate salt [redacted] the ibuprofen and he does not know if it has an effect of its own. Dr. Lipicky encouraged the sponsor to look for further information to verify the lack of activity of the salt as this information will be of greater relevance at the time of a NDA submission.

Retinopathy in European Trial

Dr. Darko said that a retrospective analysis of a major European trial comparing indomethacin, placebo, and ibuprofen in the treatment of PDA had identified less retinopathy in the ibuprofen arm compared to the indomethacin treatment arm. He asked the Division if he could include this parameter in the proposed study. Dr. Lipicky said the sponsor, for the time being, should concentrate on the primary endpoints discussed already (e.g., mortality, prevention of surgeries); he did encourage the sponsor to send an abstract of the retinopathy analysis to the Division for our review.
Pharmacokinetic Sampling

Dr. Lipicky asked the sponsor if it was possible to obtain more than 3 blood samples from the neonates for the measuring of PK parameters. Dr. Darko said the IRB's limit blood drawing to the absolute minimum and therefore it would not be possible to obtain more than the 3 indicated in the protocol.

Summary

Dr. Lipicky said the protocol submitted to the Division needs revision of the following:

1) The primary endpoint needs to be revised so that closure of the PDA is related to a clinical outcome.
2) A statistical plan should be sent to the Division outlining how dropouts from the study will be assigned and handled in the statistical analysis.
3) An abstract of the retinopathy analysis from the European study should be to the Division for review.

Minutes Preparation: _____
Edward Fromm

Concurrence: _____
Raymond Lipicky, M.D.

dr/3-07-01/03-08-01

Rd: ADorantes-3/7/01
MGordon-3/8/01
DThrockmorton-3/7/01
JHung-3/8/01

/s/

Edward Fromm
3/9/01 02:14:55 PM
Dr. Lipicky signed the minutes on March 9, 2001

FEB 23 '00

Minutes of a Internal 30 Day Safety Meeting

Date: February 23, 2000

Application: IND 59,778
Ibuprofen Lysinate Injectable

Sponsor: Farmacon-IL, LLC.

Participants:

Norman Stockbridge, M.D.,Ph.D., Team Leader/Medical, HFD-110
Pritam Gill-Kumar, Ph.D., HFD-110, Pharmacologist
Ramsharam Mittal, Ph.D., HFD-110, Chemist
Edward Fromm, HFD-110, Consumer Safety Officer

Background

Ibuprofen lysinate injectable is being studied for facilitating the closure of Patent Ductus Arteriosus (PDA) [redacted] in very low birth weight premature infants after administering within the first three hours after birth.

PHARMACOLOGY - Dr. Gill-Kumar

Dr. Gill-Kumar stated that ibuprofen injectable is being used as a [redacted] and in this way it is different from indomethacin injectable which is indicated for symptomatic treatment of PDA.

Dr. Gill-Kumar stated that the dose regimen identified as Group 1 (ibuprofen 10, 5, and 5 mg/kg for a total of 3 doses) was acceptable. She indicated that Group 2 (ibuprofen 20, 10, and 10mg/kg for a total of 3 doses) and Group 3 (ibuprofen 10,5,5,5 and 5 mg/kg for a total of 5 doses) were unacceptable because the sponsor provided no safety information for the doubling of the dose in Group 2 and the increased duration of therapy in Group 3.

Dr. Gill-Kumar mentioned that ibuprofen is a racemic mixture of R(-) and the more active enantiomer S(+). She noted that it appears that the R(-) form is converted metabolically to the S(+) form in higher amounts in adults than children. She wondered if it might be feasible to dose the S(+) form in half the amount; she also noted that the S(+) form was available in Europe.

CHEMISTRY - Dr. Ram Mittal

Dr. Mittal stated that the lysine used to in the synthesis of ibuprofen lysinate was not from a good supplier; he noted that the impurity profile was absent.

Dr. Mittal noted that [redacted] a solvent used in the manufacturing process, would have to be measured in the finished product, especially since the drug was being used in premature infants.

ADDENDUM

Due to extenuating circumstances, the medical reviewer, Dr. Williams was not able to attend the meeting as well as brief Dr. Stockbridge on his review to date. Dr. Stockbridge asked Mr. Fromm to schedule a meeting with himself, Mr. Fromm and Dr. Lipicky on February 25, 2000 to discuss the safety concerns raised at the February 23, 2000 meeting.

Meeting-February 25, 2000

Drs. Lipicky, Stockbridge, Resnick and Mr. Fromm were present.

Dr. Stockbridge began by noting that ibuprofen lysinate injectable had been studied with indomethacin in seven trials with about 100 patients to date. He noted that ibuprofen was studied with a one regimen (comparable to Group 1-see above) and the safety profile seemed to be good, although efficacy was lower than indomethacin. Dr. Stockbridge mentioned that the company was probably proposing a doubling of the dose (Group 2) to see if it improved the efficacy of the drug over indomethacin. He also noted that the dosing proposed for premature infants when viewed on a mg/kg basis was not inconsistent with that of the oral dose used in adults.

Dr. Stockbridge summarized Dr. Gill-Kumar's concerns about the lack of pre-clinical or clinical data to support the dosing regimens (Group 2 and 3) proposed by the sponsor. Dr. Resnick stated that he shared Dr. Gill-Kumar's concerns about doubling the dose in Group 2 without adequate safety information. Dr. Stockbridge thought that the company should not do the trial as proposed but rather do an outcome based study. Outcome endpoints could be, for example, the prevention of renal complications. Dr. Lipicky said any outcome trials would have to test the drug against the current surgical options. Dr. Stockbridge noted he believed that intravenous indomethacin may be effective if given earlier in the progression of the condition, even though it is not mentioned as such in the currently approved labeling. He said that a trial that included arms that were grouped such as early indomethacin, late indomethacin, early ibuprofen, late ibuprofen might yield more information than the trial that is proposed by the firm.

Dr. Lipicky noted that oral ibuprofen had undergone animal toxicology studies during the approval process and no significant problems were encountered. Dr. Lipicky said there were not any significant safety problems, at least at this time, which would prevent the proposed trial from going forward. He said he would not put the IND on "hold" but did indicate that the company should be invited to meet with the Division to discuss other trial designs that might yield more information.

Minutes Preparation: Edward A. Fromm
Edward Fromm

Concurrence, Chair: Ray Lipicky
Raymond Lipicky, M.D.

cc: IND 59,778
HFD-110
HFD-110/Blount
HFD-110/EFromm/SMatthews

drafted: 2/28/00-3/02/00

Rd: RMittal-3/1/00
PGill-Kumar-3/1/00
CResnick-3/1/00
NStockbridge-3/1/00