CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-910

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DIALYSIS SOLUTIONS INC.

September 20, 2005

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.

DIALYSIS SOLUTIONS INC.

Walter O'Rourke
President/CEO

380 Elgin Mills Road East
Richmond Hill, Ontario
4C 5H2

Tel • 905-884-6296
Fax • 416-335-9161

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: 21-910

NAME OF APPLICANT / NDA HOLDER: Dialysis Solutions Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)
NORMOCARB

ACTIVE INGREDIENT(S)	STRENGTH(S)
Na 140 mEq/L, Mg 1.5mEq/L, Cl 116 mEq/L, HCO3 25 mEq/L	25mEq/L

DOSAGE FORM
240ML Concentrate to be diluted in 3L bag of sterile water.
Bagged in dilute or split bag format 2L;3L,4L,5L

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	b. Issue Date of Patent	c. Expiration Date of Patent
10/020,882 PATENT PENDING	12/19/2001	

d. Name of Patent Owner	Address *(of Patent Owner)*	
Dialysis Solutions Inc.	14 Emmett Place	
	City/State: Whitby, Ontario	
	ZIP Code: L1R 2B4 (CANADA)	FAX Number *(if available)*: 905 666-3807
	Telephone Number: 905 665-4709	E-Mail Address *(if available)*: orourke@ca.inter.net

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.)*	
ViCro	2600 Pennsylvania Avenue Ste 9 D	
	City/State: Washington, DC	
	ZIP Code: 20037	FAX Number *(if available)*: (202) 250-6401
	Telephone Number: (202) 250-6400	E-Mail Address *(if available)*: vicrollc@earthlink.net

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

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)*: 10/020,882 PATENT PENDING

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.)*

Replacement Solution, Hemofiltration Solution, Continuous Renal Replacement Therapy

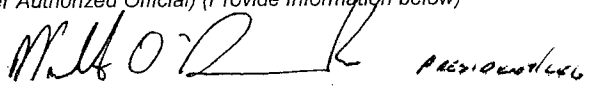
5. No Relevant Patents

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
	9/20/2005

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 Dialysis Solutions Inc., Walter O'Rourke, President/CEO	
Address !4 Emmett Place	City/State Whitby, Ontario
ZIP Code M1S 2B4	Telephone Number (905) 665-4709
FAX Number *(if available)* (905) 666-3807	E-Mail Address *(if available)* orourke@ca.inter.net

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

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1. GENERAL

a. United States Patent Number
5,945,449

b. Issue Date of Patent
8/31/1999

c. Expiration Date of Patent
10/31/2017

d. Name of Patent Owner
Dialysis Solutions Inc.

Address *(of Patent Owner)*
14 Emmett Place

City/State
Whitby, Ontario

ZIP Code
L1R 2B4 (CANADA)

FAX Number *(if available)*
905 666-3807

Telephone Number
905 665-4709

E-Mail Address *(if available)*
orourke@ca.inter.net

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)

ViCro

Address *(of agent or representative named in 1.e.)*
2600 Pennsylvania Avenue
Ste 8 D

City/State
Washington, DC

ZIP Code
20037

FAX Number *(if available)*
(202) 250-6401

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	9/20/2005

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Name Dialysis Solutions Inc., Walter O'Rourke, President/CEO	
Address !4 Emmett Place	City/State Whitby, Ontario
ZIP Code M1S 2B4	Telephone Number (905) 665-4709
FAX Number *(if available)* (905) 666-3807	E-Mail Address *(if available)* orourke@ca.inter.net

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 21-910 SUPPL # N/A HFD # 110

Trade Name NORMOCARB HF 25 and NORMOCARB HF 35

Generic Name NORMOCARB HF 25 and NORMOCAB HF 35

Applicant Name DIALYSIS SOLUTIONS INC.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☐ NO ☒

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # 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: Dianne Paraoan
Title: Regulatory Health Project Manager
Date: July 21, 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
7/27/2006 12:04:41 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-910

Stamp Date: 26 Sep 05 Action Date: 26 Jul 06

HFD: 110 Trade and generic names/dosage form: Normocarb HF

Applicant: Dialysis Solutions, Inc. Therapeutic Class: 3S

Indication(s) previously approved: None. Approved as a device

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

Number of indications for this application(s): 1

Indication #1: Use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace water and to correct electrolytes and acid-base imbalance.

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: There are NO safety concerns.

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}

_____

Dianne C. Paraoan
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

cc: NDA 21-910
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)

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/s/

Dianne Paraoan
7/12/2006 03:20:09 PM

DIALYSIS SOLUTIONS INC.

To Whom It May Concern:

Dialysis Solutions Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Yours truly,

DIALYSIS SOLUTIONS INC.

Walter O'Rourke
President/CEO

Vi CRO LLC
US Agent

Ann H. Rose
President/CEO

14 Emmett Place, Whitby, Ontario CANADA, L1R 2B4, PHONE (905) 665-4709 FAX (905) 666-3807

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		

☒ (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
Walter O'Rourke DSI / ANNH-ROSE VICRO	President/CEO
FIRM / ORGANIZATION	
Dialysis Solutions Inc. / VICRO LLC US AGENT	
SIGNATURE	**DATE**
[signature]	10/18/05

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

FORM FDA 3454 (2/03)

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

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-910

NDA ACKNOWLEDGMENT

Dialysis Solutions, Inc.
Attention: Mr. Walter O'Rourke
14 Emmett Place
Whitby, Ontario
L1R 2B4 Canada

Dear Mr. O'Rourke:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Normocarb-HF 25/Normocarb-HF 35

Review Priority Classification: Standard (S)

Date of Application: September 23, 2005

Date of Receipt: September 26, 2005

Our Reference Number: NDA 21-910

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 November 25, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 26, 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, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products, Room 4169
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Ms. Ann H. Rose
U.S. Agent for Dialysis Solutions, Inc.
ViCro LLC
2600 Pennsylvania Avenue, N.W., Suite 8D
Washington, D.C. 20037

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/s/

Edward Fromm
10/31/2005 11:20:20 AM

RHPM Overview of NDA 21-910
Normocarb HF™
Normocarb HF™ 25 and Normocarb HF™ 35
July 27, 2006

Sponsor:	Dialysis Solutions, Inc.
Classification:	3S
Receipt Date:	September 26, 2005
User Fee Goal Date:	July 26, 2006
AP Letter Issued:	July 26, 2006
Final Draft Labeling:	July 20, 2006

Background
Normocarb HF™ is being developed for use as a dialysis infusate solution in continuous renal replacement therapy (CRRT) in adults and pediatric patients. Continuous renal replacement therapy is dialysis continued for twenty four hours a day to treat critically ill patients with renal failure. The aims of CRRT are control of fluid balance, control of plasma electrolytes, control of acid-base balance and removal of products of metabolism.

The sponsor, Dialysis Solutions Inc., has developed two concentrations of this bicarbonate based solution with 35 mEq/L and 25 mEq/L, respectively, Normocarb HF™ 35 and Normocarb HF™ 25. Both concentrations of this drug product will be packaged in glass serum vials and must be diluted before use.

Normocarb HF™ is identical to Normocarb™, an FDA approved sodium bicarbonate dialysate solution which has been extensively marketed in Canada since March 1, 2001.

A Request for Designation dated May 2, 2003 recommended that solutions intended to be infused into a patient would be managed by the Center for Drug Evaluations and Research (CDER) rather than the Center for Devices and Radiological Health (CDRH), which manages dialysate solutions that passes through a device.

During the December 10, 2003 Pre-IND meeting, Dr. Throckmorton stated that their new drug application would be considered a 505(b)(2) application as long as the sponsor did not intend to include any novel claims.

Dialysis Solutions Inc. submitted a request for orphan-drug designation on December 1, 2004 and was granted orphan-drug designation on August 9, 2005 for the "use in the management of patients undergoing continuous renal replacement therapy (CRRT) with hemofiltration."

Previous correspondence and meetings regarding the development of Normocarb HF™ solutions for the use in the management of patients undergoing CRRT:

1. Pre-IND Meeting, December 10, 2003
2. Pre-NDA CMC Meeting, March 10, 2005
3. Pre-NDA Meeting, March 11, 2005

Division Director's Memo
In Dr. Stockbridge's memo dated July 12, 2006, he stated that Normocarb HF™ is a pair of sterile concentrates for infusate solution for use to replace water and to correct- acid-base and electrolyte disturbances caused by CRRT. The solutions contain sodium, magnesium, chloride, and bicarbonate only.

Thus, there are no novel or foreign molecular species and what constituents there are are not what one would ordinarily mean by "drugs." The sponsor did not conduct clinical studies, rather referred to published literature to support their application.

Other infusate constituents, include potassium, calcium, glucose, and phosphate, may need to be added; thus, the labeling includes basic advice, relying on the physician to make judgment based on individualized treatment.

The consequences of the use of infusates are predictable from first principles. Within a certain region of physiological and near-physiological concentrations, the effects can be predicted with sufficient accuracy that no clinical experience is indicated to confirm them. The concentrations of electrolytes in Normocarb are well within the bounds of comfort.

Medical Review
In his review dated July 7, 2006, Dr. Xiao stated that although the sponsor did not perform specific clinical studies on this product, support for efficacy and safety has been based on the clinical reported from published literature. Based on the results of the published clinical studies, Dr. Xiao concluded that there is sufficient documentation to adequately evaluate the safety and efficacy of Normocarb HF™ formulations in the indicated acute renal failure population when used as a replacement solution in CRRT. Dr. Xiao recommended that the sponsor include the details of the following in the label:

1. Normocarb HF™ provides two formulations with bicarbonate concentrations at 25 or 35 mEq/L. The sponsor should label the indications of each solution.

2. Citrate has been used for regional anticoagulation of the extracorporeal circuit during CRRT and is particularly appealing of patients at risk of bleeding. Since citrate can be converted to bicarbonate by the liver and by the muscle in a 1:3 ratio, the plasma concentration of bicarbonate will significantly increase and metabolic alkalosis may be a consequence after the long-term use of this anticoagulant agent. The sodium and calcium concentrations may also change significantly.

3. Normocarb HF ™ does not contain phosphate and phosphate supplementation is generally required at some stage during CRRT. Customized solutions may be necessary in patients with some electrolyte imbalances.

Financial Disclosure is included in the action package and is incorporated in the Medical Review.

The Integrated Summary of Safety and Effectiveness is incorporated in the Medical Review.

There is no Safety Update Review. The sponsor has submitted literature references to support the safety and efficacy of these products and have not provided additional literature submissions.

Statistical Review
No statistical review was warranted.

Pharmacology Review
No pharmacology review was warranted.

Biopharmaceutical Review
No biopharmaceutical review was warranted.

Chemistry Review
In her first review dated June 14, 2006, Dr. McLamore noted that the sixteen deficiencies issued to the sponsor in a CMC discipline review letter on May 1, 2006 were adequately addressed; however, because the responses to the microbiology discipline review letter were still pending review by the Dr. Langille, this application is approvable from the CMC perspective.

In her second review dated June 19, 2006, all CMC and microbiology deficiencies were adequately addressed; thus recommending overall approval from the CMC perspective.

The Office of Compliance has issued an overall acceptable recommendation for all establishments.

The Environmental Assessment (EA) and the Finding of No Significant Impact (FONSI) were adequate addressed accordingly to Dr. McLamore's review dated June 14, 2006.

No Phase 4 commitments were proposed.

Microbiology
In Dr. Langille's first review dated May 19, 2006, he stated that until the responses of the discipline review letter issued on May 23, 2006 were addressed, this application is approvable from the microbiology perspective. Overall, the sponsor failed to provide adequate information regarding the process simulation methodology, stability commitments, filter integrity testing, closure depyrogenation and product holding times. Failure to address the product quality microbiology deficiencies could result in microbial and/or endotoxin contamination of the drug product.

In his second review dated June 13, 2006, after review of the sponsor's responses to the discipline review letter, Dr. Langille noted that the sponsor adequately addressed the microbiology deficiencies and recommended approval from the product quality microbiology perspective.

DSI
During the filing meeting, it was concluded that no DSI consult was warranted.

Pediatric Rule
Based on the information provided the Division granted a full waiver from all pediatric studies because there are no safety issues.

Labeling
On July 20, 2006, the Division and Dialysis Solutions Inc. came up with a final draft package insert. Please refer to the Labeling section of the action package. Also included in the Labeling section of the action package is the proposed package insert.

DMETS
Please refer to reviews in the action package in the LNC Committee Reviews section.

DMETS objects to the proposed tradename; however, because this product is already approved as a device, indicated for use as a hemodialysis solution under the same name, the Division accepted Normocarb™ HF as the proposed name. This was communicated in an email dated November 15, 2005.

DDMAC
Please refer to review in the action package in Advertising section.

Advisory Committee Meeting
No Advisory Committee Meeting was warranted specifically for this NDA.

Project Manager's Summary
To my knowledge, there are no issues that might prevent action on this NDA.

Dianne C. Paraoan
Regulatory Health Project Manager

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/s/

John David
7/27/2006 08:38:35 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-910

DISCIPLINE REVIEW LETTER

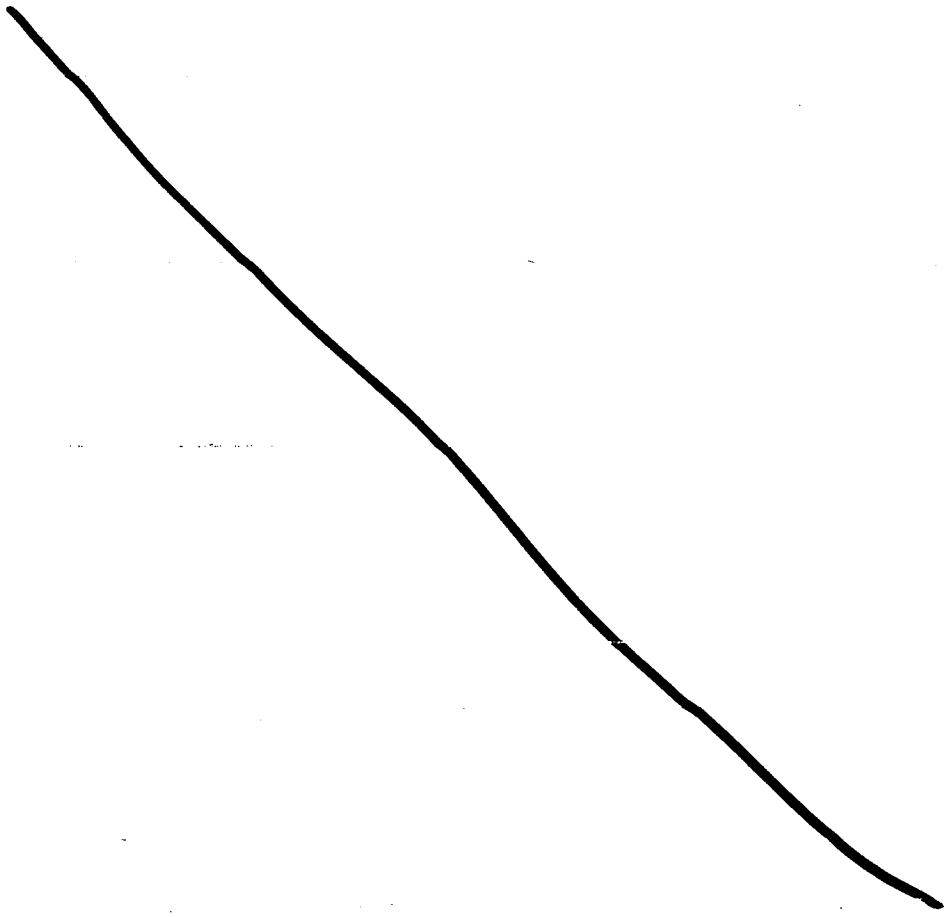
Dialysis Solutions, Inc.
Attention: Walter O'Rourke
14 Emmett Place
Whitby, On L1R 2B4
Canada

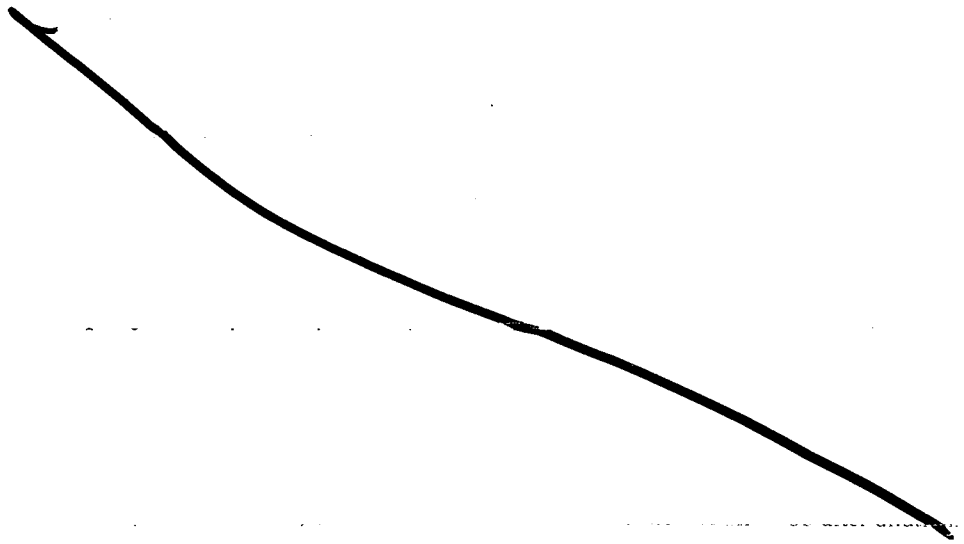
Dear Mr. O'Rourke:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Normocarb HF™ 25 and Normocarb HF™ 35.

A review of the Division of Medical Errors and Technical Support (DMETS) is complete, and we have the following recommendations:

GENERAL COMMENTS





If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page.}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Dr. Ann Rose
U.S. Agent for Dialysis Solutions Inc.
Vicro LLC
2600 Pennsylvania Avenue, N.W
Suite 8D
Washington, D.C. 20037

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/s/

Edward Fromm
7/14/2006 10:49:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-910

DISCIPLINE REVIEW LETTER

Dialysis Solutions, Inc.
Attention: Walter O'Rourke
14 Emmett Place
Whitby, Ontario
L1R 2B4 Canada

Dear Mr. O'Rourke:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Normocarb-HF 25/ Normocarb-HF 35.

We have completed the initial review of the Microbiology section of your submission and have identified the following deficiencies:

1. Provide the minimum acceptable post filtratio[redacted].
2. Provide the maximum holding times for the sterilized manufacturing equipment, vials, and stoppers.
3. Provide data summaries for the multiple [redacted]
4. Provide the method and results of [redacted]
5. Please address the following deficiencies regarding process simulations:

[redacted]

g. [redacted]

6. The WFI monitoring sites, frequencies, media and incubation conditions were not provided but should be.

7. Provide the results of container closure integrity testing conducted on the 240 mL vials and [redacted] stoppers.

8. [redacted]

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Dr. Ann H. Rose
US Agent for Dialysis Solutions, Inc.
ViCro LLC
2600 Pennsylvania Avenue, NW, Suite 8D
Washington, DC 20037

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/s/

Edward Fromm
5/23/2006 02:26:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-910

DISCIPLINE REVIEW LETTER

Dialysis Solutions, Inc.
Attention: Walter O'Rourke
14 Emmett Place
Whitby, Ontario
L1R 2B4 Canada

Dear Mr. O'Rourke:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Normocarb-HF 25/ Normocarb-HF 35.

We have reviewed the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies:

1. Please confirm that all starting material used in the manufacture of the drug substance are USP/NF grade or provide certificates of analyses for the starting materials used in the manufacture of the drug substances.

2. Please provide the BP monograph for the Limit of Bromides test and documentation to support that the BP test method is equivalent or better than the USP method.

3. On page 13 of volume 2 you indicate that the [redacted] Expiry for the WFI is "Discard after 24 hours", however, it is not clear what is meant by this statement as the WFI is not stored but used directly form the distillation apparatus. Please clarify.

4. Provide a description of the container closure system used for the storage of sodium bicarbonate and certification that the contact materials meet the appropriate 21 CFR food contact regulations.

5. Please provide stability data for sodium chloride to support your proposed re-test period.

6. The results for the normal carbonate and appearance in the stability section for sodium bicarbonate are illegible. Please re-submit these results.

7. The sterility acceptance criteria proposed for Normocarb HF™ 35 are "conforms to current USP requirements"; however, the sterility acceptance criteria proposed for Normocarb HF™ 25 are "conforms to current SOP requirements". Please confirm that this is a typographical error otherwise explain the differences in the sterility acceptance criteria for Normocarb HF™ 35 and Normocarb HF™ 25.

8. The methods used for physiochemical tests used in the Stopper Suitability Study were USP24 <381>, p. 1867-1868 and GM-63, Issue #6. It is not clear what GM-63, Issue #6 is. Please clarify.

9. The results of the tests for the dimensions and the acceptable quality levels for the Aluminum Crimp Cap w/ Polypropylene Cover in the CoA for the container closure were "n/a". It is not clear what is meant by "n/a". Please clarify how do you determine that these components comply with the specification and meet the quality attributes.

10. Please provide updated stability data for Normocarb HF™ 25.

11. You indicate that up to 24 months of data is available for 11 batches of Normocarb HF™ 35, however, you only included data for three batches of this drug product stored horizontally and vertically at 25°C/60% RH. Please explain how you selected the lots that were included in this application as primary stability lots and provide a summary of the data, which includes ranges of values observed, for the other 8 batches.

12. Please provide a post-marketing stability protocol for the drug product.

13. Your specifications for Normocarb HF™ 35 and Normocarb HF™ 25 include an identification test for carbonate, however, carbonate is not part of API in the drug product. Please clarify.

14. Please update your drug product specification to include a test and acceptance criterion for osmolarity or provide justification for not including this test in the drug product specification.

15. Your acceptance criteria for the sodium, total chlorides, magnesium and hydrogen carbonate assays for Normocarb HF™ 25 is 90-110% of label claim; however, the acceptance criteria for the corresponding assays for Normocarb HF™ 35 are given in grams per liter. Please modify acceptance criteria for the sodium, total chlorides, magnesium and hydrogen carbonate assays for Normocarb HF™ 35 to % of label claim as per Normocarb HF™ 25.

15. Your letter of authorization for the manufacture of magnesium chloride hexahydrate references DMF [redacted]. This DMF number is incorrect. Please provide a new letter of authorization with the correct DMF number. The DMF holder should check the correct DMF number from the letter that was sent to the DMF holder on January 28, 2005.

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

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Dr. Ann H. Rose
US Agent for Dialysis Solutions, Inc.
ViCro LLC
2600 Pennsylvania Avenue, NW, Suite 8D
Washington, DC 20037

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/s/

Edward Fromm
5/1/2006 09:00:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-910

Dialysis Solutions, Inc.
Attention: Mr. Walter O'Rourke
14 Emmett Place
Whitby, Ontario
L1R 2B4 Canada

Dear Mr. O'Rourke:

Please refer to your September 23, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Normocarb-HF 25/Normocarb-HF 35.

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 November 25, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129.

Sincerely,

[illegible]

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

Cc: Ms. Ann H. Rose
U.S. Agent for Dialysis Solutions, Inc
Vicro LLC
2600 Pennsylvania Avenue, N.W., Suite 810
Washington, D.C. 20037

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/s/

Norman Stockbridge
12/2/2005 03:33:39 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-910

Trade Name: Normocarb HF™
Generic Name: Normocarb HF™
Strengths: Solution with HCO3 = 25
Solution with HCO3 = 35

Applicant: Dialysis Solutions, Inc.

Date of Application: September 23, 2005
Date of Receipt: September 26, 2005
Date clock started after UN: September 26, 2005
Date of Filing Meeting: November 7, 2005
Filing Date: November 26, 2005 (Sat)
74 day Letter: December 9, 2005
User Fee Goal Date: July 26, 2006

Indication(s) requested: use in the management of patients undergoing Continuous Renal Replacement Therapy (CRRT) with hemofiltration

Type of Original NDA: (b)(2)

Therapeutic Classification: S
Chemical Classification: 3
Other: Orphan

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee Status: Exempt: Orphan

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO

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

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A

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

- Is the application affected by the Application Integrity Policy (AIP)? NO
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

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

- If an electronic NDA, does it follow the Guidance? N/A
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Additional comments:

- If in Common Technical Document format, does it follow the guidance? YES

- Is it an electronic CTD? N/A

  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Additional comments:

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? NO
  NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES

  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES

- List referenced IND numbers: P-IND 65,826

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

- Pre-NDA Meeting(s)? Date: March 11, 2005
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A

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

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 7, 2005

BACKGROUND:
Dialysis Solutions Inc. has developed Normocarb for use in the management of patients undergoing Continuous Renal Replacement Therapy (CRRT) with hemofiltration. Normocarb has been approved by the Center for Devices and Radiological Health (CDRH) for use as a hemodialysis solution. In December 2002, the sponsor submitted a Request for Designation and in May 2003 submitted a Request for Reconsideration. After several meetings with the FDA it was decided that this product for its intended use is a drug and will be regulated by CDER. Dialysis Solutions Inc met with the Division in December 2003 and March 2005 for their Pre-NDA meeting.

Dialysis Solutions Inc. is proposing a 25-mEq and a 35 mEq HCO3 formulation.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardiovascular and Renal Products (DCaRP)
Ellis Unger, M.D.	Deputy Director, DCaRP
Shari Targum, M.D.	Acting Team Leader, Medical
Juan Carlos Pelayo, M.D.	Medical Officer
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry
Monica Cooper, Ph.D.	Chemist
Sherita McLamore, Ph.D.	Chemist
Edward Fromm	Chief, Project Management Staff
Dianne Paraoan	Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer	Expected date
Medical:	Juan Carlos Pelayo	1 Apr 06
Secondary Medical:		
Statistical:		
Pharmacology:		
Chemistry:	Sherita McLamore	31 May 06
Environmental Assessment (if needed):		
Biopharmaceutical:		
Microbiology, sterility:	Steve Langille	
DSI:		
Regulatory Project Management:	Dianne Paraoan	
Other Consults:		

Per reviewers, are all parts in English or English translation? YES

If no, explain:

CLINICAL FILE X REFUSE TO FILE ___

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

N/A

MICROBIOLOGY		FILE X	REFUSE TO FILE ___
STATISTICS	N/A X	FILE ___	REFUSE TO FILE ___
BIOPHARMACEUTICS	N/A X	FILE ___	REFUSE TO FILE ___
PHARMACOLOGY	N/A X	FILE ___	REFUSE TO FILE ___
CHEMISTRY		FILE X	REFUSE TO FILE ___

- Establishment(s) ready for inspection? YES
  Microbiology YES

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ 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.

__X__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74 -December 9, 2005.
List (optional):

ACTION ITEMS:
None.

Dianne Paraoan
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

Draft: 21Nov05 Final: 12/1/05
RD
Stockbridge 11/30/05
Fromm11-30-05
Unger 11-29-05
Targum 11-28-05
Pelayo 11-28-05
Srinivasachar11-25-05
Cooper 21-Nov-2005
McLamore 11-21-05

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

/s/

Dianne Paraoan
12/2/2005 02:14:40 PM
CSO

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

August 9, 2005

ViCroLLC
2600 Pennsylvania Avenue NW, Suite 8D
Washington DC 20037

Re: Designation Request # 04-1989

Attention: Ann H. Rose, Ph.D.
U.S. Agent

Dear Dr. Rose:

Reference is made to your request for orphan-drug designation dated December 1, 2004, submitted on behalf of Novex Pharma, of bicarbonate infusate solution (trade name: Normocarb HF™) for "treatment of acute renal failure (ARF) in patients requiring continuous renal replacement therapy (CRRT) with hemofiltration." We also refer to our acknowledgment letters of December 2, 2004, and April 4, 2005, and to your submissions dated March 1 and May 16, 2005.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of bicarbonate infusate solution is granted for *use in the management of patients undergoing continuous renal replacement therapy (CRRT) with hemofiltration.* Please be advised that it is bicarbonate infusate and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you need further assistance in the clinical development of your drug, please feel free to contact Jeffrey Fritsch, R.Ph., at (301) 827-0989. Please refer to this letter as official notification. 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse 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 rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
DIALYSIS SOLUTIONS INC.(DSI)
14 EMMETT PLACE
WHITBY, ONTARIO
L1R 2B4 CANADA

2. TELEPHONE NUMBER *(Include Area Code)*
(905) 665.4709

3. PRODUCT NAME
NORMOCARB HF

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA # 21-910

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:

_____
(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)

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
[signature]	PRESIDENT/CEO ViCRO	9/23/2005

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

Pre-NDA Meeting Minutes

Meeting Date:	March 11, 2005
Type of Meeting:	Pre-NDA Meeting
P-IND Application:	65,826
Sponsor:	Dialysis Solutions, Inc.
Classification:	B
Meeting Request Date:	December 23, 2004
Confirmation Date:	January 3, 2005
Briefing Package Received:	February 1, 2005
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Dianne Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Norman Stockbridge, M.D., Ph.D.	Acting Division Director, Division of Cardio-Renal Drug Products, HFD-110
Carolyn Neuland, Ph.D.	Chief, Gastroenterology and Renal Devices Branch (GRDB), CDRH, HFZ-470
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
B. Nhi Beasley, Pharm. D.	Clinical Pharmacologist, HFD-860
Monica Cooper, Ph.D.	Chemist, HFD-810
Jeffrey Cooper, D.V.M.	Veterinary Medical Officer, GRDB, CDRH, HFZ-470
Claudia Ruiz, M.D.	Medical Officer, Nephrologist, CDRH, HFZ-470
Mary Ross Southworth, Pharm. D.	DDRE Safety Evaluator, Office of Drug Safety
Jeff Fritsch, R. Ph.	Regulatory Review Officer, Orphan Products Development, HF-35
Edward Fromm	Chief, Project Management Staff, HFD-110
Dianne Paraoan	Regulatory Health Project Manager, HFD-110

Dialysis Solutions, Inc.

Walter O'Rourke	President, Dialysis Solutions, Inc.
Sheldon Tobe, M.D.	Medical Director, Dialysis Solutions, Inc.
Ann H. Rose, Ph.D.	CEO, President, ViCro
Judi Smith, M.S.	CMC Affairs, ViCro
William V. Miller, M.D.	Medical Affairs, ViCro
Ronald J. Marler, DVM, Ph.D.	Pre-Clinical Affairs, ViCro

BACKGROUND

Dialysis Solutions Inc. (DSI), a Canadian based company, requested this Pre-NDA meeting to discuss the regulatory requirements for submission and approval of a new drug application (NDA) for Normocarb Hemofiltration Solution. This meeting is intended to confirm the material to be included in their NDA submission.

Normocarb has been approved by the Center for Devices and Radiological Health (CDRH) for use as a dialysate. The sponsor would like to obtain a 505(b)(2) approval for the product to be marketed as an infusate in hemofiltration as well. In December 2003, the sponsor met with the Division to discuss their requirements for submitting an NDA. During that meeting, Dr. Throckmorton recommended that the sponsor not make any novel claims and that they provide evidence assuring the Division that the product given as an infusate is just as safe or safer than when given as a dialysate.

A separate CMC Pre-NDA meeting was held on 10 March 2005.

DISCUSSION POINTS

Pre-Clinical
The Division agreed that no further preclinical safety/efficacy studies are needed.

Clinical
Dialysis Solutions, Inc. informed the Division that they intend for patients to be treated for about 6-7 days at 20mL/kg/hr. They do not plan on including a fixed flow rate in their label. They propose patients to remain on therapy as long as needed and discontinued from therapy at the physician's discretion. Normocarb would be administered as an adjunct to dialysis to maintain suitable acid-base balance. They will provide the Division with specific details in their NDA submission.

Dr. Stockbridge informed the sponsor that we are encouraged by their amount of clinical data; however, he suggested that they avoid specifying a population that is "pseudo specific", or carving out a patient population or specific indication, when there are no data for doing so. Dialysis Solutions, Inc. plans on focusing on patients in acute renal failure, not yet in multi-organ failure, in the Intensive Care Unit (ICU) setting only. They have not looked into other settings. They thought that it would be better to come in narrow and then, at our suggestion, go to a broader population. The sponsor added that the number of patients in acute renal failure in this setting is well within the orphan designation requirements- less than 100,000 patients/year. Furthermore, they believe they will have enough clinical exposure data in this setting.

They intend to seek orphan designation. Dr. Stockbridge informed them that the Office of Orphan Products Development, not the Division decides whether their setting is an appropriate candidate and will decide whether to grant orphan designation.

The sponsor plans on submitting their NDA as a 505(b)(2) application. They anticipate submitting literature to show efficacy and safety of Normocarb. There was a discussion about the need for the sponsor to conduct a mortality trial. The sponsor does not intend on claiming that they reduce mortality.

There was discussion about changing their indication or claim. Dr. Stockbridge informed them that it is possible for them to get other claims, but he doubted that they will be able to get another claim from supportive literature. They may, however, with supportive literature, get a claim as an adjunct to hemofiltration. Dialysis Solutions, Inc. was reminded that they should not make any novel claims if they intended to submit their application as a 505(b)(2). Seeking additional claims will require data to support their claims.

Dr. Ruiz led the discussion about clinical data in children and the lack of calcium in Normocarb. The sponsor stated that the label would not infer that their was calcium in their solution. If calcium needs to be given in conjunction with Normocarb, the sponsor stated that they are not aware of any drug-drug interactions with their solution.

There was discussion about a proposed 25-mEq formulation in addition to the 35-mEq formulation. The 35-mEq formulation is approved as a dialysate in CDRH. However, 25 mEq is not. The sponsor replied that they intended on submitting the 25-mEq formulation to CDRH as a dialysate. Dr. Stockbridge informed them that it is their decision to make as to whether they wished to submit 25 and 35 mEq together or the 35-mEq formulation first.

Dialysis Solutions, Inc. would like to use the same label for Normocarb as an infusate and dialysate. The packaging would be the same as well. Dr. Stockbridge advised the sponsor that the package insert should be straightforward and provide specific instructions for each indicated use, then the Division does not have a problem with one label. However, if Normocarb will be used in a setting where there is room for error, i.e. in one setting they need to dilute the solution and the other, they do not, then a separate label is recommended. It was suggested that at time of their NDA submission that they submit two separate labels and one combined label for review.

The sponsor asked the Division about range approval and Orphan designation. For example, if they chose to change the $NaHCO_3$ level from 30 to 35, would they still be granted orphan status? Jeff Fritsch from Orphan Products will reply directly to the sponsor.

Additional comments from the Office of Drug Safety not provided during the meeting

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

  RiskMAPs

  2.5.5 Overview of Safety with appropriate cross references to section
  2.7.4 Summary of Clinical Safety
  and any other relevant sections of the Common Technical Document for the NDA/BLA application.

  Pharmacovigilance plans

  2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
  (e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the
NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or
BLA Clinical Data Section (21 CFR 601.25(b)(3))
and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at http://www.fda.gov/cder/guidance/5766dft.pdf and http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc .

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

CONCLUSIONS/ RECOMMENDATIONS

Dialysis Solutions, Inc. intends on submitting their NDA before the end of the year, as a standard review. They should refer to the 21CFR314.50 and the CDER Guidances, specifically the 505(b)(2) Guidance, when preparing to submit their NDA application.

The sponsor should continue discussion with the Office of Orphan Drug Products in their pursuit of orphan designation.

We encourage them to contact the Division if they need additional assistance.

Recorder: Dianne C. Paraoan

Concurrence, Chair: *(see appended page for electronic signature)*
Norman Stockbridge, M.D., Ph.D.

Draft: 3/24/05 Final: 4/1/05
RD:
Stockbridge:4/1/05
Fromm:3/30/05
Karkowsky:3/29/05
Pelayo:29-Mar-2005
M. Cooper: 29-Mar-2005
Beasley: 3/28/05
J. Cooper: 3/29/05
Ruiz: 3/30/05
Southworth: 3/28/05
Fritsch: 3/28/05

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
4/1/05 08:29:04 AM

Pre-NDA Meeting Minutes

Meeting Date:	March 10, 2005
Type of Meeting:	Pre-NDA CMC Meeting
P-IND Application:	65,826
Sponsor:	Dialysis Solutions, Inc.
Classification:	B
Meeting Request Date:	January 5, 2005
Confirmation Date:	January 6, 2005
Briefing Package Received:	February 1, 2005
Meeting Chair:	Kasturi Srinivasachar, Ph.D.
Meeting Recorder:	Dianne Paraoan

Attendees:

Office of New Drug Chemistry I/Division of Cardio-Renal Drug Products Team

Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Monica Cooper, Ph.D.	Chemist, HFD-810
Dianne Paraoan	Regulatory Health Project Manager, HFD-110

ViCro on behalf of Dialysis Solutions, Inc.

Ann H. Rose, Ph.D.	CEO, President
Judi Smith, M.S.	CMC Affairs
William V. Miller, M.D.	Medical Affairs
Ronald J. Marler, DVM, Ph.D.	Pre-Clinical Affairs

BACKGROUND

Dialysis Solutions Inc. (DSI), a Canadian based company, requested this Pre-IND meeting to discuss the regulatory requirements for submission and approval of a new drug application (NDA) for Normocarb Hemofiltration Solution.

Normocarb has been approved by the Center for Devices and Radiological Health (CDRH) for use as a dialysate. The sponsor would like to obtain a 505(b)(2) approval for the product to be marketed as an infusate in hemofiltration as well. In December 2003, the sponsor met with the Division to discuss their requirements for submitting an NDA.

The purpose of this CMC meeting is to discuss the CMC requirements of a 505(b)(2) and the adequacy and sufficiency of the manufacturing process used for this product. They intend to manufacture the product in substantially the same manner as that used in their 510K application for a dialysate.

DISCUSSION POINTS

Dr. Srinivasachar provided the sponsor with general information. He reminded them that at the December 2003 meeting, we discussed that their infusate solution is considered a drug and would need to meet the CDER CMC requirements. Although the drug is approved as a dialysate under a 510(K) in CDRH, this does not mean that the same CMC requirements apply. Normocarb as an infusate should be a stand alone drug. The sponsor should not cross reference the 510(K), but should refer to the CDER Guidances available on the FDA website when preparing their submission.

The sponsor was advised by Dr. Srinivasachar to seek agreement from the Division on the following 3 issues at the Clinical Meeting on March 11: 1) the post-approval submission of a 25mEq/L solution as a dosing change rather than as a new NDA, 2) a combined package insert for the infusate and the dialysate, and 3), submitting their application as a 505(b)(2). Dr. Srinivasachar noted that the CMC requirements, whether a 505(b)(2) or (b)(1), are the same.

Pre-approval inspection process
Once their NDA is submitted, the Office of New Drug Chemistry will submit a consult to the Office of Compliance who will decide whether or not they will conduct a pre-approval inspection. The decision of inspecting their facilities is not that of the Division, but of the Office of Compliance. The Division can include in our consult that their product is approved as a dialysate through CDRH; however, the sponsor should keep in mind that the requirements may differ.

Drug Substance
Dr. Srinivasachar informed the sponsor that all three components of Normocarb are considered drug substances (NaCl, $NaHCO_3$, and $MgCl_2$). Therefore, they need to ensure they are manufactured under cGMP. Details of the manufacturing, including the purification procedure, specifications, etc., that the vendor is using should be included in their submission. In addition, a complete list of all vendors should be provided. The drug substance vendors must meet all standards and are subject to inspection.

Dialysis Solutions, Inc. can reference a vendor's Drug Master File (DMF), if available, for the drug substance manufacturing processes, stability data, etc., but will need a written letter of authorization from the vendor to access the file. This would alleviate a section in their submission. Stability data and certificates of analysis for each drug substance should also be provided.

Dr. Srinivasachar explained the importance of qualifying the suppliers and conducting confirmatory tests to ensure that the analytical results are reproducible. Then, if they are, the sponsor should conduct identification tests, as a minimum, on all incoming lots. Furthermore, the sponsor should conduct full acceptance testing on a recurring basis, repeating all of the tests to maintain a vendor's qualification. The sponsor can determine the frequency and number of lots they wish to retest. Each drug substance should have a retest date, based on stability data, established by the manufacturer. Dr. Srinivasachar reminded the sponsor that any analytical methods that differ from the USP must be validated.

Drug Product

Details of the manufacturing process should be provided in the NDA submission to include the sterilization process, batch analysis, specifications, etc. for the drug product. Dialysis Solutions, Inc. will need to assay for each of the drug substances in the drug product.

The sponsor will be requesting a 24 month expiration date. They informed us that they will provide 24 months of long term data on three batches to support their proposed expiration date.

Dr. Srinivasachar reminded the sponsor that for a sterile injectable product, every batch released should be tested for sterility, particulate matter, and endotoxins.

USP tests for extractables should be conducted because of the possible leaching of polymers from the elastomeric stoppers. Furthermore, the sponsor is recommended to determine the stability of the drug product diluted into 3L of sterile water as the solution for infusion. Dialysis Solutions, Inc. will need to provide this data to support any statements in the label concerning the duration of use of the diluted infusion solution.

Dr. Srinivasachar added that they will also need to submit master and executed batch records.

CONCLUSIONS/ RECOMMENDATIONS

The sponsor should consider the discussions and suggestions described above in preparing their NDA application. Dialysis Solutions, Inc. should refer to the CDER Guidances for the CMC requirements.

Dialysis Solutions, Inc. should contact the Division if they need additional assistance.

Recorder: Dianne C. Paraoan

Concurrence, Chair: *(see appended page for electronic signature)*
Kasturi Srinivasachar, Ph.D.

Draft: 3/17/05 Final: 3/23/05
RD:
Srinivasachar: 3/22/05
Cooper: 3/15/05

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

/s/

Kasturi Srinivasachar
3/23/05 11:56:40 AM

Pre-IND Meeting Minutes

Meeting Date:	December 10, 2003
Type of Meeting:	Pre-IND Meeting
P-IND Application:	65,826
Sponsor:	Dialysis Solutions Inc. (DSI)
Classification:	B
Meeting Request Date:	October 14, 2003
Confirmation Date:	October 23, 2003 (faxed confirmation sent)
Briefing Package Received:	November 10, 2003
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Dianne Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D.	Director, Division Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D	Team Leader, Chemistry, HFD-810
Suzanne O'Shea, Esq.	Regulatory Counsel, Office of Combination Products, HFG-3
Carolyn Neuland, Ph.D.	Chief, CDRH, Gastroenterology and Renal Devices Branch, HFZ-470
Jeffrey Cooper, D.V.M.	Veterinary Medical Officer, CDRH, Gastroenterology and Renal Devices Branch, HFZ-470
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110
Dianne Paraoan	Regulatory Health Project Manager, HFD-110

Dialysis Solutions Inc. (DSI)

Walter O'Rourke	President, Dialysis Solutions Inc.
Dr. Sheldon Tobe	Medical Director, Dialysis Solutions Inc.
Dr. LuAnn Erlich	Senior Director, Pharmaceutical & Computer Services, Apotex Corp.
Marcy MacDonald	Director, Regulatory Affairs, Apotex Corp.

BACKGROUND

Dialysis Solutions Inc. (DSI), a Canadian based company, requested this Pre-IND meeting to discuss the regulatory requirements for submission and approval of a new drug application (NDA) for Normocarb Hemofiltration Solution.

Normocarb has been approved by the Center for Devices and Radiological Health (CDRH) for use as a hemodialysis solution. The sponsor would like to obtain approval for the product to be marketed as an infusate in hemofiltration as well. To pursue Normocarb Hemofiltration Solution, the sponsor submitted a Request for Designation in December 2002, a Request for Reconsideration in May 2003, and conducted several meetings and discussions with the FDA. The FDA determined that Normocarb Hemofiltration Solution for the intended use is a drug and will be regulated by CDER.

DISCUSSION POINTS

General Discussion

Dr. Throckmorton provided the sponsor with the following general recommendations for consideration in planning their NDA submission for approval of Normocarb Hemofiltration Solution as an infusate.

1. Claim Structure
The sponsor assured the Division that the product is intended only for the current claim as an infusate in hemofiltration, and that they were not seeking any additional claims.
Dr. Throckmorton recommended that the sponsor not make any novel claims, but if the sponsor intended to seek additional claims, they should provide data to support the claim(s).

2. Chemistry, Manufacturing, and Control (CMC)
CMC requirements of a dialysate and an infusate differ. Dr. Throckmorton stated that all CMC data would need to be done according to the relevant CDER Guidances, and that the data would need to be complete at the time of submission. In addition, the sponsor should submit sufficient references to support their claim. The sponsor stated that they were aware of and followed the good manufacturing practices and guidances regarding new drug development.

3. General Safety
At the time of submission, Dr. Throckmorton suggested that the sponsor provide evidence assuring the Division that the product given as an infusate is just as safe or safer when given as a dialysate. If using publications, they should focus on the use of infusates whose compositions most match that of Normocarb (especially bicarbonate).

Pre-Clinical

Dr. Throckmorton informed the sponsor that based on the information provided, no additional pre-clinical studies are required. However, the sponsor should submit relevant references to animal testing, to support their claim as a 505(b)(2) application.

CMC

Concentration comparison as a dialysate versus an infusate

The sponsor asked if we were requiring electronic applications only. The Division stated that, to date, we are accepting electronic, paper and electronic/paper applications.

The sponsor believes they will be prepared to submit a NDA application without submitting an IND application and informed the Division that they plan on submitting the NDA application by the middle of 2004. Dr. Throckmorton invited the sponsor to meet with the Division for a pre-NDA meeting prior to their NDA submission.

CONCLUSIONS/ RECOMMENDATIONS

The Division recommended that the sponsor consider the discussions and suggestions described above in preparing their application. We encouraged them to contact the Division if they need additional assistance.

Signature recorder: _____
Dianne C. Paraoan

Concurrence, Chair: *{See appended electronic signature page}*
Douglas C. Throckmorton, M.D.

Draft: 12/12/03 Final: 1/5/04
RD:

Throckmorton: 12/30/03
Stockbridge: 12/23/03
Cooper: 12/23/03
Marciniak: 12/23/03
DeFelice:12/22/03
Srinivasachar:12-22-03
Allis: 12/22/03

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/s/

Doug Throckmorton
1/5/04 10:43:45 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-910	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: Normocarb HF™ 25 and Normocarb HF™ 35		Applicant: Dialysis Solutions Inc.	
RPM: Dianne Paraoan		HFD- 110	Phone # 301-796-1129

Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(X)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): The applicant has referred to published literature of the solutions (compounds) not a specific application. The products are physiological solutions. The solution has been approved as a dialysate as a 510(k) in the Center for Devices and Radiological Health (CDRH).

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	July 26, 2006
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number _____
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____
• User Fee exception	**(X)** Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) _____
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	[redacted]
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **(X)** Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	**(X)** N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No,**" continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	July 5, 2006 (PM)

❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	July 20, 2006
• Most recent applicant-proposed labeling	September 26, 2006
• Original applicant-proposed labeling	September 26, 2006
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: January 26, 2006 July 7, 2006 DDMAC: May 26, 2006 Labeling Meetings: June 23, July 6, 11 and 18, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	July 20, 2006
• Reviews	DMETS: January 26, 2006 July 7, 2006
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	March 11, 2005 CMC only- March 10, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Pre-IND Meeting: December 10, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A

❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary and Application Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Stockbridge: July 12, 2006
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	July 7, 2006
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A. The sponsor has submitted literature references to support the safety and efficacy of these products and no additional literature was submitted.
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	July 12, 2006
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	June 14 and 19, 2006
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	June 14, 2006
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	June 14, 2006
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	May 19 and June 13, 2006
❖ Facilities inspection (provide EER report)	Date completed: March 29, 2006 **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	**(X)** Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

John David
7/27/2006 08:21:19 AM
CSO