CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-910

CHEMISTRY REVIEW(S)

NDA 21-910

Normocarb HF™ Dialysis Solutions, Inc.

Dialysis Solutions, Inc.
HFD-110

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 21-910

2. REVIEW: 3

3. REVIEW DATE: July 26, 2006

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	November 18, 2005
Amendment	May 15, 2006
Amendment	June 12, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	July 12, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Dialysis Solutions, Inc..
Address:	14 Emmett Place Whitby, Ontario L1R2B4 Canada
Representative:	Vicro LLC (US Agent) 2600 Pennsylvania Avenue, NW Suite 8D Washington, DC 20037
Telephone:	905.884.6296

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Normocarb HF
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Renal Replacement Therapy

11. DOSAGE FORM: Dialysis Infusate Solution

12. STRENGTH/POTENCY: 35 mEq/L and 25mEq/L

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Sodium Chloride, Magnesium Chloride, Sodium Bicarbonate, Water for Injection and [redacted]
Molecular Formula: NaCl, $MgCl_2$, $NaHCO_3$, H_2O, [redacted]
Molecular Weight:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF [redacted]	Type II	[redacted]	[redacted]	1	Adequate	06-12-06	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	3/29/06	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A.
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Acceptable	6/09/06	Sherita McLamore, Ph.D.
Microbiology	Acceptable	6/12/06	Stephen Langille, Ph.D.

The Chemistry Review for NDA 21-910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application was recommended for APPROVAL in review #2. This review covers changes that were made to the package insert and to the labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Sodium Chloride, Magnesium Chloride, Sodium Bicarbonate, Water for Injection (WFI) and [redacted] were listed as drug substances in this application. All are compendial grade. The [redacted]n is used as a processing aid and the WFI is the vehicle. The applicant includes manufactures, certificates of analyses and methods on manufacture for each of the aforementioned drug substances.

The drug product, Normocarb HF™, is clear sterile, calcium-free, bicarbonate dialysis infusate solution. It is provided in 240 mL vials which are diluted with 3 liters of sterile water for injection. It is intended to be used as a dialysis infusate solution in continuous renal replacement therapy (CRRT) in adult and pediatric patients. In an effort to meet the changing needs of CRRT patients, drug product is being developed in two dosage concentration, 35 mEq/L (Normocarb HF™ 35) and 25 mEq/L (Normocarb HF™ 25). The two strengths will have the same ingredients, specifications, manufacturing and quality controls procedure but will differ only in the amounts of ingredients added. Normocarb HF™ 25 will have a higher concentration of Chloride and a lower concentration of bicarbonate than Normocarb HF™ 35 . The bicarbonate levels were decreased to provide the additional strength (25 mEq/L) and the increase in chlorine ions was done in an effort to maintain the same total concentration of anions and cations in the reconstituted product. The intended commercial batch size for Normocarb HF™ 35 and Normocarb HF™ 25 are [redacted] respectively. The drug product will be manufactured, packaged and tested by Apotex Inc. of Ontario, Canada. Both concentrations of the drug product will be packaged in 240 mL clear, type I glass serum vials that have been [redacted] prior to filling. The vials will be sealed with a [redacted] sterilized grey elastomeric serum stopper and capped with an aluminum crimp caps with a blue propylene covers. The applicant includes a complete description of each of the packaging component including manufacturers, certificates of analyses, drawings, diagrams and specifications for each of the packaging components.

The applicant has requested a 24 month shelf life for both concentrations of the drug product and a 24 hour expiry for the diluted solution. As indicated in the stability section of this review, the applicant initially included twelve months of long term and three months of accelerated stability for two full scale batches of Normocarb HF™ 25 and 24 months of long term and three months of accelerated data on three batches of Normocarb HF™ 35. In the May 15, 2006 response, the applicant provided an eighteen month stability update for Normocarb HF™ 25. All data was acceptable and within the prescribed acceptance criteria. With the eighteen month stability update, the applicant has provided adequate information to support a 24- month expiry for Normocarb HF™ 25 and Normocarb HF™ 35. Accordingly, we will grant the **24 month expiry** for **Normocarb HF™ 35** and **Normocarb HF™ 25**. The applicant also requested a 24-hour expiry for the diluted solution. The applicant provided 360 hours of data for the constituted drug product. Data was collected at room temperature and under refrigerated conditions. All data were acceptable and within the prescribed acceptance criteria, accordingly the **24-hour expiry** for the diluted solution is granted as well.

B. Description of How the Drug Product is Intended to be Used

Normocarb HF™ is being developed for use in continuous replacement therapy. Normocarb™ is an FDA approved sodium bicarbonate dialysate solution. Normocarb HF™ is identical to Normocarb™. Normocarb™ has been extensively marketed in Canada since March 1, 2001 and had never been recalled for safety. The applicant includes reconstitution instruction in the package insert.

C. Basis for Approvability or Not-Approval Recommendation

This application was recommended for approval by CMC in review #2 (June 2006). This review only summarizes the changes made to the label and package insert (PI).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood/Date
DParaoan (PM)/Date

C. CC Block

Orig. NDA 21-910
HFD-110/Division File
HFD-110/ DParaoan
SMcLamore
KSrinivasachar
RSood

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Sherita McLamore
7/26/2006 09:11:41 AM
CHEMIST

Ramesh Sood
7/26/2006 09:18:36 AM
CHEMIST

NDA 21-910

Normocarb HF™ Dialysis Solutions, Inc.

Dialysis Solutions, Inc.
HFD-110

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of Drug Quality Assessment

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B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

I. DRUG SUBSTANCE 11

1. Description & Characterization 11

a. Description 11
b. Characterization / Proof Of Structure 11

2. Manufacturer 13

3. Synthesis / Method Of Manufacture 13

a. Starting Materials - Specs & Tests 13
b. Solvents, Reagents, etc. 15
c. Flow Chart 17
d. Detailed Description 18

4. Process Controls 18

a. Reaction Completion / Other In-Process Tests 18
b. Intermediate Specs & Tests 19

5. Reference Standard 19

a. Preparation....19
b. Specifications....20
6. Regulatory Specifications / Analytical Methods....21
a. Drug Substance Specifications & Tests....21
b. Purity Profile....21
c. Microbiology....25
7. Container/Closure System For Drug Substance Storage....26
8. Drug Substance Stability....27

II. DRUG PRODUCT....
1. Components/Composition....
2. Specifications & Methods For Drug Product Ingredients....
a. Active Ingredient(s)....
b. Inactive Ingredients....
3. Manufacturer....
4. Methods Of Manufacturing And Packagingg....
a. Production Operations....
b. In-Process Controls & Tests....
c. Reprocessing Operations....
5. Regulatory Specifications And Methods For Drug Product....
a. Sampling Procedures....
b. Regulatory Specifications And Methods....
6. Container/Closure System....
7. Microbiology....
8. Drug Product Stability....

III. INVESTIGATIONAL FORMULATIONS....

IV. ENVIRONMENTAL ASSESSMENT....

V. METHODS VALIDATION....

VI. LABELING....

VII. ESTABLISHMENT INSPECTION....

VIII. DRAFT DEFICIENCY LETTER....

Chemistry Review Data Sheet

1. NDA 21-910

2. REVIEW: 2

3. REVIEW DATE: June 19, 2006

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	November 18, 2005
Amendment	May 15, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 12, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Dialysis Solutions, Inc..
Address:	14 Emmett Place Whitby, Ontario L1R2B4 Canada
Representative:	Vicro LLC (US Agent) 2600 Pennsylvania Avenue, NW Suite 8D Washington, DC 20037
Telephone:	905.884.6296

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Normocarb HF
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority:
   - Chem. Type: 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Renal Replacement Therapy

11. DOSAGE FORM: Dialysis Infusate Solution

12. STRENGTH/POTENCY: 35 mEq/L and 25mEq/L

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Sodium Chloride, Magnesium Chloride, Sodium Bicarbonate, Water for Injection and [redacted]
Molecular Formula: NaCl, $MgCl_2$, $NaHCO_3$, H_2O, [redacted]
Molecular Weight:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF [redacted]	Type II	[redacted]	[redacted]	1	Adequate	06-12-06	N/A

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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	3/29/06	Sherita McLamore, Ph.D.
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A.
LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Acceptable	6/09/06	Sherita McLamore, Ph.D.
Microbiology	Acceptable	6/12/06	Stephen Langille, Ph.D.

The Chemistry Review for NDA 21-910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All CMC and microbiology deficiencies have been adequately addressed, accordingly, NDA 21-910 is recommended for APPROVAL from a CMC perspective

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Sodium Chloride, Magnesium Chloride, Sodium Bicarbonate, Water for Injection (WFI) and [redacted] were listed as drug substances in this application. All are compendial grade. The [redacted] is used as a processing aid and the WFI is the vehicle. The applicant includes manufactures, certificates of analyses and methods on manufacture for each of the aforementioned drug substances.

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B. Description of How the Drug Product is Intended to be Used

Normocarb HF™ is being developed for use in continuous replacement therapy. Normocarb™ is an FDA approved sodium bicarbonate dialysate solution. Normocarb HF™ is identical to Normocarb™. Normocarb™ has been extensively marketed in Canada since March 1, 2001 and had never been recalled for safety. The applicant includes reconstitution instruction in the package insert.

C. Basis for Approvability or Not-Approval Recommendation

Sixteen comments were conveyed to the applicant in a May 1, 2006 Information Request (IR) letter. The applicant responded to the IR letter on May 15, 2006 (see appendix 2). The responses to the comments are summarized in this review. In the response, the applicant adequately addressed all CMC concerns. Eight comment from the microbiology reviewer were conveyed to the applicant in the agency's May 23, 2006 Discipline review letter. The applicant responded to the Micro deficiencies on June 12, 2006. The responses were reviewed and deemed adequate by the microbiology reviewer. Accordingly, NDA this application is recommended for APPROVAL from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
RSood/Date
DParaoan (PM)/Date

C. CC Block

Orig. NDA 21-910
HFD-110/Division File
HFD-110/ DParaoan
SMcLamore
KSrinivasachar
RSood

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

/s/

Sherita McLamore
6/20/2006 09:48:48 AM
CHEMIST

Ramesh Sood
6/20/2006 09:56:30 AM
CHEMIST

NDA 21-910

Normocarb HF™ Dialysis Solutions, Inc.

Dialysis Solutions, Inc.
HFD-110

Sherita D. McLamore, Ph.D.
Division of Pre-Marketing Assessment 1
Office of Drug Quality Assessment

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a. Sampling Procedures....
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8. Drug Product Stability....

III. INVESTIGATIONAL FORMULATIONS....

IV. ENVIRONMENTAL ASSESSMENT....

V. METHODS VALIDATION....

VI. LABELING....

VII. ESTABLISHMENT INSPECTION....

VIII. DRAFT DEFICIENCY LETTER....

Chemistry Review Data Sheet

1. NDA 21-910

2. REVIEW: 1

3. REVIEW DATE: June 14, 2006

4. REVIEWER: Sherita D. McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	November 18, 2005
Amendment	May 15, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Dialysis Solutions, Inc..
Address:	14 Emmett Place Whitby, Ontario L1R2B4 Canada
Representative:	Vicro LLC (US Agent) 2600 Pennsylvania Avenue, NW Suite 8D Washington, DC 20037
Telephone:	905.884.6296

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a) Proprietary Name: Normocarb HF
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 3

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Renal Replacement Therapy

11. DOSAGE FORM: Dialysis Infusate Solution

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15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

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LNC	N/A	N/A	N/A
Methods Validation	N/A	N/A	Sherita McLamore, Ph.D.
DMETS	N/A	N/A	N/A
EA	Acceptable	6/09/06	Sherita McLamore, Ph.D.
Microbiology	Approvable pending revision	5/22/06	Stephen Langille, Ph.D.

The Chemistry Review for NDA 21-910

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is APPROVABLE from a CMC perspective. Approval of this application is contingent on adequate response to the microbiology deficiencies an acceptable recommendation from the Microbiology Reviewer.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

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The applicant has requested a 24 month shelf life for both concentrations of the drug product and a 24 hour expiry for the diluted solution. As indicated in the stability section of this review, the applicant initially included twelve months of long term and three months of accelerated stability for two full scale batches of Normocarb HF™ 25 and 24 months of long term and three months of accelerated data on three batches of Normocarb HF™ 35. In the May 15, 2006 response, the applicant provided an eighteen month stability update for Normocarb HF™ 25. All data was acceptable and within the prescribed acceptance criteria. With the eighteen month stability update, the applicant has provided adequate information to support a 24- month expiry for Normocarb HF™ 25 and Normocarb HF™ 35. Accordingly, we will grant the **24 month expiry** for **Normocarb HF™ 35** and **Normocarb HF™ 25**. The applicant also requested a 24-hour expiry for the diluted solution. The applicant provided 360 hours of data for the constituted drug product. Data was collected at room temperature and under refrigerated conditions. All data were acceptable and within the prescribed acceptance criteria, accordingly the **24-hour expiry** for the diluted solution is granted as well.

B. Description of How the Drug Product is Intended to be Used

Normocarb HF™ is being developed for use in continuous replacement therapy. Normocarb™ is an FDA approved sodium bicarbonate dialysate solution. Normocarb HF™ is identical to Normocarb™. Normocarb™ has been extensively marketed in Canada since March 1, 2001 and had never been recalled for safety. The applicant includes reconstitution instruction in the package insert.

C. Basis for Approvability or Not-Approval Recommendation

Sixteen comments were conveyed to the applicant in a May 1, 2006 Information Request (IR) letter. The applicant responded to the IR letter on May 15, 2006 (see appendix 2). The responses to the comments are summarized in this review. In the response, the applicant adequately addressed all CMC concerns. Eight comment from the microbiology reviewer were conveyed to the applicant in the agency's May 23, 2006 Discipline review letter. At this time the response is pending and the microbiology reviewer has recommended an approvable recommendation for this application. Accordingly, from a CMC perspective we recommend that this application should be APPROVABLE until all micro concerns have been adequately addressed.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date

RSood/Date
DParaoan (PM)/Date

C. CC Block
Orig. NDA 21-910
HFD-110/Division File
HFD-110/ DParaoan
SMcLamore
KSrinivasachar
RSood

47 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-2

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

/s/

Sherita McLamore
6/16/2006 02:56:12 PM
CHEMIST

Ramesh Sood
6/19/2006 03:21:55 PM
CHEMIST