CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-910

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-910 (Normocarb)

Sponsor: Dialysis Solutions

Review date: 12 July 2006

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-910

HFD-110/Paraoan
HFD-110/Xiao

Normocarb HF is a pair of sterile concentrates for infusate solutions for use to replace water and to correct acid-base and electrolyte disturbances caused during Continuous Renal Replacement Therapy (CRRT; hemofiltration, hemodiafiltration). The two solutions contain sodium, magnesium, chloride, and bicarbonate only, differing only in the bicarbonate mix—25 or 35 mM—and the corresponding changes in chloride. Thus there are no novel or foreign molecular species and what constituents there are are not what one would ordinarily mean by "drugs". Their actions are not receptor-mediated and they are not heir to the complex potential interactions of drugs.

The sponsor conducted no clinical trials, but there were published accounts of these or similarly constituted solutions as infusates for hemofiltration or hemodiafiltration. These publications were reviewed by medical officer Shen Xiao (11 July 2006). And they formed the basis for his recommendation that Normocarb HF be approved. In addition, the concentrations of constituents were selected to normalize electrolytes and acid-base. Their choices appear to be reasonable based on the effects of CRRT.

Other infusate constituents—potassium, calcium, glucose, phosphate—may need to be added, but individualization of treatment renders it impractical to manufacture solutions suitable for all possible clinical scenarios. Thus, labeling provides some basic advice, but the instructions for use heavily rely on the physician's judgment about how to perform CRRT.

Former Cardio-Renal Division Director Raymond Lipicky espoused a policy that all new dialysis solutions needed clinical outcome data to support their use and the contribution of individual components, even of they had no novel constituents, represented small differences from approved products, and had composition within the normal range. Hemodialysates (handled as devices by CDRH) have never been subject to these constraints. The CDER policy was largely overturned in a memo by then Division Director Doug Throckmorton (5 February 2004), which said we would consider new variants of an existing solution to be changes to dose and we would exercise some discretion in deciding to request clinical data to support proposed changes.

In the current application, the publications would not have been sufficient had we felt there was a need for clinical data supporting effectiveness or safety. Thus, the current regulatory decision on Normocarb HF lowers the bar again; sometimes (essentially) no clinical data are required.

Infusates (and dialysates) are, effectively, bulk parenterals. The consequences of their use 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.

The reviews of microbiology (Stephen Langille; 13 June 2006) and chemistry (Sherita McLamore; 20 June 2006) recommend approval. DDMAC objected to the "Normo" prefix, reasonably arguing that it is promotional. However, the Normocarb name is already in use for use as a hemodialysate (device), so I see no merit in forcing the new name to support use as an infusate.

At this writing, final approval is pending agreement on labeling.

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/s/

Norman Stockbridge
7/12/2006 08:17:38 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-910 (505) (b) (2)
Submission Number	N000
Submission Code	N/A
Letter Date	September 23, 2005
Stamp Date	September 26, 2005
PDUFA Goal Date	July 23, 2006
Reviewer Name	Shen Xiao, M.D., Ph.D.
Review Completion Date	July 7, 2006
Established Name	Normocarb HF™
(Proposed) Trade Name	Normocarb HF™
Therapeutic Class	Infusate
Applicant	Renal therapeutics
Priority Designation	S
Formulation	Solution
Dosing Regimen	N/A
Indication	Infuse solution for Continuous Renal Replacement Therapy with Hemofiltration
Intended Population	Acute renal failure

CLINICAL REVIEW

Clinical Review Section

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CLINICAL REVIEW

Clinical Review Section

Summary of Compositions of All types of Replacement Solutions used in CRRT from Published Literature*

	Study 1		Study 2		Study 3			Study 4	
	CVVHD		CVVHF		CVVHF			CVVHDF	CVVHF
Na (mmol/L)	132	144	135	140	142	140	140	150	140
K (mmol/L)	3.5	3.7	2	2	0	0	0	0	1
Mg (mmol/L)	1.5	1.4	0.8	0.5	0.8	1	0.5	1.3	0.8
Ca (mmol/L)	3.5	3.0	0	0	2	2	1.5	0.6	1.6
C l(mmol/L)	102	111	107	109	103	111	109	113	100
HCO_3 (mmol/L)	0	37	0	35	0	0	35	38	0
Lactate (mmol/L)	35	0	34	0	45	0	0	0	46
Acetate (mmol/L)	0	4	0	0	0	35	0	0	0
Glucose (mmol/L)	7	1	0	0	0	0	0	0	0
Anion (mmol/L)	137	152	141	144	148	146	144	151	146
Cation (mmol/L)	146	157	139	143	148	146	144	153.8	145.8
Osmolarity (mOsm)	290	310	280	287	295	292	298	304.8	291.8

	Study 5		Study 6		Study 7		Study 8		Study 9	Study 10	Study 12
	CVVHF		CVVHF		CVVHDF		CVVHD		CAVH	CVVHD	CRRT
Na (mmol/L)	142	155	140	140	140	140	132	140	140	140	140
K (mmol/L)	0-6	0-6	1	0	0	0	0	0	0	0	0
Mg (mmol/L)	0.8	0.8	0.8	0.5	0.5	0.8	0.8	0.8	0.5	0.8	0.8
Ca (mmol/L)	2	1.8	1.6	1.8	1.8	1.8	1.8	0	1.8	0	1.6
Cl (mmol/L)	104	120	100	110	105	110	102	107	110	107	101
HCO_3 (mmol/L)	0	40	0	32	0	32	0	35	31	35	0
Lactate (mmol/L)	45	3	46	3	40	3	35	0	3	0	45
Acetate (mmol/L)	0	0	0	0	0	0	0	0	0	0	0
Glucose (mmol/L)	0	0	11	0	0	0	0	0	0	0	11
Anion (mEq/L)	149	163	146	145	145	145	137	142	144	142	146
Cation (mEq/L)	148-154	160-166	146	145	145	145	137	142	145	142	145
Osmolarity (mOsm)	303	329	303	290	290	290	274	284	289	283.6	301.8

*: Solution buffers including bicarbonate, acetate, and lactate.

Table B: Comparison of Compositions from Normocarb HF vs Solutions from Published Literature.

	NormocarbHF™ 25	NormocarbHF™ 35	Published Literature	
			Minimal	maximal
Na (mmol/L)	140	140	132	155
K (mmol/L)	0	0	0	6
Mg (mmol/L)	0.75	0.75	0.5	1.5
Ca (mmol/L)	0	0	0	3.5
C l(mmol/L)	117	107	100	120
HCO_3 (mmol/L)	25	35	0	40
Lactate (mmol/L)	0	0	0	46
Acetate (mmol/L)	0	0	0	35
Glucose (mmol/L)	0	0	0	11
Anion (mmol/L)	142	142	137	163
Cation (mmol/L)	141.5	141.5	137	166
Osmolality (mOsm)	283.5	283.5	274	329

Abbreviations

ACHDF	acute continuous hemodiafiltration
ARF	acute renal failure
C-ARF	acute renal failure in children
CAVH	continuous arterio-venous hemofiltration
CAVHD	continuous arterio-venous hemodialysis
CAVHDF	continuous arterio-venous hemodiafiltration
CONC	Concentration
CRRT	continuous renal replacement therapy
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
CVVHDF	continuous veno-venous hemodiafiltration
ESRD	end stage renal disease
FDA	US Food & Drug Administration
H	Hour
HD	Hemodialysis
HDF	Hemodiafiltration
HF	Hemofiltration
ICU	intensive care unit
IHD	intermittent hemodialysis
IT	intermittent treatment
IV	Intravenous
L	Liter
mEq	Milliequivalent
mL	Milliliter
mmol	Millimole
MODS	multiple organ dysfunction syndrome
NA	not available
PTH	parathyroid hormone
RRT	renal replacement therapy
TT	Treatment

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

1. It is recommended that Normocarb HF™ be approved for the indication as a replacement solution in continuous renal replacement therapy (CRRT) to treat the adult and pediatric patients with acute renal failure.

2. The sponsor should provide detailed information in labeling for the selection of formulation Normocarb HF™ 25 and Normocarb HF™ 35 that were included in the Normocarb HF™.

The sponsor did not perform specific clinical studies on this product. Support for efficacy and safety has been based on the clinical reports from published literature. The medical reviewer concludes that, based on the results of published clinical studies, there is sufficient documentation in these articles to adequately evaluate the safety and efficacy of the Normocarb HF™ in the indicated adult ARF patient population when used as replacement solutions in CRRT. Within the physiological range of osmolarity, these solutions contain a buffer and electrolytes in concentrations aiming for physiological levels and taking into account preexisting deficits or excesses. The range of concentrations of electrolytes and buffers proposed in this application is covered by the cited reports. The concentrations of electrolytes and buffers from the published literatures and from Normocarb HF™ were summarized in the following table A and B, respectively.

Table A: Summary of Compositions of Electrolytes and Buffer in Bicarbonate Replacement solutions Used in CRRT from Published Literature

Components	Bicarbonate Replacement Solution
Sodium	135-150 mEq/L
Potassium*	0-4 mEq/L
Chloride	100-120 mEq/L
Magnesium	0.5-1.5 mEq/L
Calcium*	0-4 mEq/L
Bicarbonate	31.4-40 mEq/L
Lactate	0-3 mEq/L
Dextrose*	0-200mg/dl

Calcium, potassium and dextrose will be added in solutions if necessary

Outstanding issues with regard to these solutions include:

- For the Normocarb HF™ 25 solution, the bicarbonate concentration is 25mEq/L which is lower than the most published data that was used in the CRRT. However, there were some reports of alkalosis after long-term use of bicarbonate at concentration ≥ 35mEq/L in NormocarbHF™ 35 or other customized solutions (This can be treated by temporarily discontinuing or diminishing the infusion, and substituting normal saline solution until the pH returns normal). Therefore, the Normocarb HF™ 25 solution containing the physiological range of bicarbonate of 25mEq/L should be appropriate for the patients without severe metabolic acidosis.
- Normocarb HF™ solution has been used in several pediatric studies. Although the exact composition of the infusates during the CRRT was not indicated clearly, based on the similar plasma levels of electrolytes between the children and adults, the reviewer considers that Normocarb HF™ should be approved for pediatric use.
- In patients associated with bleeding, citrate has been commonly used as an anticoagulant in CRRT treatment. After the long-term use of this anticoagulant agent, the plasma concentration of bicarbonate will significantly increase due to the hepatic conversion of metabolized citrate to bicarbonate, and the concentrations of sodium or calcium may also change significantly. Therefore, the formulations of NormocarbHF™ may need to be adjusted in that situation. This information should be added to the labeling.
- Normocarb HF™ solutions do not contain phosphate and phosphate supplementation is generally required at some stage during CRRT. Therefore, customized solutions may be necessary in patients with some electrolyte imbalances. This information should also be added into the labeling.

1.2 Recommendation on Post-marketing Actions:

1.2.1 Risk Management Activity:
NA

1.2.2 Required Phase 4 Commitments
There are no required phase 4 commitments associated with this review or submission.

1.2.3 Other Phase 4 Requests:
NA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program:
The sponsor did not conduct a specific clinical development program. All clinical data were cited from published literature.

1.3.2 Efficacy:
Based on the clinical reports from the published data, the Normocarb HF™ solutions appear to be acceptable for CRRT. In pediatric patients, Normocarb HF™ appear to match the requirements in the CRRT treatment. However, the sponsor needs to provide detailed information of the composition of electrolytes and buffers of infusates that were used in pediatric patients from published literature. Details were provided in Section 6.

1.3.3 Safety:
No specific safety studies with the solutions were reported. Based on the clinical studies published from literature, the compositions of Normocarb HF™ solution were formulated from normal physiological electrolytes, buffers, and water. Calcium, potassium and dextrose will be added if necessary. Therefore, this solution itself should have no specific safety issues.

1.3.4 Dosing Regimen and Administration:
The proposed dosing depends on the mode of therapy, solute formulation, flow rates and length of therapy and depends on the clinical condition of the patient as well as the patient's fluid, electrolyte, acid-base and glucose balance. However, indication for each formulation of the two formulations of Normocarb HF™ should be labeled.

1.3.5 Drug-Drug Interactions:
As with the use of other replacement and dialysis solutions, blood concentrations of filterable/dialyzable drugs may be influenced by CRRT. The blood concentrations of certain drugs may need to be monitored and appropriate therapy implemented to correct for removal during treatment. In patients with cardiovascular disease, especially those using cardiac glycoside medications, plasma levels of calcium, potassium and magnesium must be carefully monitored. If citrate is used as the anticoagulation agent, the formulations of Normocarb HF™ solution may need to be adjusted.

1.3.6 Special Populations
Gender Differences:
Both males and females were enrolled in several of the reported studies. No subgroup analysis by gender was submitted.

Elderly:
Geriatric patients have been reported in some studies on the general population. However, no subgroup analysis or formal specific study was carried out in the geriatric population.

Ethnic/Racial Studies:
No studies were performed in these populations.

Pediatric studies:
In pediatric patients, Normocarb HF™ solutions appear to match the requirements in the CRRT treatment. Although the exact composition of the infusates during the CRRT was not indicated clearly, based on the similar plasma levels of electrolytes between the children and adults, the Normocarb HF™ should be effective and safe for pediatric use.

Use in pregnancy:
There was no data available concerning use in pregnancy.

2 INTRODUCTION AND BACKGROUND

Continuous renal replacement therapy (CRRT) is used to complement or supplant intermittent hemodialysis (IHD) in critically ill patients with acute renal failure. This method involves the application of lower solute clearances and ultrafiltration rates for substantial periods of every day. CRRT provides

better stability due to lower ultrafiltration rates and better steady-state control of azotemia even in severely catabolic patients. The CRRT techniques are described in the following table.

Modality*	Blood pump	Dialysate (D) Infusate (I)	Urea clearance (ml/min)	Middle molecular clearance
Slow continuous ultrafiltration (SCUF)	Yes/No	No	1-3	+
Continuous arteriovenous hemofiltration (CAVH)	No	I	7-10	++
Continuous venous hemofiltration (CVVH)	Yes	I	15-17	+++
Continuous arteriovenous hemodialysis (CAVHD)	No	D	17-21	-
Continuous venovenous hemodialysis (CVVHD)	Yes	D	17-21	-
Continuous arteriovenous hemodiafiltration (CAVHDF)	No	I+D	25-26	+++
Continuous venovenous hemodiafiltration (CVVHDF)	Yes	I+D	25-26	+++

*: Johnson R, et al. Comprehensive clinical nephrology, 2nd edition, 2003. *

2.1 Product Information

2.1.1. Drug Name:

Normocarb HF™

2.1.2. Chemical Structure:

Normocarb HF™ includes two solutions, Normocarb HF™ 35 and Normocarb HF™ 25.

Normocarb HF™ 35 is a sterile non-pyrogenic bicarbonate hemofiltration concentrate (single-use 240 ml vial) for use in continuous renal replacement therapy (CRRT). It contains (g/L): NaCl 82.84, $MgCl_2.6H_2O$ 2.06, $NaHCO_3$ 39.70. The final solution contains approximately (mEq/L): Na 140, Mg 1.5, Cl 106.5, HCO_3 35.0.

Normocarb HF™ 25 is a sterile non-pyrogenic bicarbonate hemofiltration concentrate (single-use 240ml vial) for use in CRRT. It contains (g/L): NaCl 90.73, $MgCl_2.6H_2O$ 2.06, $NaHCO_3$ 28.35. The final solution contains approximately (mEq/L): Na 140, Mg 1.5, Cl 116.5, HCO_3 25.0.

Concentrations of buffer and electrolytes after dilution of Normocarb HF™

Component	Concentration Diluted NormocarbHF™ 25		Concentration Diluted NormocarbHF™ 35	
	(mmol/L)	(mEq/L)	(mmol/L)	(mEq/L)
Sodium (Na)	140.0	140.0	140.0	140.0
Magnesium (Mg)	0.75	1.5	0.75	1.5
Chloride (Cl)	116.5	116.5	106.5	106.5
Bicarbonate (HCO_3)	25.0	25.0	35.0	35.0
Total Anions	141.5 mEq/L		141.5 mEq/L	
Total Cations	141.5 mEq/L		141.5 mEq/L	

2.1.3. Proposed Trade Name:
Normocarb HF™

2.1.4. Proposed Indication:
According to proposed labeling, Normocarb HF™, after dilution, are indicated for use as adjunct therapy in CRRT using hemofiltration in adult and pediatric patients.

2.1.5. Drug Class:
Normocarb HF™ is a pharmacologically inactive solution and is used as replacement solution to replace water and electrolytes removed during CRRT. It is a sterile, pyrogen-, potassium-, calcium-free salt solution.

2.1.6. Dose/Regimens:
Doses will be based on the mode of therapy, flow rates and length of therapy as well as the patient's fluid, electrolyte, acid-base and glucose balance. Normocarb HF™ can be in intravenous use as a replacement solution and can be administered into extra-corporeal circuit before (pre-dilution) and/or after hemofilter or hemodiafilter (post-dilution).

2.1.7. Age Groups:
No published or unpublished controlled studies were found in pediatric patients with Normocarb HF™. Based on the eight non-controlled published pediatric studies and one published pediatric scientific literature review, Normocarb HF has been demonstrated to be safe and effective.

The general study population included elderly patients. In these studies, there were no differences in management of Normocarb HF™ use due to age and no age-related safety or efficacy issues. However, no subgroup analysis or formal specific study was carried out in the geriatric population.

2.2 Currently Available Treatment for Indications:
In the US, up to now, only customized solutions compounded by the hospitals have been used as replacement solutions in CRRT. CRRT replacement solutions for hemofiltration and hemodiafiltration with formulations similar to Normocarb HF™ have been in use worldwide for many years. Normocarb HF™ has been marketed extensively in Canada since March 1, 2001 with sales of approximately [redacted] vials per year. It is registered as a drug in Canada. Normocarb™ with 35mEq/L bicarbonate (not 25 mEq/L bicarbonate), another product from the sponsor, was approved by the CDRH, FDA as a hemodialysate solution. Normocarb™ has the same exact packaging, same range of composition, and the same manufacturing site as Normocarb HF™ 35.

2.3 Availability of Proposed Active Ingredient in the United States:
Normocarb HF™ is not currently marketed in this country.

2.4 Important Issues With Pharmacologically Related Products:
As with the use of other replacement and dialysis solutions, blood concentrations of filterable/dialyzable drug may be influenced by CRRT.

2.5 Pre-submission Regulatory Activity:
During the pre-NDA meeting held on December 23, 2004, the division has agreed that this application would be submitted under section 505 (b) (2) of the Federal Food, Drug, and cosmetic Act. (Please

appendix 10.3 pre-NDA meeting minutes)

2.6 Other Relevant Background Information:
NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable):
Please see their reviews.

3.2 Animal Pharmacology/Toxicology:
The drug substances of the Normocarb HF™ solutions are normal constituents of the physiological plasma in human and they do not exert any real pharmacological action. In addition, considering the available clinical experience with similar solutions, the non-clinical studies of pharmacology and toxicology were not required.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical studies were not conducted with this specific product.

4.2 Tables of Clinical Studies

N/A

4.3 Review Strategy
Data were from published literatures provided by sponsor and reviewer.

4.4 Data Quality and Integrity
N/A

4.5 Compliance with Good Clinical Practices
Not submitted

4.6 Financial Disclosures:
Not submitted

5 CLINICAL PHARMACOLOGY:

Not submitted

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication
The Normocarb HF™ consists of two different pre-packaged sterile solutions and was proposed as replacement solutions for CRRT with hemofiltration.

6.1.1 Methods

The main data source for this review was based on the published data provided by sponsor. In addition, the reviewer also performed a PubMed search using the words of "replacement solutions, infusates, CRRT, hemofiltration, or hemodiafiltration".

6.1.2 General Discussion of Endpoints:

The therapeutic goal of replacement solutions is to compensate for fluid loss and to restore or normalize the acid-base and electrolyte balance in the blood of patients suffering of acute renal failure (ARF) during CRRT. The compositions of replacement solutions are made to correspond to normal electrolytes including sodium, chloride, magnesium and bicarbonate as closely as possible. Calcium and potassium may be needed additionally if necessary.

6.1.3 Study Design:

Data were collected from published journals. A total of 29 studies including fifteen published controlled, five published and one unpublished non-controlled adult clinical studies, and eight non-controlled pediatric clinical studies are provided in this application (approximately 2000 patients in total). In addition, according to the sponsor, one large multi-centered study is ongoing accruing approximately 1100 patients who are receiving a sodium bicarbonate infusate solution during CRRT/HF (study is expect to be finished in early 2007).

6.1.4 Efficacy Findings:

In CRRT, buffered electrolyte solutions are required for parenteral replacement of volume lost. Currently, there is no FDA approved commercial infusate solution for CRRT. Pharmacy compounding of custom replacement solutions has been used but also has some risks like mis-formulation, microbiological contaminations, etc.

In evaluation of the clinical efficacy of Normocarb HF^{TM} solutions as the replacement in CRRT, the clinical studies from published literature were summarized in the following to determine the appropriate concentrations of buffers and electrolytes in the replacement solutions.

6.1.4.1 Studies in adults.

Study 1. Bicarbonate dialysate for CRRT in intensive care unit (ICU) patients with acute renal failure. LeBanc M, et al (American Journal of Kidney Diseases 1995; 26(6): 910-917).

Fifty patients with multiple organ failure from surgical and medical ICUs including 33 men and 17 women with a mean age of 59.9±16.6 years were treated with CRRT. A non-commercial bicarbonate based solution was used as a replacement solution. A subgroup of 13 patients received a commercially prepared lactate buffer (Dianeal 1.5%), followed by the bicarbonate buffer. This subgroup served as its own control to compare the metabolic control achieved. Results indicated that acid-base balance and blood carbon dioxide levels were improved in the bicarbonate group compared to the group receiving lactate. No bicarbonate buffer-related adverse events were reported. The concentrations of the bicarbonate solution and Dianeal 1.5% were summarized in the following table.

Buffer and electrolytes	Dianeal 1.5%	Bicarbonate solution
Sodium (mEq/L)	132	144±3
Potassium (mEq/L)	3-4*	3.7±0.2
Calcium (mEq/L)	3.5	3.0±0.3
Magnesium (mEq/L)	1.5	1.4±0.3
Chloride (mEq/L)	102	111±3
Lactate (mEq/L)	35	-
Bicarbonate (mEq/L)	-	37±2
Acetate (mEq/L)	-	2-4
Glucose (anhydrous, mg/dl)	1300	205±15

*: potassium, as potassium chloride, was added as the concentration of 3-4mEq/L

Study 2. Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. Barenbrock M, et al. Kidney International 2000; 58: 1751-1757.
One hundred and seventeen patients between the age of 18 and 80 years were randomized to CVVHF (continuous venovenous hemofiltration) with either bicarbonate replacement fluid (RF-bic) (n=610 or lactate replacement fluid (RF-lac, n=56). Patients were treated with CVVHF for five days or until renal function was restored or the patient was removed from the study. Results indicated that blood lactate levels were significantly lower and blood bicarbonate levels significantly higher in patients with RF-bic than those treated with RF-lac. The number of hypotensive crisis was lower in RD-bic treated patients. The composition of the replacement fluids were summarized in the following table.

Buffer and electrolytes	RF-bic		RF-lac	
	Free of K^+	With K^+	Free of K^+	With K^+
Sodium (mmol/L)	140	140	135	135
Potassium (mmol/L)	0	2	0	2
Calcium (mmol/L)	1.5	1.5	1.88	1.875
Magnesium (mmol/L)	0.5	0.5	0.75	0.75
Chloride (mmol/L)	109	111	106.5	108.5
Lactate (mmol/L)	-	-	33.75	33.75
Bicarbonate (mmol/L)	35	35	-	-
Glucose (mmol/L)	5.6	5.6	7.5	8.3

Study 3. The use of different buffers during continuous hemofiltration in critically III patients with acute renal failure. Heering P, et al. Intensive Care Med (1999); 25: 1244-1251.
One hundred and thirty two critically ill patients between the ages of 43 and 77 (89 men, 43 women) with ARF and continuous venovenous hemofiltration were studied. Fifty-two patients received lactate replacement fluid (group 1), 32 patients received acetate based replacement fluid (group 2), while 48 were treated with a bicarbonate buffer replacement fluid. The mean CVVHF duration was 9.8 days ± 8.1 days, and mortality was 65%. Lactate- and bicarbonate-based hemofiltration led to significantly higher serum bicarbonate levels and arterial pH values as compared to the acetate-based hemofiltration. Cardiovascular hemodynamics including mean arterial blood pressure, peripheral vascular resistance, cardiac output were superior in lactate or bicarbonate treated patients. No safety issues were noted with patients receiving bicarbonate-based solutions. The composition of the replacement fluids were summarized in the following table.

	Lactate-buffer	Acetate-buffer	Bicarbonate-buffer
Sodium (mmol/L)	142	140	140
Potassium (mmol/L)	0	0	0
Calcium (mmol/L)	2.0	2.0	1.5
Magnesium (mmol/L)	0.75	1.0	0.5
Chloride (mmol/L)	103	111	109
Lactate (mmol/L)	44.5	-	-
Bicarbonate (mmol/L)	-	-	35
Acetate	-	35.0	-
Osmolarity (mosmol/L)	292	289	292

Study 4. CRRT: Does technique influence electrolyte and bicarbonate control? Morimatsu H, et al. International Journal of Artificial Organs 2003; 26(4):269-296.
This is a retrospective controlled study in two tertiary care ICUs. Ninety-nine adult patients between 42 and 79 years of age (67 men, 32 women) were treated with CRRT for ARF. Forty-nine were treated with CVVHDF and 50 were treated with CVVHF. The results indicated that CVVHDF was more likely to achieve sodium concentration in the normal range. Both treatments decreased the mean serum potassium during the first 48 hours of treatment, but there was no difference in treatment effectiveness thereafter. Both treatments increased serum bicarbonate concentration over the first 48 hours. There were no safety issues related to the replacement fluid. The composition of replacement fluid in CVVHDF and CVVH were summarized in the following table.

	Replacement fluid for CVVHDF	Replacement fluid for CVVHF
Sodium (mmol/L)	150	140
Potassium (mmol/L)	0	1
Calcium (mmol/L)	0.55	1.6
Magnesium (mmol/L)	1.25	0.8
Chloride (mmol/L)	112.5	100
Lactate (mmol/L)	0	46
Bicarbonate (mmol/L)	37.5	0

Study 5. Comparison of lactate and bicarbonate buffered hemofiltration fluids: use in critically III patients. Thomas AN, et al. Nephrology Dialysis Transplantation. 1997; 12: 1212-1217.
This is a prospective, randomized trial to compare acid-base balance, lactate concentration, and hemodynamic and oxygen transport variables during hemofiltration with replacement fluid containing 44.5mmol/L of sodium lactate or 40mmol/L of sodium bicarbonate. 41 adults between the ages of 45 and 78 (21 men, 20 women) with ARF in the ICU of a university hospital, who were randomized to receive either lactate or bicarbonate buffer during the first 24 hours of hemofiltration. None of the patients had overt hepatic failure. Results indicated that the degree of correction of acidosis (measured by pH and bicarbonate) during the first 24 hours of hemofiltration was correlated with the patient's outcome. However, the outcome was not affected by the substitution of bicarbonate- or lactate- containing replacement fluids. The composition of the replacement fluids was summarized in the following table.

	Lactated solution	Bicarbonate solution
Sodium (mmol/L)	142	155
Potassium (mmol/L)	0-6	0-6
Calcium (mmol/L)	2.0	1.8
Magnesium (mmol/L)	0.75	0.77
Chloride (mmol/L)	104	120
Lactate (mmol/L)	44.5	3
Bicarbonate (mmol/L)	0	40

Study 6.The acid-base effects of continuous hemofiltration with lactate or bicarbonate buffered replacement fluids. Tan HK, et al. International Journal of Artificial Organs 2003; (6): 26: 477-483. The investigators performed a randomized double crossover study in 8 adult patients between the ages of 39 and 72 (four men and four women) with ARF in the ICU of a tertiary care medical center in Australia. Patients were randomized to either 2 hours of isovolemic lactate-buffered CVVHF or 2 hours of bicarbonate buffered CVVHF with crossover. Results showed that after the initial two hours, both groups had a slight metabolic alkalosis despite slight hyperlactatemia in both groups. Within 60 minutes of treatment, however, the lactate group led to significantly higher lactic academia and significantly lower bicarbonate levels in the presence of unchanged pCO_2. These differences persisted throughout the study period. The composition of both replacement fluids were summarized in the following table.

	Lactate Replacement fluid	Bicarbonate Replacement fluid
Sodium (mmol/L)	140	140
Potassium (mmol/L)*	1	0
Calcium (mmol/L)	1.6	1.75
Magnesium (mmol/L)	0.8	0.5
Chloride (mmol/L)	100	109.5
Lactate (mmol/L)	46	3
Bicarbonate (mmol/L)	0	32
Glucose (mmol/L)	10.8	-

*: Potassium chloride was added to each 5 liter bag of replacement fluid in the final concentration of 3.7mmol/l to prevent hypokalemia.

Study 7. Effect of bicarbonate and lactate buffer on glucose and lactate metabolism during HDF in patients with multiple organ failure. Bollman MD, et al. Intensive Care Medicine (2004); 30:1103-1110. This is a prospective cross-over controlled study to compare the effects of bicarbonate replacement fluid and lactate replacement fluid for CVVHDF in the ICU. Eight adult patients between the ages of 55 and 77 (five men and three women) with multiple organ dysfunction syndrome received two buffers in a randomized sequence over two consecutive days. Results indicated that lactate was rapidly cleared from the blood of critically ill patients without acute liver failure, and was comparable to bicarbonate in that group. Where there was acute liver failure, however, bicarbonate was better at maintaining acid-base balance. The compositions of two buffers were summarized in the following table.

	Lactate Replacement fluid	Bicarbonate Replacement fluid
Sodium (mmol/L)	140	140
Potassium (mmol/L)*	0	0
Calcium (mmol/L)	1.75	1.75
Magnesium (mmol/L)	0.5	0.75
Chloride (mmol/L)	105	109.5
Lactate (mmol/L)	40	3
Bicarbonate (mmol/L)	0	32

Study 8. CVVH with a novel bicarbonate dialysis solution: Prospective cross-over comparison with a lactate buffered solution. Zimmerman D, et al. Nephrology Dialysis Transplantation. 1999; 14: 2387-2391.

This is a prospective randomized cross-over multi-center trial, with 26 critically ill adult patients starting with CVVHD for ARF. Their ages ranged from 51 to 69 years; 19 males and 7 females. Each patient received either 48 hours of lactate followed by 48 hours of bicarbonate (Nomorcarb™), or vice versa, with the order randomized at trial entry. Results showed that bicarbonate buffer solution provided equal acid base balance but maintained more normal lactate levels than a lactate buffered dialysis solution. The compositions of both buffer solutions were summarized in the following table.

	Lactate Replacement fluid	Bicarbonate Replacement fluid
Sodium (mmol/L)	132	140
Potassium (mmol/L)*	0	0
Calcium (mmol/L)	1.75	0
Magnesium (mmol/L)	0.75	0.75
Chloride (mmol/L)	102	106.5
Lactate (mmol/L)	35	0
Bicarbonate (mmol/L)	0	35
	83	0

Study 9. Bicarbonate-buffered instead of lactate buffered substitution fluid for continuous hemofiltration in intensive care. Olbricht CJ, et al. Anasth Intensivther Notfallmed. 1990; 25: 164-167.

This study addresses and solves some of the early concerns with bicarbonate-buffered solutions during CRRT. These concerns included 1) precipitation of calcium carbonate and magnesium carbonate; 2) pH is usually 8.4; and 3) evaporation of CO_2 increases pH. The results showed that using two bags with 3mmol/L of lactic acid can prevent the precipitation of calcium and magnesium. The pH was 7.37. Evaporation of CO_2 was prevented by bags made of special plastic sheeting. The "new" solution was then administered to 7 intensive care adult patients with ARF being treated for 6 days with CRRT. Their age ranged from 38-66 years. The values of calcium, bicarbonate, pH, and pCO_2 remained normal under clinical conditions. The composition of the buffer solution was summarized in the following table.

	Bicarbonate Replacement fluid
Sodium (mmol/L)	140.10
Potassium (mmol/L)*	0
Calcium (mmol/L)	1.75
Magnesium (mmol/L)	0.5
Chloride (mmol/L)	110.24
Lactate (mmol/L)	2.9
Bicarbonate (mmol/L)	31.40
pH	7.4
pCO_2 mmHg	58

Study 10. A novel regional citrate anticoagulation protocol for CRRT using only commercially available solutions. Tobe S, et al. Journal of Critical Care. 2003; 18(2): 121-129.
The investigator designed and then clinically tested a citrate regional anticoagulation (CRA) protocol for patients with ARF and contra-indications to heparin who required CRRT. The commercially available bicarbonate solution, Normocarb™ was used as the infusate during CVVHD. Results showed that there was a dramatic improvement of dialysis filter survival in the index patient that was seen in the subsequently patients receiving CRA. This was accompanied by excellent control of the clinical and biochemical parameters as well as nursing acceptance and ownership of the protocol. The composition of the buffer solution was summarized in the following table.

	Replacement fluid
Sodium (mmol/L)	140
Potassium (mmol/L)*	0
Calcium (mmol/L)	0
Magnesium (mmol/L)	0.75
Chloride (mmol/L)	106.5
Lactate (mmol/L)	0
Bicarbonate (mmol/L)	35

Study 11. Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: a case report. Naka T, et al. Critical Care. 2005; 9(2) R90-95.
In this case report, a 53 year old woman presenting with serotonin syndrome complicated by severe rhabdomyolysis and oliguric renal failure was treated with CVVHF. A bicarbonate-based commercial replacement fluid (Hemosol, Gambro, Sydney, Australia) was used as an infusates. There was no safety issues related to the bicarbonate solution. The composition of the bicarbonate solution was not described.

Study 12. Continuous hemofiltration in the treatment of acute renal failure. Forni LG, et al. Review from New England J Med 1997; 336(18): 1303-1309.
This review describes the many forms of CRRT that have emerged over the years with emphasis difference between diffusion and convection (and their combined use) as ways to control blood wastes. The composition of buffer solution proposed by the author was summarized in the following table.

	Replacement fluid
Sodium (mmol/L)	140
Potassium (mmol/L)*	0
Calcium (mmol/L)	1.6
Magnesium (mmol/L)	0.75
Chloride (mmol/L)	101
Lactate (mmol/L)	45
Glucose (mmol/L)	11

Study 13. University of Alabama Medical Center (Personal Communication). Tolwani A. 2005. Twenty-two critically ill patients, ages 31-78, were treated with CRRT using a variety of replacement fluids. All received some form of bicarbonate solution (not described), five received only Normocarb™. There were no therapy related deaths or episodes of metabolic alkalosis in any of the patients reported. Eight of the 22 recovered.

6.1.4.2. Studies in children

Study 1. Pediatric hemofiltration: Normocarb replacement fluid with citrate anticoagulation. Bunchman TE, et al. Pediatric Nephrology. 2002; 17: 150-154. Normocarb™ was used as an infusate in 14 children at the ages between newborn to 17 years treated with CRRT. Diagnosis included 11 children with sepsis and 3 with tumor lysis syndrome; all had ARF. No infusate-related side effects were observed.

Study 2. Citrate anticoagulation in pediatric continuous venovenous hemofiltration. Elhanan N, et al. Pediatric Nephrology. 2004; 19: 208-212. This is a retrospective study in 9 critically ill children in age from 2 to 16 years treated with CVVHF for 1-14 days (mean 5.3 days). Normocarb™ was used as in infusate and the citrate was used for anticoagulation. The results indicated that Normocarb™ with a citrate anticoagulation protocol is simple to perform, and safe with respect to metabolic side effects.

Study 3. CRRT in children up to10kg. Symons JM, et al. Am J Kidney Diseases, 2003; 41(5):984-989. The study describes a cohort of 85 patients weighting 10kg or less who underwent CRRT at five US children's hospitals between 1993 and 2001. Age and gender were not stated; weights ranged from 1.5kg to 10kg. All patients were critically ill and in the ICU. The infusates were made of 50% blood/albumin and saline). No safety issues were found with the infusates. **(Sponsor mentioned that bicarbonate sodium solution was used in this study, however, it was not confirmed by the reviewer from the original article).**

Study 4. Multi-Centre evaluation of anticoagulation in patients receiving CRRT. Brophy PD, et al. Nephrology Dialysis Transplantation. 2005; 20: 1416-1421. This study compared a heparin CRRT protocol with the citrate anticoagulation CRRT protocol. 138 children received CRRT, 69 with hemodialysis, 55 with hemofiltration,and14 with hemodiafiltration. Nine patients receiving heparin experienced life-threatening systemic bleeding, but there was no systemic bleeding with citrate anticoagulation. Normocarb™ was used in this study and there were no hemodynamic problems or other serious adverse effects with Normocarb™. The small number of patients experiencing transient metabolic alkalosis, responded quickly to temporary cessation of Normocarb™ and saline replacement fluid.

Study 5. Children's Hospital of Grand Rapids (unpublished personal communication). Hackbarth and Bunchman TE. 2005, DeVos Children's Hospital. Grand Rapids, MI. The authors described their continuing experience with CRRT using Normocarb™ as an infusate in 36 children fro one month of age to 19 years. Citrate was used as the anticoagulant. In most patients there was no metabolic alkalosis, but 12 had mild metabolic alkalosis easily resolved by temporarily discontinuing Normocarb™ and starting a saline infusion.

Normocarb TM has been discussed in above pediatric studies. However, the exact composition of the buffer and electrolytes in the solution were not described.

6.1.5 Efficacy Conclusions

In CRRT, buffered electrolyte solutions are required for parenteral replacement of volume lost during HF and HDF. Currently, there are no FDA approved commercial replacement solutions available in USA. Pharmacy compounding of custom replacement solutions has been used but also has some risks like mis-formulation, microbiological contaminations, etc. Based on the clinical reports from the published data, replacement fluid in most situations should contain physiological concentrations of electrolytes except for those that are protein-bound. In the buffer selection, lactate solutions are usually well tolerated. However, it appears that bicarbonate is the first choice for replacement solutions than the lactate and acetate. Bicarbonate-containing solutions provide benefit to the patient, especially when liver function is compromised, when there is circulatory failure or when a large volume of replacement fluid is used during CRRT. The appropriate concentrations of bicarbonate were in the range of 30 to 40 mmol/L with or without 3mmol/L lactate. Magnesium and sodium solutions should be the same as the normal physiological conditions in the range of 1 to 1.5mEq/L and about 140mEq/L, respectively. The concentration of chloride was determined based on the concentrations of cations and bicarbonate and generally in the range of 100 to 120mEq/L. Calcium and potassium concentrations can be variable from 0 to 4mEq/L based on the individual patient conditions, and treatment modalities. Calcium and potassium can also be added separately in the calcium- and/or potassium free replacement solutions during CRRT. The dextrose concentration to use in replacement solutions should be determined based on the dextrose loss in the ultrafiltrate and administration of dextrose via the same solutions.

According to the published clinical data, NormocarbHF™ 35 solution appears to be acceptable for CRRT. For the NormocarbHF™ 25 solution, the bicarbonate concentration is 25mEq/L which is lower than the published data that was used in the CRRT. However, there were some reports of the alkalosis after long-term use of bicarbonate at concentration ≥ 35mEq/L in NormocarbHF™ 35 or other customer solutions. Therefore, the NormocarbHF™ 25 solution containing the physiological range of bicarbonate of 25mEq/L should be appropriate for the patients without severe metabolic acidosis.

In pediatric patients, the use of CRRT in pediatric critical care is now commonplace. This therapy provides for the nearly continuous removal of fluid, toxins, urea, and inflammatory mediators from critically ill patients. Moreover, the establishment of automated volumetric/gravimetric devices has also demonstrated a clinical benefit in patients with sepsis and multi-organ dysfunction syndrome. Based on the published data, Normocarb™ solution has been used in several pediatric studies, however, the exact composition of the infusates during the CRRT was not indicated clearly. The sponsor needs to provide more details about the use of NormocarbHF™ in pediatric studies.

7 INTEGRATED REVIEW OF SAFETY

Methods:

NormocarbHF™ for CRRT includes NormocarbHF™ 35 and NormocarbHF™ 25 which provide two formulations for the prescribing physician in the management of patient with acute renal failure (ARF). No specific clinical study related to the safety of these solutions was provided with this application. All data were cited from the published literature.

Findings:

1. In ARF patient population, the mortality rate is high and can be predicted using APACHE II scores. The expected mortality rate in this patient population is usually over 50%. Regarding the fluid balance errors, the sponsor reported that the incidence rate was 6% based on data from the largest hemofiltration study in which lactate-containing replacement solutions were used and ultrafiltration doses were compared (Lancet 2000; volume 355:26-30).
2. In small studies, a direct comparison between lactate- and bicarbonate-buffered solutions demonstrated a significant reduction in cardiovascular events (volume change-related hypotension, angina) with bicarbonate-buffered solutions (Kidney International 2000; vol 58:1751-1757).
3. Factors extrinsic to the patient and the solution, such as local medical practice, specific CRRT technique, choice of membrane, and monitoring of the patient, may influence safety of the patient but should not interfere with the safety of the solution used.
4. The excessive electrolyte/fluid addition or depletion can be prevented by close monitoring of the patients volume and biochemical status. This occurrence can be managed by changes in the flow rates of replacement fluid, or by changes in the concentrations of solute constituents in these fluids.

In conclusion, no specific sponsor-generated safety studies with the solutions were reported. Based on the results of published clinical studies as shown in the efficacy studies, no significant replacement solution-related safety issues were reported. The reviewer considered that these studies adequately evaluate the safety of the NormocarbHF™ formulations in the indicated adult ARF patient population when used as replacement solutions in CRRT. The solution itself should have no specific safety issues. In the pediatric patients, however, the exact composition of buffer and electrolytes used as infusates in children during CRRT treatment were not clear. The sponsor needs to provide more references in order to support the use of NormocarbHF™ in pediatric studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dose regimen and administration depend on the local medical practice, specific CRRT technique, choice of membrane, and monitoring of the patient.

8.2 Drug-Drug Interactions

No additional formal drug interaction studies have been conducted. Based on the published data, citrate was commonly used in patents with hemorrhagic trend and may induce alkalosis if the bicarbonate concentration was not adjusted. In addition, some electrolytes may also need to be changed.

8.3 Special Populations
No formal subgroup analyses were conducted for age, gender or race. No data were available in the condition of pregnancy. Based on the published data, no significant age-related findings of using infusates were observed in the general population studies.

8.4 Pediatrics
Clinical studies have been shown that CRRT can be used to treat pediatric patients. Although the exact composition of the infusates during the CRRT was not indicated clearly, based on the similar plasma levels of electrolytes between the children and adults, Normocarb HF™ should be safe for pediatric use.

8.5 Advisory Committee Meeting
No additional advisory committee meeting is planned at the present time.

8.6 Literature Review
All the clinical data were from literature review.

8.7 Post-marketing Risk Management Plan
Bicarbonate replacement solutions have been in clinical use for many decades, and have been shown to be safe. As of March 1, 2005, the sponsor had distributed 225,504 vials of NormocarbHF™ in the U.S., which is sufficient for 451, 008 hours of treatment of an estimated 3,758 patients. In addition, another ——— vials have been sold in Canada as a drug since March 2001. No adverse events have been report.

8.8 Other Relevant Materials
N/A

9. Overall Assessment
9.1 Conclusions
In determining the fluid composition, there is general consensus that replacement fluid and/or dialysate should contain a buffer and electrolytes in concentrations aiming for physiological levels and taking into account preexisting deficits or excess and all inputs and losses. In most situations, replacement fluid should contain physiological concentrations of electrolytes except for those that are protein-bound. As replacement solutions in CRRT, NormocarbHF™ solutions provide two formulations which contain physiological ranges of sodium, chloride, magnesium, and bicarbonate at concentrations of 25 or 35mEq/L. The potassium and calcium should be added if necessary. Based on the review of the literature and journal citations, there is sufficient documentation in these articles to adequately evaluate the safety and efficacy of the NormocarbHF™ formulations in the indicated ARF patient population when used as replacement solutions in CRRT.

From this reviewer's perspective, this NDA should be approved. However, three issues need to be labeled in detail.

1. NormocarbHF™ provides two formulations with bicarbonate concentrations at 25 or 35mEq/L. The sponsor should label the indications of each solution.
2. Citrate has been using 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. This information should be added to the labeling.

3. NormocarbHF™ solutions do 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. This is not a major concern but should be added into the labeling.

9.2 Recommendation on Regulatory Action

1. It is recommended that NormocarbHF™ be approved as replacement solutions for the indication of CRRT to treat the adult and pediatric patients with acute renal failure.

2. The sponsor should provide detailed information in labeling for the selection of each formulation from the proposed two formulations in the different practice or modality.

9.3 Recommendation on Post-marketing Actions:
NA

9.4 Labeling Review
Details of the labeling will be submitted separately.

This reviewer has recommended:

1. Describe detailed indication for two formulations of the NormocarbHF™ .

2. Citrate may be used as an anticoagulant agents during CRRT, adjustment of the composition of NormocarbHF™ solutions may be needed. This should be added to the labeling.

3. Phosphate which is not in the Normocarb HF™ solutions may be required at some stage during CRRT. This should be added to the labeling.

Comments to Applicant
The recommendations should be conveyed to the applicant.

10 APPENDICES

10.1 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

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Shen Xiao
7/11/2006 12:10:28 PM
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7/12/2006 07:16:34 AM
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