DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18883/S-051
NDA 20171/S-033

SUPPLEMENT APPROVAL

Fresenius Medical Care
Attention: Ruth Turner
Director, Regulatory Affairs - Pharmaceuticals
920 Waltham Street
Waltham, MA 02451

Dear Ms. Turner:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 11, 2013, received September 11, 2013, submitted under section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DELFLEX Peritoneal Dialysis (PD) Solutions (1.5%, 2.5% and 4.25% Dextrose with Standard Calcium/Standard Magnesium and with Standard Calcium/Low Magnesium) and for DELFLEX PD Solutions (1.5%, 2.5% and 4.25% Dextrose with Low Calcium/Low Magnesium).

We acknowledge receipt of your amendments dated March 12 and April 9, 2014.

These Prior Approval Supplemental New Drug Applications provide for harmonization of the structure and content of the Final Labeling across all DELFLEX product lines and provide for labeling revisions as follows:

Conventional DELFLEX Single Bag

1. Minor editorial changes have been made throughout the label.

2. The barcode was moved from the lower right to the top of the front page and rotated 90º.

3. The statement **"No Latex"** was added.

4. Under **DESCRIPTION,** the last three sentences of the first paragraph were moved to the last paragraph in this section. The first paragraph has been changed from:

(b) (4)

To:

"The DELFLEX® peritoneal dialysis solutions (standard, low magnesium and low magnesium/low calcium) are sterile, non-pyrogenic formulations of dextrose and electrolytes in

water for injection, USP, for use in peritoneal dialysis. These solutions do not contain antimicrobial agents or additional buffers. Composition, calculated osmolarity, pH, and ionic concentrations are shown in Table 1."

5. The following text and tables were deleted. In their place, a single table containing all of the information was added (see item #9).

(b) (4)

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(b) (4)

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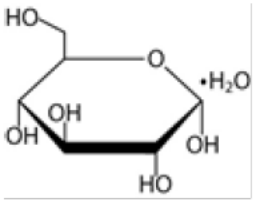
(b) (4)

6. Under **DESCRIPTION**, the structure has been changed from:

(b) (4)

To:



7. Under **DESCRIPTION**, the eighth paragraph has been changed from:

(b) (4)

To:

"Hydrochloric Acid or Sodium Hydroxide may be added for pH adjustment. pH is 5.5± 0.5"

8. Under **DESCRIPTION**, the last paragraph has been changed from:

(b) (4)

To:

"Exposure to temperatures above 25°C (77°F) during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. Since the flexible inner bag is compounded from a specific polyvinyl chloride, water may permeate from the inner bag into the outerwrap in quantities insufficient to affect the solution significantly. Solutions in contact with the plastic inner bag can cause certain chemical components of the bag to leach out in very small amounts; however, the safety of the plastic formulation is supported by biological tests for plastic containers."

9. Under **DESCRIPTION,** Table 1 Composition, Calculated Osmolarity, pH, and Ionic Concentration for all three DELFLEX Solutions has been added:

Table 1

	Composition/100mL					Total Osmolarity (mOsmol/L) (calc)	pH (5.0 - 6.0)	Ionic Concentration (mEq/L)				
	Dextrose Hydrous, USP ($C_6H_{12}O_6 \cdot H_2O$)	Sodium Chloride, USP (NaCl)	Sodium Lactate ($C_3H_5NaO_3$)	Calcium Chloride, USP ($CaCl_2 \cdot 2H_2O$)	Magnesium Chloride, USP ($MgCl_2 \cdot 6H_2O$)			Sodium	Calcium	Magnesium	Chloride	Lactate
DELFLEX Standard with 1.5% Dextrose	1.5 g	567 mg	392 mg	25.7 mg	15.2 mg	347	5.5	132	3.5	1.5	102	35
DELFLEX Standard with 2.5% Dextrose	2.5 g	567 mg	392 mg	25.7 mg	15.2 mg	398	5.5	132	3.5	1.5	102	35
DELFLEX Standard with 4.25% Dextrose	4.25 g	567 mg	392 mg	25.7 mg	15.2 mg	486	5.5	132	3.5	1.5	102	35
DELFLEX Low Magnesium with 1.5% Dextrose	1.5 g	538 mg	448 mg	25.7 mg	5.08 mg	346	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium with 2.5% Dextrose	2.5 g	538 mg	448 mg	25.7 mg	5.08 mg	396	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium with 4.25% Dextrose	4.25 g	538 mg	448 mg	25.7 mg	5.08 mg	485	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium, Low Calcium with 1.5% Dextrose	1.5 g	538 mg	448 mg	18.4 mg	5.08 mg	344	5.5	132	2.5	0.5	95	40
DELFLEX Low Magnesium, Low Calcium with 2.5% Dextrose	2.5 g	538 mg	448 mg	18.4 mg	5.08 mg	394	5.5	132	2.5	0.5	95	40
DELFLEX Low Magnesium, Low Calcium with 4.25% Dextrose	4.25 g	538 mg	448 mg	18.4 mg	5.08 mg	483	5.5	132	2.5	0.5	95	40

10. Under **CLINICAL PHARMACOLOGY**, the following last sentence in the second paragraph was bolded:

"Addition of potassium chloride should be made after careful evaluation of serum and total body potassium and only under the direction of a physician."

11. Under **INDICATION AND USAGE**, the applicant removed (b) (4) from the following sentence. The sentence was change from:

(b) (4)

To:

"DELFLEX® peritoneal dialysis solutions are indicated in the treatment of chronic renal failure patients being maintained on peritoneal dialysis when nondialytic medical therapy is judged to be inadequate."

12. Under **WARNINGS**, the following text was moved from the eighth paragraph to the third paragraph and the sentence was changed from:

(b) (4)

To:

"After removing the outerwrap, check for minute leaks by squeezing the solution bag firmly. If leaks are found, discard the solution because the sterility may be impaired. (A small amount of moisture may be present inside the outerwrap, which is normal condensation from the sterilization process)."

13. Under **PRECAUTIONS**, the following sentence was moved from the 'General' section to a newly added section 'Information for Patients' and was changed from:

(b) (4)

To:

"*Administer only if the solution is clear, all seals are intact, and there is no evidence of leaking."*

14. Under **PRECAUTIONS,** the following text was moved from the second to eighth paragraph and was changed from:

(b) (4)

To:

"Care should be taken to ensure that there is not any leakage around the catheter, since if not controlled, the leakage can create edema from subcutaneous infiltration of the dialysis solution.

The leakage will also create an inaccurate fluid balance measurement. If any leakage is identified do not proceed with infusion and notify your physician."

15. Under **PRECAUTIONS**, the following text was moved from the eighth paragraph to the third: *"Significant loss of protein, amino acids and water soluble vitamins may occur during peritoneal dialysis. Replacement therapy should be provided as necessary."*

16. Under **PRECAUTIONS**, the following sentence was deleted:
(b) (4)

17. Under **PRECAUTIONS**, the following sentence was moved from the sixth paragraph to the fifth and changed from:
(b) (4)

To:

"The outerwrap should remain intact until time of use."

18. Under **PRECAUTIONS**, the following subtitle was added:
"Information for Patients"

19. Under **PRECAUTIONS**, under subsection **Information for Patients**, the following text has been added:

"Do not heat in a microwave oven. Microwave ovens heat unevenly and can leave hot spots, which can burn the peritoneum."

20. Under **DOSAGE AND ADMINISTRATION**, the following paragraphs were deleted:
(b) (4)

(b) (4)

And the following text was added:

"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Additives may be incompatible. Please refer to manufacturer's product insert. Do not store solutions containing additives.

For administration see Directions for Use section."

21. Under **HOW SUPPLIED**, the word (b) (4)" has been change to "bag". The sentence has been changed from:

(b) (4)

To:

*"DELFLEX® peritoneal dialysis solutions are delivered in single-dose flexible bags. All DELFLEX® peritoneal dialysis solutions have overfills declared on the **bag** label. The flexible **bag has** the capacity for drainage in excess of their stated fill volume for ultrafiltration from the patient."*

22. Under **HOW SUPPLIED**, the following text has been changed from:

(b) (4)

To:

"DELFLEX® peritoneal dialysis solutions are available in the sizes and formulations shown in Table 2."

23. Under **HOW SUPPLIED**, three tables have been combined into one. The new table is as follows:

Table 2	1L	1.5L/2L	2L	2L/3L	2.5L/3L	3L	5L
DELFLEX Standard with 1.5% Dextrose	X	X	X	X	X	X	X
DELFLEX Standard with 2.5% Dextrose	X	X	X	X	X	X	X
DELFLEX Standard with 4.25% Dextrose	X	X	X	X	X	X	X
DELFLEX Low Magnesium with 1.5% Dextrose	X	X	X	X	X	X	X
DELFLEX Low Magnesium with 2.5% Dextrose	X	X	X	X	X	X	X
DELFLEX Low Magnesium with 4.25% Dextrose	X	X	X	X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 1.5% Dextrose	X	X	X	X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 2.5% Dextrose	X	X		X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 4.25% Dextrose	X	X		X	X	X	X

24. Under **STORAGE CONDITIONS**, the following text was changed from:

[redacted] (b) (4)

To:

"Storage Conditions Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C and 30 °C (between 59 °F and 86 °F). See USP Controlled Room Temperature. Brief exposure to temperatures up to 40 °C (104 °F) may be tolerated provided the mean kinetic temperature does not exceed 25 °C (77 °F); however, such exposure should be minimized."

25. Under **STORAGE CONDITIONS,** the following safety statement was added:
"Keep DELFLEX® and all medicines out of the reach of children."

26. The following was added prior to the **Directions for Use** section:

"Not for Intravenous Injection. Do not microwave. Warm solution as directed by your health care provider."

27. **DIRECTIONS FOR USE** has been added to the end of the label with step-by-step instructions for patients:

Directions for Use (Aseptic technique is required)
Get Ready

1. Clean work surface
2. Gather supplies:
    - DELFLEX® Peritoneal Dialysis bag.
    - Prescribed medication(s), if ordered by your healthcare provider.
    - Mask.
3. Put on mask. Wash your hands.
4. Tear the outerwrap from the slit edge down the length of the inner bag to open. Wipe away any moisture from the solution bags. Some opacity may be observed in the plastic of the bag and/or tubing and is due to moisture absorption during the sterilization process. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Inspect DELFLEX® Solution Bag:

5. Visually inspect the solution to ensure that it is clear and free of particulate matter prior to administration. Color may vary from clear to slightly yellow but does not affect efficacy and may be used.
6. Check the expiration date. Check for correct dextrose concentration
7. Firmly squeeze the Solution Bag to check for leaks.

Do not use DELFLEX® solution if:

- Leaks are found
- The solution bag is damaged
- Solution is cloudy or discolored

Note: Retain DELFLEX® peritoneal dialysis bag sample for manufacturer evaluation and notify your healthcare provider if any of the above defects are found.

8. DELFLEX® peritoneal dialysis solutions utilize a Safe-Lock® Connection System. This unique system consists of two Safe-Lock® connectors, one located on the administration port of the bag, and the mating connector is located on the fluid delivery set. The Safe-Lock® connectors were designed to prevent touch contamination of the internal connection components.
9. DELFLEX® peritoneal dialysis solutions utilize a Safe-Lock® Connection System. This unique system consists of two Safe-Lock® connectors, one located on the administration port of the bag, and the mating connector is located on the fluid delivery set. The Safe-Lock® connectors were designed to prevent touch contamination of the internal connection components.
10. Once the fluid delivery set is secured, to initiate solution flow, break the cone of the bag connector by placing the thumb firmly on the tube over the cone and pressing towards the outer wall of the tube and away from the bag. Once the cone is broken, a white retaining guide maintains the cone at a specific distance from the connector so it will not impede the flow of solution through the Safe- Lock® connector.

11. Look at the drained fluid for cloudiness. Throw away the fluid and used set as instructed by your healthcare provider. **In case of cloudiness, save the fluid and the used set and immediately contact your healthcare provider.**

Conventional DELFLEX Double Bag

1. Minor editorial changes have been made throughout the label.

2. The statement **"No Latex"** was added.

3. Under **DESCRIPTION**, the following paragraph was changed from:

(b) (4)

To:

"The DELFLEX® peritoneal dialysis solutions (standard, low magnesium and low calcium) are sterile, non-pyrogenic formulations of dextrose and electrolytes in water for injection, USP, for use in peritoneal dialysis. These solutions do not contain antimicrobial agents or additional buffers. The stay•safe® Exchange Set utilizes an easy to use dial designed to eliminate the use of clamps and to prevent touch contamination of internal connection components. Composition, calculated osmolarity, pH, and ionic concentrations are shown in Table 1."

4. Under **DESCRIPTION,** the following table has been revised and moved to the end of the **DESCRIPTION** section. The table has changed from:

(b) (4)

(b) (4)

To:

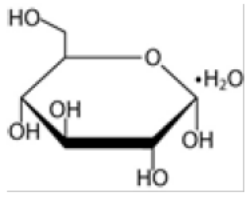
Table 1

	Composition/100mL					Total Osmolarity (mOsmol/L) (calc)	pH (5.0 - 6.0)	Ionic Concentration (mEq/L)				
	Dextrose Hydrous, USP ($C_6H_{12}O_6 \cdot H_2O$)	Sodium Chloride, USP (NaCl)	Sodium Lactate ($C_3H_5NaO_3$)	Calcium Chloride, USP ($CaCl_2 \cdot 2H_2O$)	Magnesium Chloride, USP ($MgCl_2 \cdot 6H_2O$)			Sodium	Calcium	Magnesium	Chloride	Lactate
DELFLEX Standard with 1.5% Dextrose	1.5 g	567 mg	392 mg	25.7 mg	15.2 mg	347	5.5	132	3.5	1.5	102	35
DELFLEX Standard with 2.5% Dextrose	2.5 g	567 mg	392 mg	25.7 mg	15.2 mg	398	5.5	132	3.5	1.5	102	35
DELFLEX Standard with 4.25% Dextrose	4.25 g	567 mg	392 mg	25.7 mg	15.2 mg	486	5.5	132	3.5	1.5	102	35
DELFLEX Low Magnesium with 1.5% Dextrose	1.5 g	538 mg	448 mg	25.7 mg	5.08 mg	346	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium with 2.5% Dextrose	2.5 g	538 mg	448 mg	25.7 mg	5.08 mg	396	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium with 4.25% Dextrose	4.25 g	538 mg	448 mg	25.7 mg	5.08 mg	485	5.5	132	3.5	0.5	96	40
DELFLEX Low Magnesium, Low Calcium with 1.5% Dextrose	1.5 g	538 mg	448 mg	18.4 mg	5.08 mg	344	5.5	132	2.5	0.5	95	40
DELFLEX Low Magnesium, Low Calcium with 2.5% Dextrose	2.5 g	538 mg	448 mg	18.4 mg	5.08 mg	394	5.5	132	2.5	0.5	95	40
DELFLEX Low Magnesium, Low Calcium with 4.25% Dextrose	4.25 g	538 mg	448 mg	18.4 mg	5.08 mg	483	5.5	132	2.5	0.5	95	40

5. Under **DESCRIPTION**, the structure has been changed from:

(b) (4)

To:



6. Under **DESCRIPTION**, the following sentence has been changed from:

(b) (4)

To:

"Hydrochloric acid or sodium hydroxide may be added for pH adjustment. pH is 5.5 ± 0.5."

7. Under **DESCRIPTION**, the last paragraph has been changed from:

(b) (4)

To:

"Exposure to temperatures above 25°C(77°F) during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. Since the flexible inner bag is compounded from a specific polyvinyl chloride, water may permeate from the inner bag into the outerwrap in quantities insufficient to affect the solution significantly. Solutions in contact with the plastic inner bag can cause certain chemical components of the bag to leach out in very small amounts; however, the safety of the plastic formulation is supported by biological tests for plastic containers."

8. Under **CLINICAL PHARMACOLOGY**, the last sentence was bolded:
"Addition of potassium chloride should be made after careful evaluation of serum and total body potassium and only under the direction of a physician."

9. Under **INDICATION AND USAGE**, the applicant removed (b) (4) from the following sentence. The sentence was change from:

(b) (4)

To:

"DELFLEX® peritoneal dialysis solutions are indicated in the treatment of chronic renal failure patients being maintained on peritoneal dialysis when nondialytic medical therapy is judged to be inadequate."

10. Under **WARNINGS**, the following text was moved from the eighth paragraph to the third and the sentence was changed from:

(b) (4)

To:

"After removing the outerwrap, check for minute leaks by squeezing the solution bag firmly. If leaks are found, discard the solution because the sterility may be impaired. (A small amount of moisture may be present inside the outerwrap, which is normal condensation from the sterilization process)."

11. Under **PRECAUTIONS,** the following text was moved from the first paragraph to the sixth under "Information for Patients" and reworded:

(b) (4)

To:

"Administer only if the solution is clear, all seals are intact, and there is no evidence of leaking."

12. Under **PRECAUTIONS,** the following text was moved from second to ninth paragraph and was changed from:

(b) (4)

To:
"Care should be taken to ensure that there is not any leakage around the catheter, since if not controlled, the leakage can create edema from subcutaneous infiltration of the dialysis solution. The leakage will also create an inaccurate fluid balance measurement. If any leakage is identified do not proceed with infusion and notify your physician."

13. Under **PRECAUTIONS,** the following text was added:
"Chronic patients that have been stabilized on peritoneal dialysis therapy should have routine evaluation of electrolyte blood chemistries and hematologic factors measured in order to determine the patient's ongoing condition."

14. Under **PRECAUTIONS,** the following text was bolded:
"DELFLEX® peritoneal dialysis solutions do not include potassium. Potassium chloride should only be added under the direction of a physician after careful evaluation of both serum and total body potassium."

15. Under **PRECAUTIONS,** the following text was moved from the seventh paragraph to the third:
"Significant loss of protein, amino acids and water soluble vitamins may occur during peritoneal dialysis. Replacement therapy should be provided as necessary."

16. Under **PRECAUTIONS,** the following text was moved from the fourth paragraph to the fifth and was reworded. The text has been changed from:

(b) (4)

To:

"The outerwrap should remain intact until time of use."

17. Under **PRECAUTIONS,** the following text was moved from the fifth paragraph to the ninth and reworded. The sentence has been changed from:

(b) (4)

To:

"Disconnect from disk only when knob is in position 4 (••••) to ensure patient connector is sealed."

18. Under **PRECAUTIONS,** the following text was added under "Information for Patients": *"Do not heat in a microwave oven. Microwave ovens heat unevenly and can leave hot spots, which can burn the peritoneum."*

19. Under **DOSAGE AND ADMINISTRATION**, the following text was added to the fourth paragraph. The sentence has been changed from:
(b) (4)

To:

"Additives may be incompatible. Please refer to manufacturer's product insert. Do not store solutions containing additives."

20. Under **DOSAGE AND ADMINISTRATION**, the final sentence has been changed from:
(b) (4)

To:

"For administration see Directions for Use section."

21. Under **HOW SUPPLIED**, the word (b) (4) has been change to "bag". The sentence has been changed from:
(b) (4)

To:

"DELFLEX® peritoneal dialysis solutions are delivered in single-dose flexible bags. All DELFLEX® peritoneal dialysis solutions have overfills declared on the bag label. The flexible bag has the capacity for drainage in excess of their stated fill volume for ultrafiltration from the patient."

22. Under **HOW SUPPLIED**, the second paragraph has been changed from:
(b) (4)

To:

"DELFLEX® peritoneal dialysis solutions with an attached stay•safe® Exchange Set are available in the sizes and formulations shown in Table 2."

23. The following table has been moved from DESCRIPTION to HOW SUPPLIED and labeled as Table 2:

Table 2	1L	1.5L/2L	2L	2.25L/3L	2.5L/3L	3L
DELFLEX Standard with 1 5% Dextrose	X	X	X	X	X	X
DELFLEX Standard with 2 5% Dextrose	X	X	X	X	X	X
DELFLEX Standard with 4 25% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium with 1.5% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium with 2.5% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium with 4.25% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 1.5% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 2.5% Dextrose	X	X	X	X	X	X
DELFLEX Low Magnesium, Low Calcium with 4.25% Dextrose	X	X	X	X	X	X

24. Under **HOW SUPPLIED**, the Storage Conditions has been changed from:

(b) (4)

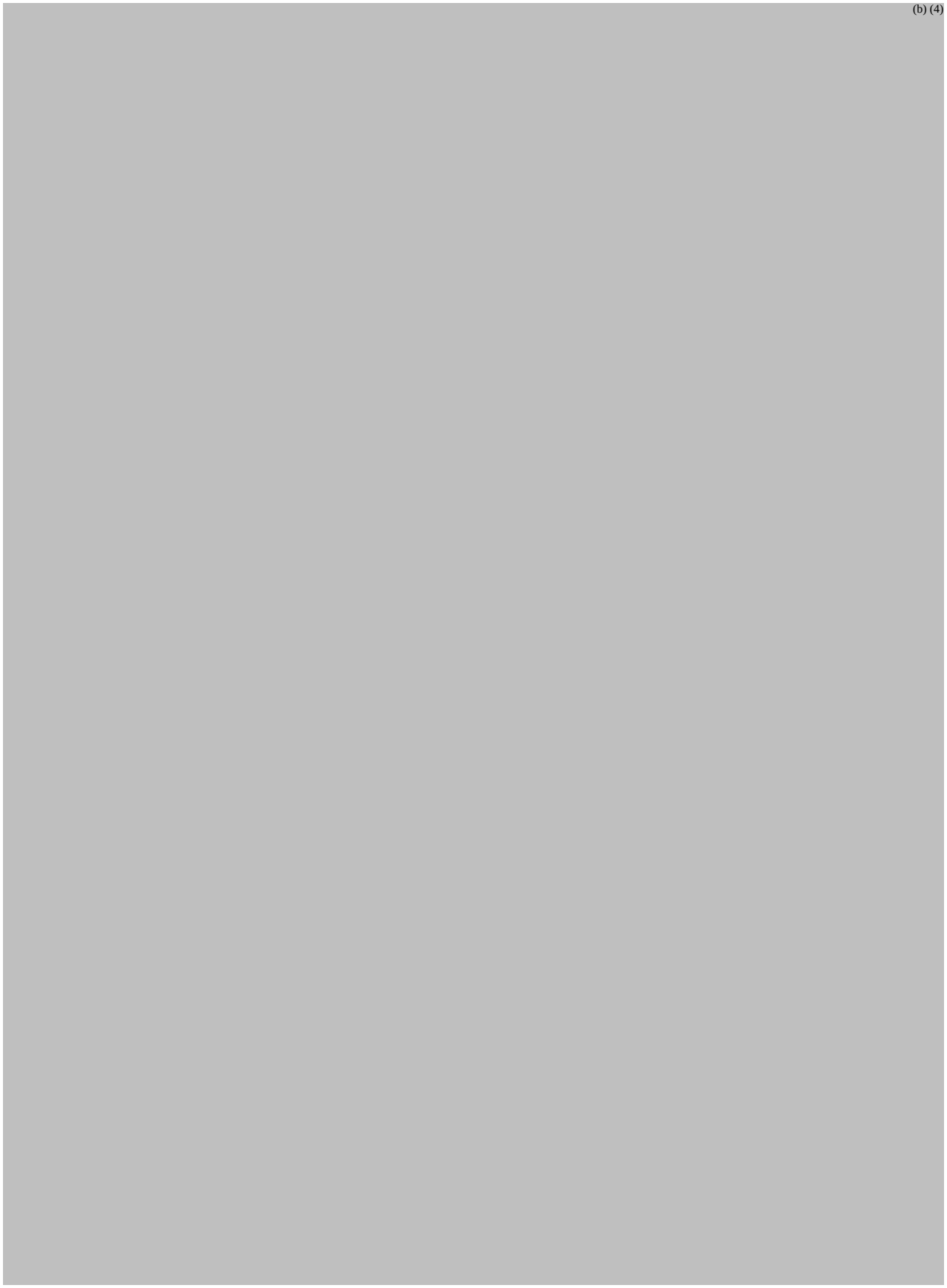
To:

"Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F). See USP Controlled Room Temperature. Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F); however, such exposure should be minimized."

25. The following statement has been added just prior to the **Directions for Use** section:
"Keep DELFLEX® and all medicines out of the reach of children."
"Not for Intravenous Injection. Do not microwave. Warm solution as directed by your health care provider."

26. The **Exchange Procedure** has been changed from:

(b) (4)


(b) (4)

To:

Directions for Use (Aseptic technique is required)
Get Ready:

1. Clean work surface.
2. Gather supplies:
   - DELFLEX® Peritoneal Dialysis bag with attached stay•safe® Exchange Set.
   - Povidone iodine prefilled stay•safe® cap, a stand alone item provided separately.
   - stay•safe® Organizer ,a stand alone item provided separately (Optional; FMCNA recommends its use).
   - Prescribed medication(s), if ordered by your healthcare provider.
   - Mask.
3. Put on mask. Wash your hands.
4. Ensure that the Extension Set coming from your catheter is clamped.
5. Tear the outerwrap from the slit edge down the length of the inner bags to open. Wipe away any moisture from the solution bags. Some opacity may be observed in the plastic of the bag and/or tubing and is due to moisture absorption during the sterilization process. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Inspect DELFLEX® Solution Bag:

6. Place the DELFLEX® solution set on the work surface. Separate the fill and drain bag.
7. Visually inspect the solution to ensure that it is clear and free of particulate matter prior to administration. Color may vary from clear to slightly yellow but does not affect efficacy and may be used.
8. Check the expiration date. Check for correct dextrose concentration.
9. Firmly squeeze the Solution Bag to check for leaks.

Do not use DELFLEX® solution if:

- Leaks are found
- The solution bag is damaged
- Solution is cloudy or discolored

10. Turn the blue position indicator on the stay•safe® disc counter-clockwise until it fits into the cut-out portion of the colored plastic cover on the disc. See Figure A, Step 1. Remove the colored plastic cover while the indicator is in this position (Position 1: •). See Figure A, Step 2. Once the cover is removed, do not turn counter-clockwise. (This step is done in preparation to allow the fluid in your peritoneal cavity to drain later on in this procedure).

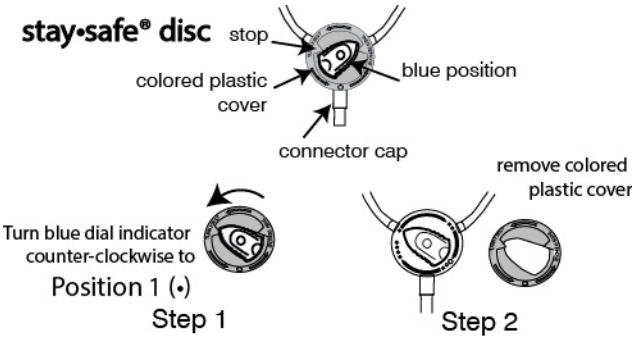


Figure A

Administer DELFLEX® Peritoneal Dialysis Solution

1. If you will be adding medication(s):
   - Clean the medication port as instructed by your healthcare provider.
   - Add the medicine(s).
   - Turn the bag upside down several times to mix the medicine(s).
2. Hang the solution bag on an I.V. pole and place the drain bag at floor level.
3. Break the frangible in the solution bag outlet port. (If using the Organizer, place the stay•safe® disc in the Organizer as illustrated in Figure B.)

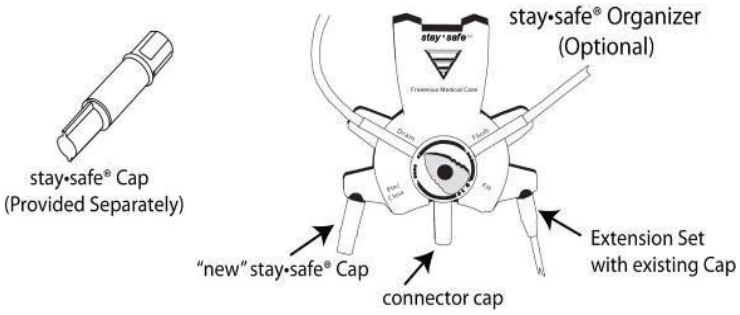


Figure B

4. Remove the stay•safe® cap from its package. (The new stay•safe® Cap is the stand alone item provided to the patient separately). (If using the Organizer, place the new stay•safe® Cap in the left notch of the Organizer. Place the existing cap of stay•safe® Extension Set, connected to the patient's catheter, in the other notch of the Organizer). See Figure B.
5. Aseptically remove the connector cap from the stay•safe® disc and throw the cap away. Remove the existing cap from the Extension Set connected to the patient's catheter by twisting the connection counter-clockwise. (If using the Organizer, leave the capped end

of the Extension Set in the Organizer and twist the Extension Set connector counter-clockwise to remove the set from its cap.)

6. Aseptically connect the Extension Set to the connector on the stay•safe® disc. Twist clockwise to secure the connection.
7. Remove your mask. Do not open the system during exchange.
8. Open the Extension Set clamp to start drain.
9. When patient drain is complete, turn the stay•safe® disc position indicator to Position 2 (••). See **Figure C**. This will start the flush from the solution bag to the drain bag.

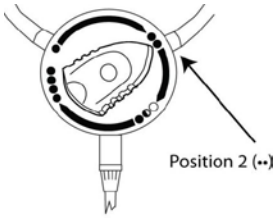


Figure C

10. After approximately 5 seconds, turn the stay•safe® disc position indicator to Position 3 (•••). See **Figure D**. This will start the patient fill.

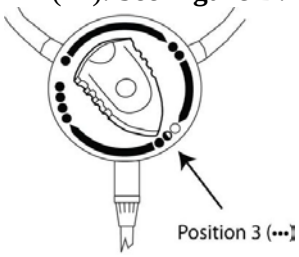


Figure D

11. When fill is complete, turn the stay•safe® disc position indicator to Position 4 (••••).See **Figure E**. This will insert the closure pin of the disc into the Extension Set connector and seal the system.

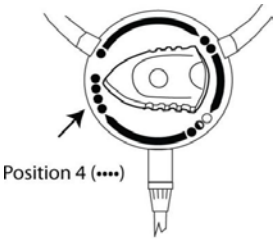


Figure E

12. Close the clamp on the Extension Set. Remove the white protective cover from the new stay•safe® Cap. Save for later use.
13. Remove the Extension Set from stay•safe® disc and attach the new stay•safe® cap. Twist clockwise to secure the connection.

14. Seal the disc by attaching the white protective cover from the new stay•safe® Cap to the disc connector. Twist clockwise to secure the connection and prevent leakage from the used system.
15. Look at the drained fluid for cloudiness. Measure the amount of fluid drained. Throw away the fluid and used set as instructed by your healthcare provider. **In case of cloudiness, save the fluid and the used set and immediately contact your healthcare provider.**

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical*

Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDAs 18883/S-051 and 20171/S-033.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your applications, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director of Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
04/24/2014