DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

September 8, 2003

LuAnn Erlich, Ph.D.
Senior Director
Pharmaceutical and Computer Services
Apotex Corporation
616 Heathrow Drive
Lincolnshire, Illinois 60069

Re: Normocarb
Request for Reconsideration
Our file: 2002.038
Dated May 30, 2003

Dear Dr. Erlich:

This letter responds to your May 30, 2003, request that the Office of the Ombudsman reconsider its decision that Normocarb is a drug when used as a pre-filter hemofiltration solution. Because of the extensive review the agency has conducted of this matter, your letter has been forwarded to me for reply.

The Food and Drug Administration (FDA) has completed its review of your request. For the reasons set forth below, we reaffirm our previous conclusion that Normocarb is a drug. If an application is submitted to FDA, Normocarb will be reviewed and regulated by FDA's Center for Drug Evaluation and Research (CDER) under the new drug provisions of the Federal Food, Drug, and Cosmetic Act. Please note the information contained at the end of this letter regarding discussions the Office of Combination Products (OCP) has had with CDER regarding various regulatory mechanisms that may be applied to Normocarb's regulation as a drug product.

Background

Apotex submitted a request for designation (RFD) covering Normocarb to the Office of the Ombudsman on December 12, 2002. This RFD was filed on December 19, 2002, and the original designation deadline was February 17, 2003. Upon receiving the initial RFD, FDA held numerous internal meetings and consultations that included representatives from both CDER and the Center for Devices and Radiological Health (CDRH). It became clear that a meeting with the company would be useful to clarify the issues, and so on March 17, 2003, representatives of Apotex and FDA met to discuss the issues further. Following that meeting, FDA held further extensive internal discussions on the matter, including a meeting on April 17, 2003, attended by Dr. Janet Woodcock, Director, CDER, Dr. David Feigal, Director, CDRH, and other members of FDA's senior

staff. On April 17, 2003, Apotex submitted additional information to the Ombudsman's Office and agreed to extend the designation deadline to May 2, 2003. The Ombudsman's Office issued the initial designation decision by letter dated May 2, 2003.

Apotex requested reconsideration of the May 2, 2003, designation letter on May 30, 2003. Shortly thereafter, FDA's OCP was assigned the responsibility for determining the regulatory identity of products (i.e., designating whether a product is a drug, biologic, device, or combination product) when such identity is unclear or in dispute. Accordingly, by letter dated June 17, 2003, OCP stated that, although the time frames contained in 21 CFR 3.8(c) do not apply because Apotex's request for reconsideration was submitted more than 15 days from the day it received FDA's initial determination, OCP would respond to the request by July 29, 2003. Upon consideration of the new issues raised by Apotex's request for reconsideration, however, FDA believed that a meeting with the company would be helpful. Accordingly, another meeting with Apotex, and several FDA representatives, including Drs. Woodcock and Feigal, was held on July 29, 2003. Representatives of OCP and Apotex participated in an additional in-depth telephone discussion of the mechanisms by which Normocarb exerts its activity on August 26. Following the August 26 meeting, OCP again consulted with numerous senior agency representatives, including Drs. Woodcock and Feigal, the Office of the Chief Counsel, and me. This letter reflects the agency's extensive deliberations of this matter and is consistent with Apotex's August 22, 2003, e-mail that it expects a reply from FDA on or around September 3.

Description of the Product

Normocarb is a solution containing water, magnesium chloride hexahydrate, sodium chloride, and sodium bicarbonate. It is already cleared for marketing under 510(k) K001059, when intended for use as a dialysate for use in hemodialysis systems. Apotex now seeks to market the product as a pre-filter hemofiltration solution.

Hemofiltration is one method used to treat kidney failure. In hemofiltration, blood is diverted either by venopuncture or arteriopuncture from the patient and run through an extracorporeal filter to remove toxins. Although blood can be filtered in this manner without the addition of a solution,[1] a solution is generally used when performing

[1] At a meeting held on March 17, 2003 between Apotex and FDA, Apotex explained ultrafiltration, which is hemofiltration in which no hemofiltration solution is used. Apotex explained then and again in its background information for the July 29 meeting that, without a "hemofiltration fluid, the amount of fluid removed from the blood by ultrafiltration is limited, so the quantity of toxins removed is limited." (See page 1 of background information.) As we understand it, only a limited amount of fluid can be removed from the blood when a hemofiltration solution is not used because the patient suffers adverse health consequences when a significant amount of fluid is removed and not replaced (although common practice would be to replace such fluid in the line in

hemofiltration. In this case, Apotex intends to label Normocarb to be injected into the extracorporeal bloodline before the blood enters the filter chamber. While part of the Normocarb solution will be discarded with the toxins and certain amounts of blood itself, a significant portion of the Normocarb enters the patient along with the blood that is re-injected into the patient.

Because of the removal of significant quantities of water during hemofiltration and because of the electrolyte imbalances and metabolic derangements resulting from hemofiltration that must be corrected, water and appropriate concentrations of electrolytes must be infused into patients undergoing hemofiltration. The water and electrolytes in the Normocarb that is infused into the patient (that is, the electrolytes and water contained in the Normocarb that is not filtered out and discarded) are clearly intended to replenish the patient's fluid volume and to help correct electrolyte imbalances that occurred as a result of the hemofiltration process.

Kidney patients often have problems with acidosis. The sodium bicarbonate in Normocarb is intended to correct this metabolic imbalance that exists independent of the hemofiltration process.

Product Classification: Drug

In its initial RFD, Apotex recommended that Normocarb be classified as a device to be regulated by CDRH. In our initial May 2, 2003, decision, we concluded that Normocarb does not meet the definition of a device because it achieved its primary intended purpose (electrolyte and fluid replacement, and pH balancing) through chemical or metabolic action within or on the body. We concluded further that Normocarb does meet the definition of a device, and therefore classified the product as a drug. Because of discussions that occurred at the March 17, 2003, meeting between Apotex and the agency, the initial designation letter noted in passing our conclusion that Normocarb is not a combination product.

Apotex's request for reconsideration argues that Normocarb is a "device-based" combination product. Apotex argues that the sodium bicarbonate is included in Normocarb to correct a deficiency that existed prior to hemofiltration. Therefore, according to Apotex, sodium bicarbonate is the drug component of Normocarb.

According to Apotex, the water and electrolytes form the device component of Normocarb. Apotex states that the pressure of Normocarb's water and electrolytes inside

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which the blood is returning to the patient). Apotex re-confirmed this understanding at the July 29 meeting.

the filter will help push the toxins and excess water in the blood through the filter. According to Apotex, this is Normocarb's primary purpose.

Apotex states that a further purpose of the water and electrolytes in Nomocarb is to replace, or substitute for, some plasma water and electrolytes that are removed from the blood in the filtering process. Apotex emphasizes, however, that with respect to the non-bicarbonate electrolytes, the patient's blood would have been normal to begin with. Therefore, according to Apotex, it is more accurate to say that the electrolytes in Normocarb ensure that the filtering process does not harm the biochemical make-up of the blood. Apotex argues further that, with respect to ensuring that the biochemical make-up of the patient's blood remains normal, Normocarb works just like a dialysis solution, which is a device.

A combination product is a product comprised of two or more regulated components, i.e., a drug and a device. 21 CFR § 3.2(e)(1). We agree with Apotex that the sodium bicarbonate in Normocarb meets the definition of a drug. However, we conclude that the water and electrolytes in Normocarb do not meet the definition of a device. Therefore, Normocarb is not a combination product.

We agree that the water in Normocarb perhaps enhances the process of filtering toxins from the blood.[2] We also agree that the non-bicarbonate electrolytes help ensure that the biochemical make-up of the patient's blood is not harmed by the filtering process. Similarly, we conclude that water from Normocarb is returned to the patient to replace the plasma water removed from the patient during the filtering process (see footnote 1).

We further conclude that the electrolytes and water also work by chemical or metabolic action within the body to help ensure fluid and metabolic homeostasis. Apotex acknowledges this fact on the first page of its request for reconsideration, but argues that because the filtering causes the water and electrolyte deficiencies, the water and electrolytes in Normocarb should not be considered drugs. However, the definition of a drug does not address the cause of the condition to be remedied. The water and electrolytes in Normocarb meet the definition of a drug even though the deficiency was caused by hemofiltration. The water and electrolytes in Normocarb do not meet the definition of a device because they work by chemical or metabolic action within the body.

[2] Apotex submitted no information intended to demonstrate that the electrolytes other than sodium bicarbonate also enhance the filtering process. Whether they do or not is not critical to our conclusion. Therefore, this discussion refers only to water as enhancing the filtering process.

Apotex argues that because the water and electrolytes work as both a drug and a device[3], it should be classified according to whether it achieves its "primary intended purpose" through chemical or metabolic action. According to Apotex, the use of the plural "purposes" in the definition of a device is a Congressional oversight, and that the definition of a device is actually intended to exclude products that achieve their "primary intended purpose[4] through chemical or metabolic action...." According to Apotex, the definition of a device instructs FDA "to determine a product's primary intended use and consider whether it is achieved through a drug-like or device-like mode of action."[5] Apotex asserts that the plain meaning of primary is "first in importance," and states that the filter enhancing function of Normocarb is first in importance or primary. Therefore, according to Apotex, Normocarb should be classified as a device, notwithstanding the fact that it works by chemical action within the body.

As stated in our initial RFD decision, the argument that the use of the plural form of "purposes" was a Congressional oversight is not persuasive. Like Normocarb, many products have more than one primary intended purpose, a fact suggesting that use of the plural "purposes" was not an oversight. Moreover, even if Apotex were correct that the definition of a device tacitly requires selection of one primary intended purpose when a product has multiple purposes, it has not shown that Normocarb would be a device. Apotex has not demonstrated why the filter enhancing function of Normocarb is primary when it has also stated that hemofiltration is hardly ever done without an infusate (that is, ultrafiltration) because the patient would suffer from the removal of so much fluid without it being replaced. (See Footnote 1, above.) It is clear, therefore, that the replacement of fluid, electrolytes, and bicarbonate requires the infusate, but the process of removing fluid and toxins can occur, even though less efficiently, and arguably, more dangerously, without the infusate.

We recognize the similarities between Normocarb used as a dialysate in hemodialysis, and Normocarb used as an infusate in hemofiltration. We also recognize a major difference. When used as an infusate in hemofiltration, Normocarb will be injected directly into the patient's blood and ultimately, in large portion, into the patient him- or herself. Direct infusion into the patient's blood does not occur when Normocarb is used as a dialysate in hemodialysis where the dialysate creates the diffusion gradient across the filter which is required to remove toxins. Without the dialysate, hemodialysis would not be possible.

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[3] According to Apotex, when the water enhances the filtering process, it meets the definition of a device. When the water and electrolytes are infused into the patient, they meet the definition of a drug.

[4] Rather than "purposes."

[5] Page 4 of Request for Reconsideration

A solution that works by chemical action and is directly injected into the patient's blood to primarily correct fluid and metabolic deficiencies falls squarely within the definition of a drug. Accordingly, we conclude that Normocarb is a drug and not a combination product.

Assignment of Lead Center: CDER

CDER's Division of Cardio-Renal Drug Products (DCRDP) will be responsible for the premarket review of Normocarb under the new drug provisions of the act.[6] In addition to the new drug provisions, Normocarb will need to comply with other requirements that apply to human drugs, such as the current good manufacturing practices for finished pharmaceuticals.[7]

The Office of Combination Products has met with representatives of CDER and CDRH to discuss CDER's regulation of Normocarb. At that meeting, Dr. Douglas Throckmorton, Director of DCRDP, assured the Office of Combination Products that DCRDP intends to work with you to determine the database that would be needed to establish the safety and efficacy of Normocarb as a hemofiltration solution. We discussed the possibility that a 505(b)(2) application[8] would be acceptable for the review of Normocarb, and concluded that in the absence of information about the claims you intend to make for Normocarb, the appropriate type of application cannot be determined with certainty. Nevertheless, we recommend that you consider whether a 505(b)(2) application might be appropriate. Information about 505(b)(2) applications is contained in a draft guidance document, www.fda.gov/cder/guidance/2853dft.doc. Among other things, it was suggested at our meeting that some of the information needed to support a 505(b)(2) application might be found in publicly available information about hemofiltration products.

Dr. Throckmorton asked the Office of Combination Products to encourage you to schedule a meeting with DCRDP at your earliest convenience to discuss the content of your marketing application. Dr. Throckmorton would like to attend the meeting, as would Dr. Carolyn Neuland, Chief of the Gastroenterology and Renal Devices Branch, Division of Reproductive, Abdominal and Radiological Devices, CDRH, and a representative of the Office of Combination Products. Please call Zelda McDonald, Chief Project Manager, DCRDP, at 301-594-5328, to schedule the meeting.

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[6] Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355. See also 21 CFR. § 314.50, Content and Format of an Application, and 21 CFR § 314.90, Waivers.

[7] See 21 CFR § Parts 210 and 211.

[8] A 505(b)(2) application contains full reports of investigations of safety and effectiveness but at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

Alternatively, if you prefer, the Office of Combination Products would be happy to schedule the meeting on your behalf.

Finally, although Normocarb is not a combination product, the Office of Combination Products remains available to you as a resource for questions or issues that may arise throughout its development and review. Please feel free to call the Office of Combination Products at any time at 301-827-9229.

Sincerely,

Murray M. Lumpkin, M.D., MSc
Principal Associate Commissioner

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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May 2, 2003

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Re: Request for Designation
Normocarb
Our file: RFD 2002.038

Dear Dr. Erlich:

The Food and Drug Administration has completed its review of the Request for Designation Apotex submitted on behalf of [redacted] (RFD 2002.038). The RFD covers Normocarb, which is intended for use as an infusate in hemofiltration for continuous renal replacement therapy in acute renal failure. The RFD requests that, for this intended use, Normocarb be classified as a device. As discussed in more detail below, we conclude that, for this intended use, Normocarb is a drug.

We filed the RFD on December 12, 2002. Since that time we have held numerous meetings, received supplemental information, and engaged in much internal discussion about whether Normocarb, when intended for use as an infusate in hemofiltration, is a drug or a device. Because of the continuing deliberations, Apotex agreed to extend the designation deadline to May 2, 2003.

On March 17, 2003, representatives of Apotex met with the agency to present its views in person and to answer questions from FDA staff concerning the product. On April 7, 2003, the Ombudsman's Office received information supplementing Apotex' RFD, including a written summary of the March 17 meeting.

Normocarb is a solution containing water, magnesium chloride hexahydrate, sodium chloride, and sodium bicarbonate. It is already cleared for marketing under 510(k) 001059, when intended for use as a dialysate for use in hemodialysis systems.

In its initial RFD submission, Apotex argues that, when used as a hemofiltration solution, Normocarb meets the definition of a device for two reasons: it is used outside the body and it falls within section VIII of the Drug – Device Intercenter Agreement, which states that

> A liquid, powder, or other similar formulation intended only to serve as a component, part, or accessory to a device with a primary mode of action that is physical in nature will be regulated as a device by CDRH.

In the RFD, Apotex claims that, because the main purpose of hemofiltration is to remove unwanted solutes from the blood, and not to administer compounds to the body, Normocarb is an accessory to the hemofiltration system and should be regulated as a device by CDRH.

In its summary of the March 17 meeting, Apotex argues that deletion of the word "any" before "primary intended purposes" in the 1990 amendment to the definition of device in section 201(h) indicates that a determination whether a product is a device is to be based on the product's single primary intended purpose, notwithstanding the use of the plural "purposes." According to Apotex, the primary intended use of hemofiltration is the removal of toxins and excess fluids, and that maintenance of salt concentrations and acid/base balance are secondary intended uses. Apotex states that the primary and secondary uses for Normocarb as a pre-filter hemofiltration solution are identical to those for Normocarb when used as a dialysis solution and, consequently, that when intended for use in hemofiltration, Normocarb is also a device.

Apotex raises an alternative theory for why Normocarb should be regulated as a device: Normocarb is a combination product because it acts as both a drug (acid / base balance) and a device (filtration of toxins from the blood). According to Apotex, the primary intended use of the product is removal of toxins from the blood (device action) and so the product should be regulated by CDRH.

We have considered the information contained in the initial RFD and presented at the March 17 meeting, as well as Apotex' summary of that meeting. We have consulted with representatives of the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Office of the Chief Counsel (OCC). We have reviewed the CDER – CDRH Intercenter Agreement. On April 17, 2003, the Ombudsman's Office met with Dr. Janet Woodcock, Director, CDER, and Dr. David Feigal, Director, CDRH, and other senior members of FDA staff to discuss the issue further. On the basis of all this information, discussion, and analysis, we conclude that when intended for use as a hemofiltration solution, Normocarb meets the definition of a drug.

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The ingredients other than water contained in Normocarb (magnesium chloride hexahydrate, sodium chloride, and sodium bicarbonate) are electrolytes. In the body, electrolytes are critical to cell function; they help regulate the transport of molecules across cell membranes. Abnormal electrolyte concentrations can have serious consequences. Healthy kidneys clean blood by removing excess fluid and waste (toxins). When kidneys fail, harmful wastes and excess fluid accumulate in the body. Hemofiltration removes toxins from the blood of patients with renal disease; the infusate replaces plasma water and electrolytes removed along with the toxins during filtration.

Hemofiltration can be analogized to a kitchen strainer. Blood is removed from the body and is pressured through a filter. Toxins, electrolytes, and significant amounts of plasma water pass through the filter; other blood components are too large and therefore remain in the blood. Hemofiltration infusate is intended to replace the electrolytes and plasma water removed during hemofiltration. Its purpose is to restore the volume and biochemical make-up of the patient's blood to that of a healthy person. Because of the volume of plasma water removed during

hemofiltration, significant amounts of infusate must be administered to the patient. The physician will select an infusate of appropriate composition given the amount of plasma water removed from the patient and the patient's electrolyte levels upon completion of the filtering.

At the March 17 meeting, Apotex stated that it would label Normocarb to be administered into the tubing through which the blood passes on its way to the filter. According to Apotex, when infusate is added in this way before the blood is filtered, it performs a function in addition to replacing the plasma water and electrolytes lost during the filtering: it increases the pressure within the filter, and helps prevent clogging of the filter that can occur when pure blood is filtered. Normocarb is not intended to make any other contribution to the filtering process.

Apotex's argument that the definition of a device requires a determination of one single primary intended purpose is not persuasive. Like Normocarb, many products have more than one primary intended purpose. Indeed, the use of the plural "purposes" in section 201 (h) expressly recognizes this possibility. However, a product cannot be a device if it fulfills its primary intended purposes through chemical action within or on the body of man. When intended for use in hemofiltration, Normocarb achieves its primary purpose through chemical action within the body. The primary intended purpose of an infusate used in hemofiltration is to replace the electrolytes and plasma water removed during the filtering of the blood. It is administered to blood and enters the body with blood. In serving as a replacement for removed plasma water, the infusate is similar to other large volume parenteral drug products intended for rehydration. Moreover, electrolytes work chemically within the body. Therefore, Normocarb meets the definition of a drug, but does not meet the definition of a device.

A single article may achieve one intended purpose through drug action, while achieving another intended purpose through device action. When administered into the blood before it passes over the hemofiltration filter, Normocarb has a second intended purpose: to increase pressure within the filter and to prevent the filter from clogging. These are physical functions, but because Normocarb also functions as a drug, these physical functions do not make Normocarb a device.

The fact that Normocarb is placed in the patient's blood while the blood is outside the patient's body does not make Normocarb a device. As explained above, Normocarb is infused into the tubing outside the body with the intention that the infusate enter the body and perform chemical action once it is there. Accordingly, Normocarb fails to meet the definition of a device.

Normocarb does not fall under section VIII of the Drug – Device Intercenter Agreement. That provision refers to products intended to serve only as an accessory to a device. As explained above, in addition to the physical functions of increasing pressure within the filter and preventing the filter from clogging, Normocarb is intended to enter the body and achieve a primary intended purpose through chemical action once there. Clearly, Normocarb is not intended to serve only as an accessory to a device.

Finally, we conclude that Normocarb does not meet the definition of a combination product. A combination product is comprised of two or more regulated components. 21 CFR § 3.2(e)(1).

The Division of Cardio-Renal Drug Products, HFD-110, will be the review group within CDER. For further information contact Zelda McDonald at 301-594-5300.

You may request reconsideration of this decision within 15 days of receipt of this letter. See 21 CFR § 3.8(c). If you have any questions about this letter, please contact me at 301-827-3390.

Sincerely,

Suzanne O'Shea
Product Jurisdiction Officer

cc: Zelda McDonald