April 30, 2020

Denise Oppermann
Fresenius Medical Care
920 Winter Street
Waltham, MA 02451

Dear Denise Oppermann:

This letter is in response to Fresenius Medical Care's request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the multiFiltrate PRO System[1] and multiBic/multiPlus Solutions[2] to provide continuous renal replacement therapy (CRRT) to treat patients in an acute care environment during the Coronavirus Disease 2019 (COVID-19) pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §360bbb-3).

On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[3] Pursuant to section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared on March 24, 2020, that circumstances exist justifying the authorization of emergency use of medical devices, including alternative products used as medical devices, due to shortages during the COVID-19 outbreak, subject to the terms of any authorization issued under that section.[4] Again pursuant to section 564 and on the same basis, the Secretary of HHS declared on March 27, 2020, that circumstances exist justifying the

[1] The multiFiltrate PRO System includes the multiFiltrate PRO delivery unit, the Ultraflux AV 400S/600S/1000S hemodialyzers/hemofilters, and the multiFiltrate PRO hemodiafiltration cassette (bloodline/tubing systems for blood purification). All components of the system have a current CE (European Conformity) mark. The multiFiltrate PRO system, including any device accessories, are devices regulated by the Center for Devices and Radiological Health (CDRH).

[2] The multiBic/multiPlus Solutions include multiBic dialysate and replacement fluid and multiPlus dialysate. All of these solutions are authorized for marketing in the European Union. The multiBic dialysate and the multiPlus dialysate solutions are regulated as devices by CDRH. The multiBic replacement fluid is regulated as a drug by the Center for Drug Evaluation and Research (CDER). The composition of the solutions can be referenced in tables 1 and 2 of this authorization letter.

[3] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. 85 FR 7316 (February 7, 2020).

[4] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 17335 (March 27, 2020).

authorization of emergency use of drugs and biological products during the COVID-19 pandemic, subject to the terms of the authorization issued under that section.[5]
Based on published data from China and preliminary reports in the U.S., it has been noted that SARS-CoV-2, the virus that causes COVID-19, has led to an increased population with critical illness and multiple organ failure, including acute kidney injury, increasing the need for CRRT. As a result, there is a shortage of devices, accessories and solutions to provide CRRT in critically ill patients. Based on the totality of scientific evidence available, FDA has concluded that the multiFiltrate PRO System and multiBic/multiPlus Solutions may be effective in providing CRRT in an acute care environment and in turn, may provide clinical benefit during the shortage situation.

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act are met, I am authorizing the emergency use of your MultiFiltrate PRO System and multiBic/multiPlus Solutions, as described in the Scope of Authorization (Section II) of this letter, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of the multiFiltrate PRO System device and multiBic/multiPlus Solutions, as described in the Scope of Authorization (Section II) of this letter to provide CRRT in an acute care environment, meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. SARS-CoV-2, the virus that causes COVID-19, can cause a serious or life-threatening disease or condition, including severe respiratory illness and multiple organ failure, including acute kidney injury, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that your multiFiltrate PRO System and multiBic/multiPlus Solutions may be effective in delivering CRRT in an acute care environment, and that the known and potential benefits of the multiFiltrate PRO System and multiBic/multiPlus Solutions, when used for the indication above, outweigh the known and potential risks of the multiFiltrate PRO System and multiBic/multiPlus Solutions; and

3. There is no adequate, approved, and available alternative to the emergency use of the multiFiltrate PRO System and the multBic/multiPlus Solutions when there are shortages of FDA-approved alternatives during the COVID-19 pandemic.[6]

II. Scope of Authorization

[5] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).
[6] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the multiFiltrate PRO System and multiBic/multiPlus Solutions to deliver CRRT to treat patients in an acute care environment during the COVID-19 pandemic.

Authorized Product Details

The multiFiltrate PRO System is designed to provide CRRT by controlling and monitoring extracorporeal blood and fluid circuits.

The following CRRT modalities are available with the multiFiltrate PRO System:

- CVVHD - Continuous Veno Venous Hemodialysis
- CVVH - Continuous Veno Venous Hemofiltration, with pre-dialyzer dilution, post-dialyzer dilution, and pre-post-dialyzer dilution
- CVVHDF - Continuous Veno Venous Hemodiafiltration, with both pre-dialyzer dilution and post dialyzer dilution

MultiFiltrate PRO System Components

multiFiltrate PRO Delivery Unit

A high-resolution touchscreen monitor and four mechanical buttons allow the user to view, monitor, and input or change parameters to manage the treatment. In the extracorporeal blood circuit, blood is pumped from the patient, through a dialyzer attached to the tubing cassette and back to the patient. Blood, filtrate, dialysate, replacement fluid and heparin pumps are used as indicated to meet individual patient's needs and various therapy modes. There is a range of options for delivering CRRT with pre-dialyzer, post-dialyzer or pre- and post-dialyzer dilution. Fluid balance is achieved via scale-based technology. Integrated heaters can be used to heat the dialysate and/or replacement fluids as necessary.

There are a total of four scales for continuous control of fluid. Scales 1 and 2 weigh the dialysates and/or replacement fluids. Scales 3 and 4 weigh the filtrate. The difference between these two sets of scales is monitored to control the fluid balance. The maximum load capacity of each scale is 12 Kg, allowing the user to load as much as 10 L of treatment solution per scale. Handles are located on the front and on the back for ease in transporting the device. The card slot allows for role-dependent access to machine functionality.

Disposable Bloodline/Tubing

The multiFiltrate PRO Hemodiafiltration (HDF) Cassette is used for any treatment modality with heparin anticoagulation.

Hemodialyzers/Hemofilters

Three models of the ultrafluX AV-series dialyzers are used with the system:

- AV-400
- AV-600
- AV-1000

Solutions

Dialysate Solutions

multiBic and multiPlus dialysate Solutions are provided in a two-compartment bag. One compartment contains 4.75L of a slightly alkaline hydrogen carbonate solution. The second compartment contains 0.25L of an acidic electrolyte, glucose solution. The two solutions are combined before use by opening the peel seam between the two compartments, yielding 5L of a ready-to-use sterile solution.

The dialysate bags are made of Biofine SiOx gas barrier foil, an environmentally friendly material which is manufactured without PVC, latex or DEHP. multiBic dialysate solutions are used for hemodialysis and hemodiafiltration modalities (Table 1).

Table 1: multiBic / multiPlus Dialysate Composition

	multiBic	multiPlus
Sodium (Na+) (mmol/L)	140	140
Potassium (K+) (mmol/L)	0, 2, 3, or 4	2
Magnesium (Mg2+) (mmol/L)	0.5	0.75
Calcium (Ca2+) (mmol/L)	1.5	1.5
Chloride (Cl-) (mmol/l)	109, 111, 112, or 113	110.5
Bicarbonate (HCO3-) (mmol/L)	35	35
Phosphate (mmol/L)	0	1
Glucose (mmol/L)	5.55	5.55

Replacement Fluids

Replacement solutions are regulated as drugs by the FDA. Labeling for products used exclusively as dialysate (e.g., multiPlus) contraindicates the use of dialysate solutions as replacement solutions (i.e. direct infusion into the bloodstream).

multiBic replacement solutions are provided in a two-compartment bag. One compartment contains 4.75L of a slightly alkaline hydrogen carbonate solution. The second compartment contains 0.25L of an acidic electrolyte, glucose solution. The two solutions are combined before use by opening the peel seam between the two compartments, yielding 5L of a ready-to-use sterile solution.

The bags are made of Biofine SiOx gas barrier foil, an environmentally friendly material which is manufactured without PVC, latex or DEHP. multiBic Solutions are used for hemodialysis, hemofiltration and hemodiafiltration modalities (Table 2).

Table 2: multiBic Replacement Fluid Composition

Sodium (Na+) (mmol/L)	140
Potassium (K+) (mmol/L)	0, 2, 3, or 4
Magnesium (Mg2+) (mmol/L)	0.5
Calcium (Ca2+) (mmol/L)	1.5
Chloride (Cl-) (mmol/L)	109, 111, 112, or 113
Bicarbonate (HCO3-) (mmol/L)	35
Phosphate (mmol/L)	0
Glucose (mmol/L)	5.55

Performance

The multiFiltrate PRO System and the multiBic/multiPlus Dialysate Solutions comply with the following standards:

- EN ISO 13485:2016 – Medical Devices – Quality Management Systems
- EN ISO 9001:2015 – Quality Management Systems
- MDD 93/42/CE
- ISO 11607-1:2019 - Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems
- ISO 11607-2:2019 - Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes
- EN 1041:2008+A1:2013 – Information supplied by the manufacturer of medical devices
- EN ISO 15223-1:2016 – Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements
- EN 556-1:2001/AC:2006 - Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices
- ISO10993 series – Biological evaluation of medical devices
- EN ISO 14971:2012 Medical devices - Application of risk management to medical devices (ISO 14971:2007, Corrected version 2007-10-01)
- IEC 60601-1: 2005 + CORR.1:2006 + CORR.2:2007 + AM1:2012 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-2: 2014 - Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances - Requirements and tests
- IEC 60601-2-16 Edition 5.0 2018-4 - Medical electrical equipment - Part 2-16: Particular requirements for the basic safety and essential performance of haemodialysis, haemodiafiltration and haemonfiltration equipment
- EN ISO 8637-1: 2017 – Extracorporeal systems for blood purification – Part 1: Haemodialyzers, haemodiafilters, haemofilters and haemoconcentrators
- EN ISO 8637-2:2018 Extracorporeal systems for blood purification - Part 2: Extracorporeal blood circuit for haemodialysers, haemodiafilters and haemofilters (ISO

8637-2:2018)
- EN 1707:1996 - Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment. Lock fittings
- EN ISO 80369-7:2017 Small-bore connectors for liquids and gases in healthcare applications – Part 7: Connectors for intravascular or hypodermic applications (ISO 80369-7:2016, Corrected version 2016-12-01)
- EN ISO 80369-20:2015 Small-bore connectors for liquids and gases in healthcare applications - Part 20: Common test methods (ISO 80369-20:2015)

MultiBic/multPlus replacement solutions
- All applicable European Pharmacopoeial (Ph. Eur.) and/or USP/NF standards.

The multiFiltrate PRO System and multiBic/multiPlus Solutions, when labeled consistently with the labeling authorized by FDA entitled "multiFiltrate PRO Instructions for Use," "Bloodline/Tubing systems for blood purification - Instructions for Use," "Ultraflux AV400S/600S/1000S Instructions for Use," "multiPlus Instructions for Use," and the "Summary of Product Characteristics (SmPC)" for the multiBic Solutions, (available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations),[7] is authorized under the terms and conditions of this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

Your multiFiltrate PRO System and multiBic/multiPlus Solutions are authorized to be accompanied by the following product-specific information pertaining to the emergency use, which is required to be made available to healthcare providers and patients:

- Fact Sheet for Healthcare Personnel: Emergency Use of multiFiltrate PRO System and multiBic/multiPlus Solutions during the COVID-19 Pandemic
- Fact Sheet for Patients: Emergency Use of multiFiltrate PRO System and multiBic/multiPlus Solutions during the COVID-19 Pandemic

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the multiFiltrate PRO System and multiBic/multiPlus Solutions, when used for CRRT in an acute care environment and used consistently within the Scope of Authorization of this letter (Section II), outweigh the known and potential risks of your multiFiltrate PRO System and multiBic/multiPlus Solutions.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the multiFiltrate PRO System and multiBic/multiPlus Solutions may be effective in providing CRRT in an acute care environment, when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

[7]As part of this authorization, the multiFiltrate PRO System and multiBic/multiPlus Solutions will be distributed with the labeling that accompanies these products for distribution in the European Union.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the multiFiltrate PRO System and multiBic/multiPlus Solutions, when used to provide CRRT in an acute care environment (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized products under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the multiFiltrate PRO System and multiBic/multiPlus Solutions, with the required labeling set forth in this section (Section II), are authorized to provide CRRT in an acute care environment.

III. Waiver of Certain FDA Requirements

I am waiving applicable current good manufacturing practice requirements, including the quality system requirements under 21 CFR Part 820 with respect to the design, manufacture, packaging, labeling, storage, and distribution of the authorized devices, including the multiFiltrate PRO System, and multiBic dialysate and multiPlus dialysate Solutions, that are used in accordance with this EUA Conditions of Authorization.

IV. Conditions of Authorization

Pursuant to section 564(e) of the Act, I am establishing the following conditions on this authorization:

Fresenius Medical Care

A. Fresenius Medical Care may request changes to the authorized labeling and fact sheets. Such requests will be made in consultation with, and require concurrence of, the Division of Renal, Gastrointestinal, Obesity and Transplant Devices (DHT3A)/Office of GastroRenal, ObGyn, General Hospital and Urology Devices (OHT3)/Office of Product Evaluation and Quality (OPEQ)/Center for Devices and Radiological Health (CDRH) or the Division of Cardiology and Nephrology (DCN)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER), as appropriate.

B. Fresenius Medical Care may request changes to the components and materials. Such requests will be made in consultation with, and require concurrence of, DCN/OCHEN/OND/CDER or DHT3A/OHT3/OPEQ/CDRH, as appropriate.

C. Fresenius Medical Care may request changes to the Scope of Authorization (Section II in this letter) of the product. Such requests will be made in consultation with, and require concurrence of, the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC), the DCN/OCHEN/OND/CDER, and the DHT3A/OHT3/OPEQ/CDRH.

D. Fresenius Medical Care may request the addition of other instruments and associated software for use with the product. Such requests will be made in consultation with, and require concurrence of, DHT3A/OHT3/OPEQ/CDRH.

E. For the multiBic Solutions used as a replacement solution, Fresenius Medical Care will continue to manufacture the multiBic Solutions in compliance with EU good manufacturing practice (GMP) and pursuant to the European Medicines Agency (EMA) marketing authorization.

F. Fresenius Medical Care will have a process in place to collect information on the performance of the multiFiltrate PRO System and multiBic dialysate and multiPlus dialysate Solutions and for reporting adverse events of which they become aware to FDA under 21 CFR Part 803. Adverse events of which the Fresenius Medical Care becomes aware will be reported to FDA.

G. For the multiBic Solutions when used as replacement solution, Fresenius Medical Care should have a process in place to ensure that adverse events and all medication errors associated with the use of the authorized multiBic Solutions reported to Fresenius Medical Care are reported to FDA, to the extent practicable given emergency circumstances. Prescribing health care providers or designee may report adverse events related to the use of multiBic Solutions during the pandemic to the FDA MedWatch system using one of the following methods:

- Complete and submit the report online: https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home, or
- By using a postage-paid Form FDA 3500 (available at https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting

Submitted reports should state: "use of multiBic Solution was under an EUA".

H. Fresenius Medical Care is authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

I. Fresenius Medical Care will notify FDA of any authorized distributor(s) of the product, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of this EUA.

Fresenius Medical Care and Authorized Distributor(s)[8]

J. Fresenius Medical Care and authorized distributor(s) will make multiFiltrate PRO System devices and multiBic/multiPlus Solutions available with the authorized labeling and fact sheets, described in the Scope of Authorization (Section II) of this letter.

K. Fresenius Medical Care and authorized distributor(s) will make available on their website(s) the Fact Sheet for Healthcare Providers and the Fact Sheet for Patients.

[8] "Authorized Distributor(s)" are identified by the sponsor in EUA requests as an entity allowed to distribute the product.

L. Fresenius Medical Care and authorized distributor(s) will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

M. Through a process of inventory control, Fresenius Medical Care and authorized distributor(s) will maintain records of the healthcare settings to which they distribute the multiFiltrate PRO System and multiBic/multiPlus Solutions and number of multiFiltrate PRO Systems and multiBic/multiPlus Solutions they distribute.

N. Fresenius Medical Care and authorized distributor(s) are authorized to make available additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of this letter of authorization.

Conditions Related to Printed Matter, Advertising and Promotion

O. All descriptive printed matter, including advertising and promotional material, relating to the use of the multiFiltrate PRO System device and multiBic/multiPlus Solutions shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

P. No descriptive printed matter, including advertising or promotional material, relating to the use of the multiFiltrate PRO System and multiBic/multiPlus Solutions may represent or suggest that such products are safe or effective for the delivery of CRRT in an acute care environment.

Q. All descriptive printed matter, including advertising and promotional material, relating to the use of the multiFiltrate PRO System device and multiBic/multiPlus Solutions clearly and conspicuously shall state that:

- the multiFiltrate PRO System device and multiBic/multiPlus Solutions have neither been cleared or approved to provide CRRT in an acute care environment;
- the multiFiltrate PRO System device and multiBic/multiPlus Solutions have been authorized by FDA under an EUA;
- the multiFiltrate PRO System device and multiBic/multiPlus Solutions are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the multiFiltrate PRO System device and multiBic/multiPlus Solutions under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

V. Duration of Authorization

This EUA will be effective until the declarations that circumstances exist justifying the authorization of the emergency use of the multiFiltrate PRO System and multiBic/multiPlus

solutions during the COVID-19 pandemic are terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures