

TechFlash: Extracorporeal blood filtration devices for cytokine removal in COVID-19 patients

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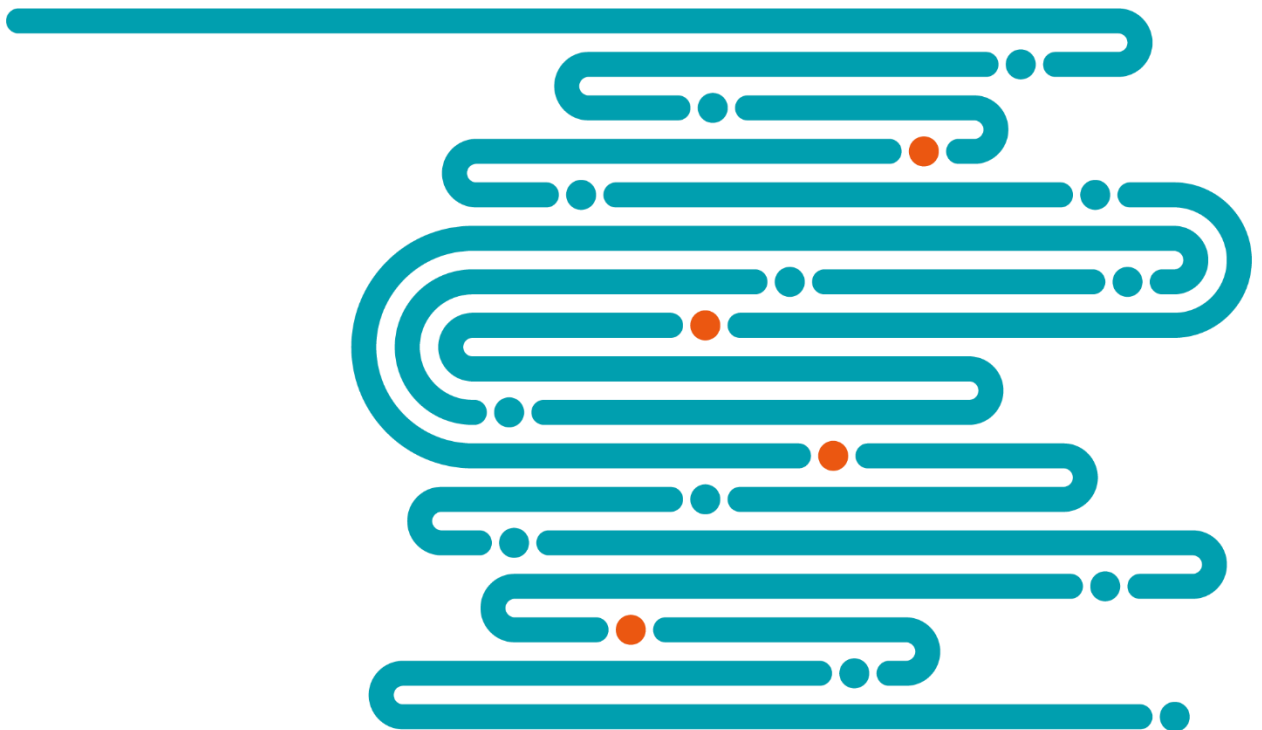


Table of contents

Technology overview and status.....	1
Technology significance.....	2
Current practice and alternatives	2
Clinical evidence summary.....	3
Financial issues	5
Patient selection criteria.....	5
Future developments.....	6
Conclusions and recommendations	6
Related links.....	7
References.....	8

This report comprises a review of abstracts identified through a search of the recent biomedical literature and does not constitute a comprehensive analysis. The report focus is on clinical evidence and outcomes.



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Technology overview and status

Overproduction of cytokines by the immune system, sometimes called a “cytokine storm,” has been associated with the pathogenesis of severe COVID-19 in some patients.¹⁻³ Therefore, removal of excess levels of circulating cytokines may help to reduce the progressive lung injury, multi-organ damage and other symptoms associated with a hyperactive immune response. Various non-pharmacologic, extracorporeal blood filtration devices that target removal of cytokines, pathogens and other inflammatory mediators are now commercially available that may play a role in treatment of COVID-19.⁴⁻⁷

The Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) in April 2020 to four different blood purification devices. None of these devices were previously FDA cleared for this indication, but they were in the latter stages of research and development, were CE Marked for use in Europe and/or met safety criteria for EUA clearance and availability throughout the duration of the declared crisis. Notably, the EUA recognizes the lack of rigorous scientific evidence of effectiveness, but justifies availability under the caveat that it is “reasonable to believe” they may be effective and that there are no approved alternatives for this indication.

The four COVID-19 EUA-cleared blood purification technologies include the **CytoSorb** 300 mL device (CytoSorbents Inc., Monmouth Junction, New Jersey), **Seraph 100** blood filter (ExThera Medical, Martinez, California), **Oxiris** filter set (Baxter Inc., Deerfield, Illinois) and **Spectra Optia** apheresis system (Terumo BCT, Lakewood, Colorado). Though serving a similar purpose, there are unique differences between these devices regarding proprietary materials, filtration methods, adsorption properties and system compatibility. There are, however, no comparative trials between devices to determine any differences in safety or effectiveness outcomes for the treatment of COVID-19.

CytoSorb has been available in Europe since 2011 and reportedly used in more than 100,000 patients for the treatment of hyperinflammation, sepsis, toxicity and other conditions, like hyperbilirubinemia, hypermyoglobinemia and Ticagrelor removal. The device contains polymer-coated beads (~500 microns in size) contained in a cylindrical column with a 200 micron pore mesh on both ends to contain the beads (see Figure 1). Channels and pores in the beads themselves increase the surface area (~46,000 m² per cartridge) for adsorption and limit the entry and removal of large molecules greater than about 60-kiloDaltons in size. Removal of proteins and other hydrophobic molecules traversing the pores occurs through a concentration-dependent chemical adsorption. The CytoSorb filter can be integrated into the circuit of most conventional systems used for continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO).



Figure 1. CytoSorb[®].
CytoSorbents, Inc.

The Seraph 100 Microbind Affinity blood filter device received a CE Mark in 2019 for the reduction of pathogens in the blood stream. The filter consists of ultra-high molecular weight polyethylene beads coated with heparin. (see Figure 2) Heparin has specific chemical binding sequences similar to cell surface receptors that can adsorb various inflammatory mediators and cytokines. Notably, this device claims to also remove circulating pathogens, like bacteria, viruses and fungi, from the bloodstream. This filter may also be placed in-line with most conventional systems used for hemodialysis or hemoperfusion.

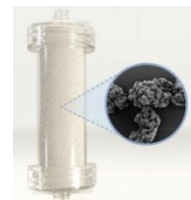


Figure 2. Seraph[®] 100.
CytoSorbents, Inc.

The Oxiris device is a dual-purpose filter set that can be used for simultaneous CRRT and removal of inflammatory cytokines. (see Figure 3) As such, it is used in an extracorporeal circuit as part of the Baxter Prismaflex CRRT system. Oxiris uses a hollow fiber dialysis membrane with blood flow through the fibers and conventional diffusion-mediated removal of low molecular weight solutes and urea through the semi-permeable membrane. The fibers are comprised of a specialized polymer blend (AN69) and a surface coating (PEI, polyethyleneimine). AN69 and PEI adsorb certain endotoxins and cytokines through different chemical interactions. Oxiris has been commercially available in Europe since 2008.



Figure 3. Oxiris® filter set. Baxter Healthcare Corp.

The Spectra Optia system is an apheresis platform used to separate plasma from blood cells for different therapeutic applications. For the COVID-19 application, plasma separated by the Spectra Optia system is filtered through the Depuro D2000 Plasma Adsorption Cartridge (Marker Therapeutics AG, Switzerland). The D2000 cartridge contains activated carbon granules (charcoal) and proprietary nonionic resins (Amberlite XAD-7HP and Amberchrom GC300C) for adsorption of cytokines. (see Figure 4) The D2000 cartridge reportedly has recent CE Mark approval and has undergone early stage pre-clinical and human study in both the U.S. and internationally.



Figure 4. D2000 cartridge. Marker Therapeutics AG.

Technology significance

The normal immune system response to viral infection includes the release of various pro-inflammatory signaling compounds from immune cells. Cytokines, like interferons, interleukins (e.g., IL-6) and other growth factors, are proteins involved in the acute phase inflammation process. Severe COVID-19 has been associated with very high levels of circulating cytokines in some patients and this is often referred to as cytokine storm syndrome.^{1, 8, 9} In some cases, it is believed that the immune response is hyperactive, leading to excessive inflammation and subsequent correlation to acute lung injury and progression to acute respiratory distress syndrome (ARDS). Further complications may include acute kidney injury, cardiac effects and liver dysfunction. Thus, modulating the immune response by cytokine removal is a potential treatment strategy to improve multi-organ outcomes and mortality in COVID-19 patients.

Despite the promise of this technology, there remain many unknowns regarding clinical safety and effectiveness. This is typical of emerging innovative technology in the pre-approval stages of development and particularly for technology being rapidly implemented during a crisis. In addition, there is a lack of firm definition defining a threshold for cytokine storm to help with patient selection, a lack of standardized laboratory tests with validated cytokine target levels and the optimal timing for initiation and discontinuation of cytokine removal therapy remains unknown.¹⁰ For example, in the latter too much cytokine removal could result in immunosuppression and increased rate of secondary infections. Therapeutic antibiotics can also be removed by the non-specific filtration process.

Current practice and alternatives

The current treatment for COVID-19 patients with evidence of cytokine storm syndrome is largely supportive and may include mechanical ventilation, CRRT, maintenance of fluid balance, blood thinners, hemodynamic support and other conventional therapies used in critically ill patients. Pharmacologic therapies may include antivirals (e.g., Remdesivir), corticosteroids (e.g., dexamethasone) and blood derived products

(convalescent plasma, SARS-CoV-2 immunoglobulins).¹¹ The supporting evidence and recommendations for use of these therapies, however, is a rapidly evolving and continually changing process.

Interestingly, a large number of investigational pharmacologic therapies act through immunomodulatory effects targeting inflammatory syndromes; thus, similar to the mechanism for the devices covered in this report. These drugs include corticosteroids, interleukin inhibitors, interferons, kinase inhibitors and others.¹¹ For example, Tocilizumab is a monoclonal antibody directed against the IL-6 receptor with potential effects to mitigate cytokine storm syndrome and reduce mortality in ICU patients.¹² Other investigational drugs like this include Anakinra (IL-1 inhibitor), Sarilumab (IL-6 receptor inhibitor) and Siltuximab (anti IL-6).

Like the IL-inhibitors, kinase inhibitors are drugs that interfere with cytokine signaling pathways that result in an inflammatory response and immune cell activation. Some of the agents under investigation include Acalabrutinib, Ibrutinib, Zanubrutinib, Baricitinib, Ruxolitinib and Tofacitinib. Notably, these drugs induce significant immunosuppression which may be associated with secondary infections and other adverse effects.

The above drugs may be considered alternatives to blood purification devices; though they are not yet recommended due to limitations in the clinical evidence.¹¹ In contrast to drugs, blood purification devices are non-specific and act against a wide range of inflammatory mediators rather than just targeting a single specific molecule or pathway. The kinetics of cytokine removal may also be more controlled with extracorporeal devices since they are concentration dependent and can be immediately reversed by removing them from the extracorporeal circuit. It is not yet known, however, whether there are comparative advantages due to these different mechanisms and approaches.

Therapeutic plasma exchange is an established plasmapheresis technique where the patient's plasma, including circulating pathogens and cytokines, is removed and replaced with a substitute like fresh frozen plasma. The rationale is the same as that for blood purification through hemoadsorption. Further study of this technique in COVID-19 is also underway.¹³⁻¹⁶

Numerous other devices and membrane types are available and have been investigated for cytokine removal. These include hemofiltration devices with medium cutoff and high cutoff membranes that remove inflammatory mediators by diffusion and convection, rather than adsorption.¹⁷ Polymethyl methacrylate (PMMA) membranes and a polymyxin B endotoxin-adsorbing filter (Toraymyxin; Toray Industries, Tokyo, Japan) have also been trialed in sepsis patients, though high quality evidence of efficacy is still lacking.¹⁸ Use of other microporous resin adsorbing bead type filters (HA130, HA230, and HA330, Jafron, Zhuhai City, China) has also been reported in China.¹⁹ These filters, however, are not commercially available in the U.S.

Clinical evidence summary

The [Medline/PubMed](#) bibliographic database, [MedRxiv](#) preprint server for health sciences and [ClinicalTrials.gov](#) database of registered clinical studies were searched in August 2020 to identify clinical evidence related to the use of the EUA approved blood purification [devices](#). Keywords used in the literature search strategy included: *extracorporeal, blood purification, filtration, hemofiltration, adsorption, hemoadsorption, cytokine, cytokine storm, Oxiris, Cytosorb, ExThera Seraph, Terumo Spectra Optia, coronavirus* and/or *COVID-19*.

Prior to the pandemic, numerous case reports and case series were available studying various methods for extracorporeal cytokine removal for different indications.^{18, 20} Many of these reported reduced levels of circulating cytokines and, to a lesser extent, improved clinical outcomes. However, the evidence quality is

rated as low with a high degree of uncertainty for clinical outcomes. Data from subsequent small randomized trials have also generally not shown a definitive improvement in clinical outcomes.^{4,21-23} Overall, the pre-pandemic clinical evidence is promising but inconclusive.

Cytosorb has reportedly been used in more than 1,200 COVID-19 patients worldwide as of August 17, 2020.²⁴ COVID-19 specific clinical evidence includes a preliminary report of use in eight German patients (4 using Cytosorb treatment and 4 controls) with integration of the filter into the ECMO circuit.²⁵ Results showed IL-6 levels were lower in the Cytosorb group at 72 hours after treatment initiation. A pre-print study from Bergamo, Italy reported pilot use in 11 COVID-19 patients.²⁶ Cytosorb use for 24 to 48 hours was shown to result in a transient decrease in IL-6 levels. Improvement in some clinical indicators were reported and there were no reported adverse events associated with the filter itself. An Italian case study also reported use of Cytosorb in conjunction with tocilizumab drug therapy.²⁷ A large number of non-peer-reviewed case studies have also been compiled in a company-sponsored literature [database](#).

Based on positive early results, a number of larger [trials](#) have reportedly been initiated and are recruiting patients. These include a large observational patient registry ([NCT04391920](#)), a small German RCT ([NCT04344080](#)), another German RCT, called CYCOV, comparing Cytosorb in conjunction with veno-venous ECMO ([NCT04324528](#)) and a related multi-center RCT called CYCOV-II ([NCT04385771](#)). CytoResc ([DRKS00021447](#)) is a planned multi-center, phase IIb RCT expected to enroll 80 to 100 patients to study the use of Cytosorb in COVID-19 patients with suspected hyperinflammation.²⁸

The pre-pandemic clinical experience and rationale for use of the Seraph 100 device has been recently described.²⁹ Binding of the SARS-CoV-2 spike (S1) surface protein by heparin has been reported; thus suggesting the ability of Seraph 100 to adsorb and remove virus particles.³⁰ An in vitro study found Seraph 100 did not remove chloroquine or hydroxychloroquine, implying dosing adjustments for these agents are not necessary.³¹

Anecdotal results from the first 23 patients treated with the Seraph 100 device were reported on the company website in May 2020.³² Preliminary results suggested high survival rates, no device-related adverse events, improved hemodynamic stability and a reduction in various biomarkers of inflammation (D-dimer, serum ferritin, IL-6 and C-reactive protein). A case study of the first two COVID-19 patients treated with Seraph 100 in the U.S. suggested no associated adverse events and quantitative improvement in patient hemodynamics and inflammatory biomarkers.³³

Ongoing registered clinical [trials](#) of the Seraph 100 device include a German ([NCT04361500](#)) and U.S. ([NCT04413955](#)) patient registry. A pivotal US-based RCT funded by the Department of Defense and run by the Uniformed Services University in Bethesda has also reportedly been initiated.³⁴

Use of the Oxiris device in COVID-19 patients has been reported in a number of case studies and small case series.³⁵⁻³⁸ A European case series preliminarily reported on use in 15 patients ([NCT04478539](#)) with reductions in inflammation markers and clinical improvements.³⁸ Chinese case series have included reports of use in 3 to 5 patients and shown reduction in cytokine levels, stabilization in hemodynamic status and some improvement in organ functions.^{35, 36} The first use of Oxiris in U.S. patients included three case reports.³⁷ The Oxiris therapy in these patients was reportedly well-tolerated, but no quantifiable clinical improvements were noted.

A small 10patient pilot study of the Terumo Spectra Optia apheresis system equipped with the Depuro D2000 adsorption cartridge was conducted in Saudi Arabia in patients with COVID-19, ARDS and septic shock.³⁹ Reported improvements in organ function, lung parameters and inflammation markers were noted

compared to baseline with no device-related adverse events. Potential improvements in survival, days on mechanical ventilation and ICU length of stay were noted. The Saudi group has also begun a randomized trial using this method of plasma exchange.⁴⁰ A large 2,000 patient, single-arm, manufacturer-sponsored U.S. multi-center study is currently enrolling COVID-19 patients ([NCT04348003](#)).

Financial issues

Prior to the pandemic, these devices were not commercially available in the U.S.; therefore, U.S. prices were not set. In Europe, the single-use blood purification filters typically cost in the range of about \$1,000 to \$2,000.^{41, 42} However, discounts may be applicable for use in research studies and for compassionate use in COVID-19 patients during the pandemic. A typical procedure could use three to five filters (e.g., one filter per day for three or more days).

Additional disposable tubing and connection sets may also be required. Capital costs are associated with the extracorporeal systems, like ECMO, hemodialyzers and apheresis systems. In patients with severe disease, ECMO and/or CRRT may be indicated for primary organ support, in which case the filters may simply be incremental to the circuit. Standalone hemofiltration using an adsorption filter would accrue some cost for the system itself. Extracorporeal systems can cost around \$15,000 to \$75,000, depending on the system and features, though most hospitals already have these devices for critical care.^{41, 42}

Because they are in the early stages of development, there remain many unknowns surrounding the clinical and economic outcomes for these technologies. Further study is needed, therefore, to better delineate the inputs for financial modeling. If these technologies are associated with improved clinical outcomes, reduced ICU LOS and faster ventilator weaning, there is potential for significant cost savings to offset the filtration expenses. A mortality benefit would potentially provide a favorable cost-effectiveness ratio. However, rigorous calculations of cost-effectiveness cannot be made yet because of the lack of comparative efficacy outcomes data.

Patient selection criteria

FDA [EUA](#) labeling suggests use of these devices may be indicated for adult patients with confirmed cases of COVID-19 in the ICU with any of the following conditions:

- Early acute lung injury/early acute respiratory distress syndrome
- Severe disease, defined by:
 - dyspnea
 - respiratory frequency $\geq 30/\text{min}$
 - blood oxygen saturation $\leq 93\%$
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
 - lung infiltrates $> 50\%$ within 24 to 48 hours
- Life-threatening disease, defined by:
 - respiratory failure, septic shock and/or multiple organ dysfunction or failure

Further criteria based on cytokine levels and markers of inflammatory status would seem reasonable, but are not yet well-defined.⁴ These may include blood concentration of cytokines, like interleukins (e.g., IL-6), Tumor Necrosis Factor (TNF), interferons, colony stimulating factors (CSFs) and chemokines. The cytokine panels used in current COVID-19 research, however, vary widely and have ill-defined thresholds. Other biomarkers associated with severe COVID-19, include procalcitonin levels, D-dimer, serum ferritin and C-reactive protein (CRP). An improvement in these biomarkers could be a surrogate for filtration therapeutic

success. Similarly, clinical criteria, like the sequential organ failure assessment (SOFA), may also play a role in patient selection and therapeutic monitoring.

The optimal timing for device use in COVID-19 patients is still unknown, so patient selection based on early or late stage parameters also requires further study. General usage so far has mostly been after initiation of extracorporeal circuits for lung or kidney therapy.

Future developments

Continued development of clinical evidence is expected and needed in the near future. Though well-designed and conducted trials often require a significant amount of time, the pandemic has accelerated many phases of the clinical trial process, including rapid patient enrollment and early pre-print publication of interim results. In this accelerated timeframe, more clinical data on use of these devices may be expected in late 2020 and early 2021. Therefore, efforts should be made to update the literature search to account for rapid developments in evidence.

Of note, clinical data from large patient registries are expected in the near future from both European and American sources. Some small RCTs are also reportedly underway. Institutions using these devices in the early stage of development should be doing so within the context of a research study with thorough collection of data and planned publication of results. This is needed to better determine potential efficacy, patient selection criteria and appropriate use of these devices.

Beyond COVID-19, this technology may have a high impact on the treatment of sepsis and septic shock due to other infectious agents. Some pre-pandemic clinical trials were already underway for this indication and results may be available in the near future. These results may then be considered as part of the full FDA approval process, with FDA consideration possibly in late 2021 or 2022.

There are currently many different types of membranes and filters for blood purification. Comparative trials are needed to determine whether these design differences result in differences in clinical outcomes. New membranes targeting removal of specific pathogens, immune cells, cytokines and other involved molecules may be developed in the future.

Conclusions and recommendations

The following conclusions and recommendations are based on the material presented in this report:

- A hyperactive immune response has been associated with acute lung and other organ injury in patients with severe COVID-19. Therefore, removal of immune signaling compounds associated with the hyperactive response may play a role in treatment.
- Four different blood filtration technologies that target removal of cytokines, pathogens and other inflammatory mediators have been cleared through the FDA EUA process for COVID-19. These devices did not have full FDA approval for cytokine removal indications prior to the pandemic; therefore, they should still be considered investigational. Notably, there are potentially significant differences among these devices due to different adsorption materials, mechanisms and filtration methods. However, no clinical differences have been shown as yet.
- These blood purification technologies are not new. Some, like Cytosorb, have reportedly been used in more than 100,000 patients in Europe and Asia over the past 10 years. Various indications have

been targeted and previously studied, including a similar indication of sepsis with pneumonia and ARDS. Despite a significant amount of pre-pandemic published evidence, strong recommendations for use in sepsis have not been made due to ongoing limitations in the quality and quantity of evidence.

- Blood filtration devices have reportedly been used in more than 1,000 COVID-19 patients worldwide as of August 2020 and this number may be growing rapidly. Significant usage has been reported by investigators in China, Germany and Italy. Anecdotal reports, case studies and small case series have also been reported at U.S. sites. Nonetheless, the use of these devices in COVID-19 is not widespread and is occurring mostly at research institutions.
- Overall, the evidence base for these technologies when used in COVID-19 patients is very limited. Benchtop testing and small case series have mostly shown the capability of these devices to reduce select cytokine levels in some patients. The effect on clinical outcomes, however, is not well proven. In particular, a lack of well-matched controls makes it difficult to determine if reported clinical improvements were due to blood filtration therapy or other mechanisms. Patient selection bias due to compassionate use in the sickest patients also complicates clinical data interpretation.
- Safety outcomes are also not well proven. Though most studies report no adverse events related to use of the device itself, the effect from alteration of the immunological cascade could be deleterious in some patients. For example, because they are non-selective they may also remove therapeutic drugs, like antibiotics, nutrients and other non-specific immune compounds that may be needed to fight secondary infections.
- Due to a lack of high-quality prospective clinical evidence on safety and efficacy, usage decisions at this time are based mostly on clinical expertise and opinion. Consideration of the lack of treatment alternatives for severe COVID-19 may be factored into the overall risk benefit calculation. Appropriate patient selection criteria are still not yet known. Hospitals choosing to use these devices should do so in the context of a research study intended to help future clinical usage decisions.
- The ICU is one of the most high-cost, resource-intensive settings in the hospital. Therefore, any technology improving outcomes in critically ill patients has the potential to provide significant savings that offset upfront costs. Unfortunately, at this time there is not enough clinical and financial data to calculate the cost benefit of these technologies.
- A significant amount of ongoing research was identified during the literature search. Efforts should be made to update the evidence included in this report before decision-making.

Related links

Technology Assessments:

[CADTH Tech Update \(June 18, 2020\)](#)

[Penn Medicine EPC annotated bibliography \(June 2020\)](#)

[U.K. NICE Medtech Briefing \(May 21, 2020\)](#)

[Wales Health Technology \(July 2020\)](#)

Company/product websites:

Baxter Oxiris filter set

CytoSorbents CytoSorb

ExThera Medical Seraph 100

Terumo BCT Optia apheresis system

Marker Therapeutics Depuro D2000 cartridge

FDA materials: [EUA list](#)

FDA EUA letter	Information sheets	Instructions for use
Baxter Healthcare Corporation Extracorporeal Blood Purification (EBP) Device	Healthcare Providers Patients	IFU
CytoSorbents, Inc. Extracorporeal Blood Purification (EBP) Device	Healthcare Providers Patients	IFU
ExThera Medical Corporation Extracorporeal Blood Purification (EBP) Device	Healthcare Providers Patients	IFU
Terumo BCT Inc. and Marker Therapeutics AG Extracorporeal Blood Purification (EBP) Devices	Healthcare Providers Patients	IFU-a IFU-b IFU-c

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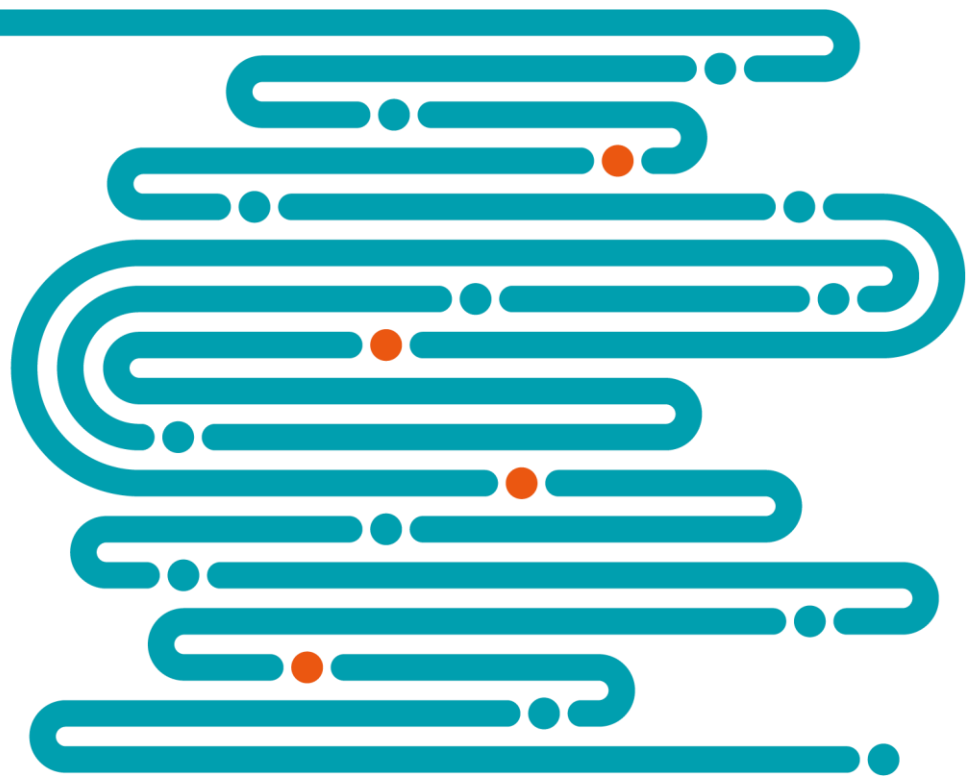
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