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The U.S. Blood Supply and the COVID-19 Response: In Brief

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The U.S. Blood Supply and the COVID-19 Response: In Brief

The nation's blood supply is largely managed by a network of independent blood centers and the American Red Cross, with some oversight from the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA). These private organizations collect blood product donations (e.g., whole blood, plasma, and platelets) from individual volunteers through scheduled appointments, walk-in appointments, and blood drives. Independent blood centers and the American Red Cross each collect nearly half of blood products nationwide, with the remainder collected in hospital settings.

The response to the Coronavirus Disease 2019 (COVID-19) pandemic has posed significant challenges for maintenance of the U.S. blood supply. Mitigation strategies to prevent the spread of COVID-19, such as closures of schools and workplaces, have led to blood drive cancellations at the places where such events are often held. In addition to blood drive cancellations, individual state stay-at-home orders and general fear of contracting the COVID-19 virus might dissuade individuals from scheduling appointments to donate blood.

Both FDA and Congress have taken action to address some of these issues. For example, FDA—the agency that regulates the blood supply and blood products—issued guidance in April 2020 to broaden the pool of eligible blood donors and create alternative procedures for blood establishments during the COVID-19 pandemic. In addition, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act; P.L. 116-136), enacted on March 27, 2020, included a provision requiring the Secretary of HHS to create a nationwide awareness campaign regarding the importance of donations to maintain the blood supply.

Various drugs and biologics, including blood-derived therapies, are under investigation for treating and preventing COVID-19. FDA has issued treatment and research guidance regarding two blood-derived treatments: convalescent plasma and hyperimmune globulin. However, data regarding the safety and effectiveness of such treatments are still being generated. In the absence of any approved drugs or biologics for COVID-19, FDA has used its existing authorities to increase access to unapproved products through mechanisms such as expanded access and emergency use authorization (EUA). On August 23, 2020, FDA issued an EUA for COVID-19 Convalescent Plasma (CCP)—blood plasma that is collected from an individual who has recovered (i.e., “convalesced”) from COVID-19 and is then administered to a patient actively sick with COVID-19 for treatment.

Some concern has been raised regarding FDA's issuance of an EUA for CCP in the absence of evidence from randomized controlled trials (RCTs), which are the gold standard for evaluating the effectiveness of therapies. It is not clear the extent to which an EUA will increase access to convalescent plasma, as its availability is limited by donations. If patients are more readily able to access CCP through the EUA, participation in clinical trials may be hindered, making it more difficult to generate data regarding the effectiveness of convalescent plasma for COVID-19. Given the therapeutic potential of blood-derived therapies and that availability is limited based on donations, Congress may wish to consider further action regarding the maintenance of the U.S. blood supply as part of its efforts to respond to the COVID-19 pandemic.

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Introduction

The nation's blood supply is largely managed by a network of independent blood centers and the American Red Cross, with some oversight from the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA), an agency within HHS.¹ These organizations collect donated blood and its components (e.g., plasma, red blood cells, and platelets) from individuals through scheduled appointments, walk-in appointments, and blood drives. Independent blood centers and the American Red Cross each collect nearly half of blood products nationwide, and the remainder is collected in hospital settings.² Because blood products have a limited shelf-life, ongoing donations are necessary.³

Blood is used for transfusions—one of the most common medical procedures in which healthy blood is given to an individual.⁴ Transfusions are generally considered safe. However, there is a small risk of complications. Certain infectious diseases can be transmitted through contact with an infected individual's blood, which is mitigated through FDA guidance and implementation of safety protocols by blood establishments, such as deferral requirements for certain potential blood donors who may be at higher risk of transmitting an infectious disease.

In addition to its use in transfusions, blood and blood components can also be used in the manufacture of blood-derived pharmaceutical products. The manufacture of blood products is also regulated by FDA.

The response to the COVID-19 pandemic has posed significant challenges for the U.S. blood supply. Mitigation strategies to prevent the spread of COVID-19, such as closures of schools and workplaces, have led to blood drive cancellations. In addition to blood drive cancellations, individual state stay-at-home orders and general fear of contracting the COVID-19 virus might dissuade individuals from scheduling appointments to donate blood.

This issue first emerged in early March 2020, when a critical blood supply shortage was identified in the Pacific Northwest as Washington State was responding to localized COVID-19 outbreaks.⁵ Around that same time, other blood establishments across the country began to issue press releases indicating an urgent need for donated blood.⁶ Some evidence showed that a large

¹ For more information on independent blood centers, see <https://americasblood.org/about/>. For more information on the American Red Cross, see <https://www.redcross.org/give-blood.html>.

² FDA Center for Biologics Evaluation and Research, Office of Blood Research and Review, "FDA Regulation of Blood and Blood Components in the United States," seminar, August 20, 2019, p. Slide 15, <http://fda.yorkcast.com/webcast/Play/7febcdc6189646e5b6f1a18e392815fb1d>.

³ Whole blood expires 21-35 days from donation. The shelf-life of other blood products ranges in length from five days (platelets) to one year (plasma); see <https://www.redcrossblood.org/donate-blood/how-to-donate/types-of-blood-donations/blood-components.html>.

⁴ <https://www.nhlbi.nih.gov/health-topics/blood-transfusion>.

⁵ On March 9, 2020, one blood center, Bloodworks Northwest, headquartered in Seattle, WA, issued a press release warning that the Pacific Northwest blood supply was at the risk of collapse in coming days due to COVID-19 concerns. The release notes that the closure of schools, businesses, and events had led to the cancellation of blood drives in the area. For the press release, see <https://www.bloodworksnw.org/wp-content/uploads/2020/03/coronavirus-press-release-march-9-2020.pdf>.

⁶ In early March, blood establishments were acting independently to issue press releases raising concern and calling for individuals to donate. For an example, see New York Blood Center's March 4, 2020, press release: <https://nybloodcenter.org/news/articles/new-york-blood-center-announces-urgent-need-blood-and-platelet-donors-fears-coronavirus-keep-healthy-donors-away/>.

percentage of blood establishments were facing critical shortages, which typically means that the establishment has a day or less of supply.⁷

Following the initial blood supply shortage, far fewer blood establishments were reporting critical or low supplies,⁸ and this was attributed to outreach efforts and the ability to share blood and blood components through a national resource-sharing program, the National Blood Exchange (NBE).⁹ (See the “Oversight of the U.S. Blood Supply” section below for information on the NBE.) In addition, widespread deferral of elective and non-emergent medical procedures during the initial response to COVID-19 decreased the demand for transfusions.¹⁰

In May 2020, as elective and nonemergent medical procedures resumed, blood centers reported inventories falling to their lowest levels since the early stages of the pandemic. This shortage prompted industry groups to issue a joint statement urging individuals to donate.¹¹ More recently, industry groups have issued statements regarding an ongoing critical need for COVID-19 convalescent plasma donors, in particular.¹²

FDA issued guidance relaxing restrictions on blood donation, which did not mitigate the immediate need for blood in March 2020, but may have the effect of increasing the donor pool for supply shortages in the future as the country continues to respond to the COVID-19 pandemic.

Now, the industry is implementing recommended changes to expand the size of the donor pool and creating blood banks of donations from donors who may have already contracted and recovered from COVID-19, whose blood may be used for a potential treatment.

This report provides a brief background of the regulatory framework for the U.S. blood supply, explains the federal response to the current crisis, and discusses potential treatment of COVID-19 using blood-derived products.

Regulation and Oversight of U.S. Blood Supply

The U.S. blood supply is largely regulated by FDA, which includes, among other things, oversight through licensing of organizations and products. Oversight regarding emergency response preparedness and the monitoring of local and national blood supply is a collaborative

⁷ America’s Blood Centers, a network of non-Red Cross blood centers representing about half of the nation’s blood supply, maintains a stoplight report with publicly available real-time data on regional blood supply availability. On any day in the first two weeks of March 2020, the stoplight report shows that at least 40% of blood centers had a critical or low supply of blood; see <https://americasblood.org/for-donors/americas-blood-supply/>.

⁸ The America’s Blood Centers stoplight report shows that, as of May 6, 2020, a far lower percentage of blood centers were experiencing shortages of blood. In addition, as of that date, industry groups had not issued urgent calls for blood donations in several weeks.

⁹ Monica B. Pagano, John R. Hess, and Hamilton C. Tsang, et al., “The blood supply management amid the COVID-19 outbreak,” *Transfusion*, vol. 60, no. 5 (March 21, 2020), pp. 908-911.

¹⁰ *Ibid.*

¹¹ AABB, America’s Blood Centers, and American Red Cross, “Joint Statement on the Blood Supply,” press release, May 28, 2020, <https://mk0americasbloogf2jd.kinstacdn.com/wp-content/uploads/2020/05/Joint-Statement-on-Blood-Supply.pdf>.

¹² America’s Blood Centers, “ABC Statement on Ongoing Critical Need for COVID-19 Convalescent Plasma Donors,” press release, August 21, 2020, <https://americasblood.org/news/abc-statement-on-ongoing-critical-need-for-covid-19-convalescent-plasma-donors/>.

effort between HHS and industry groups, which includes professional organizations representing blood establishments.¹³

FDA Regulation of the Blood Supply

FDA oversees the collection of blood and its components (e.g., plasma, red blood cells, and platelets) intended for transfusion or for the manufacture of pharmaceutical products. FDA regulates *blood and blood products* (“blood products”) as biologics under two statutes: the Federal Food, Drug and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA).¹⁴ The FDA Center for Biologics Evaluation and Research (CBER) Office of Blood Research and Review (OBRR) establishes regulatory policies and standards; reviews regulatory applications and grants licenses for blood products; performs mission-related research; and conducts emergency preparedness and outreach.¹⁵

Establishments that manufacture blood products must register with FDA and are subject to inspection by the agency.¹⁶ Certain establishments—those manufacturing blood-derived pharmaceutical products or intending to ship blood products across state lines—also must be licensed by FDA under a biologics license application (BLA).¹⁷ For example, the American Red Cross and other blood centers are licensed for blood collection because they supply blood products to multiple hospitals, often across state lines.¹⁸ In contrast, hospitals typically do not ship blood products across state lines and thus do not require a license, although they must register with FDA for blood collection.

Blood establishments must comply with FDA regulations governing blood collection, storage, testing, and processing, among other things. FDA regulations also describe eligibility criteria to donate blood that both protect the health of the donor and ensure the safety, purity, and potency of the blood product.¹⁹ Current FDA guidance recognizes an industry-prepared standardized donor

¹³ 21 C.F.R. §607.3. The term *establishment* refers to “a place of business under one management at one general physical location and includes, among others, human blood and plasma donor centers, blood banks, transfusion services, other blood product manufacturers and independent laboratories that engage in quality control and testing for registered blood product establishments.”

¹⁴ 42 U.S.C. §262, §264 and 21 U.S.C. §§301 et seq. FDA regulations pertaining to blood products are set forth at 21 C.F.R. Parts 600 (Biological products; general); 601 (Licensing); 606 (Current good manufacturing practice for blood and blood components); 607 (Establishment registration and product listing for manufacturers of human blood and blood products and licensed devices); 610 (General biological products standards); 630 (Requirements for blood and blood components intended for transfusion or for further manufacturing use); and 640 (Additional standards for human blood and blood products). The regulation of blood products is described in further detail in the “FDA Regulation of Biologics” section of this report.

¹⁵ For CBER product jurisdiction by office, see FDA, “CBER Product Jurisdiction,” March 26, 2018, <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-product-jurisdiction>. For more information on FDA regulation of biologics and drugs, see CRS In Focus IF11083, *Medical Product Regulation: Drugs, Biologics, and Devices*.

¹⁶ 21 C.F.R. §607.3. The term *manufacture* refers to “the collection, preparation, processing or compatibility testing by chemical, physical, biological, or other procedures of any blood product which meets the [FFDCA] definition of a drug.”

¹⁷ 42 U.S.C. §262. FDA, “FDA Regulation of Blood and Blood Components in the United States,” <https://www.fda.gov/media/81654/download>. Biologics licensure is described in further detail in the “FDA Regulation of Biologics” section of this report.

¹⁸ For additional information, see “FDA Regulation of Blood and Blood Components in the United States” at <https://www.fda.gov/media/81654/download>.

¹⁹ 21 C.F.R. §630.10(a).

history questionnaire as an acceptable mechanism for determining eligibility.²⁰ The donor history questionnaire incorporates all FDA guidance and regulations pertaining to donor eligibility.²¹

FDA often issues guidance documents that recommend how to comply with statutes and regulations in general, as well as in specific scenarios, such as when there is stress on the blood supply due to the COVID-19 response.²² These guidance documents are not legally binding.²³ However, blood establishments use FDA guidance to create standard operating procedures.

Oversight of the U.S. Blood Supply

Coordination of blood availability and emergency preparedness is a collaborative effort between many stakeholders, with input from HHS, FDA, and other federal entities, as well as from nonfederal partners. The HHS Office of Infectious Disease and HIV/AIDS Policy (OIDP) supports the coordination of blood safety and emergency preparedness and response activities. OIDP staff serve as liaisons on a number of councils, task forces, advisory committees, and programs.²⁴

Of particular interest for the COVID-19 pandemic response is the Inter-organizational Task Force on Domestic Disasters and Acts of Terrorism (the task force), which is led by the American Association of Blood Banks (AABB).²⁵ When an event affects the local blood supply (e.g., disaster, terrorism), the affected blood center contacts AABB. After this initial contact, AABB convenes a conference call with task force members, which typically results in issuance of coordinated recommendations and messages to the blood community, donors, and the public.

Concurrently, AABB assists the affected blood center(s) to increase the local blood supply through a resource-sharing program, the National Blood Exchange. NBE is the primary resource-sharing program for blood centers in the United States.²⁶ NBE facilitates sharing of blood products, in general, and in response to an emergency. NBE can move blood from blood centers with surpluses to those that cannot meet anticipated need. This program, administered by AABB, allows for the transfer of surplus blood products at any time of the day to areas in need. NBE monitors the blood supply across blood centers and across regions for potential shortages.

In general, HHS does not monitor in real time the U.S. blood supply. Licensed blood establishments are required to report significant interruptions in manufacturing to FDA.²⁷

²⁰ FDA, “Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Blood and Blood Components,” May 15, 2015, <https://www.fda.gov/media/124193/download>.

²¹ The donor history questionnaire is available at <http://www.aabb.org/tm/questionnaires/Documents/dhq/v2/DHQ%20v2.0.pdf>.

²² 21 C.F.R. §10.115. For FDA blood guidance, see <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/blood-guidances>.

²³ 21 C.F.R. §10.115(d).

²⁴ OIDP maintain a list of its roles and responsibilities for the various entities; see <https://www.hhs.gov/oidp/topics/blood-tissue-safety/roles/index.html>.

²⁵ Membership on the task force includes federal agencies (HHS, FDA, and CDC) and nonfederal entities such as the AABB and the American Red Cross. For more information, see <http://www.aabb.org/programs/disasterresponse/Pages/default.aspx#1>.

²⁶ For more information on the NBE, see NBE, “System at Work,” <http://www.aabb.org/programs/nbe/Pages/default.aspx#2>.

²⁷ 21 C.F.R. §600.82

However, real time monitoring is only available through the NBE system and only registered AABB members can access information on blood supply availability through NBE.

Industry and Federal Response to COVID-19

FDA, HHS, and the blood industry have responded to a potential critical shortage of blood due to the COVID-19 pandemic. In addition, Congress included a provision in the Coronavirus Aid, Relief, and Economic Security Act (CARES Act; P.L. 116-136), enacted on March 27, 2020 that directed the Secretary of HHS to carry out a national awareness campaign regarding the nation's blood supply.

FDA first issued information for blood establishments on February 4, 2020, including considerations for altering blood donation practices in response to COVID-19.²⁸ This information was updated on March 11, 2020, and again on May 11, 2020.²⁹

The May 11 release suggests that some blood establishments may want to consider donor education, encourage self-deferral, and manage post-donation information about COVID-19. The May 11 release recommends that individuals self-defer from donating blood for 14 days after either (1) resolution of symptoms after a diagnosis of COVID-19 or (2) the last positive diagnostic test if no symptoms developed. Donors are also directed to report a subsequent diagnosis after donation. The May 11 release does not recommend using laboratory tests to screen asymptomatic donors or deferral for recent travel to specific areas with COVID-19 cases.³⁰

Historically, FDA has recommended donor deferrals that vary from short periods of time after a specific event to indefinite, lifetime deferrals for individuals that are at risk of transmitting infectious diseases.

To date, there is no reported transfusion-transmitted case of COVID-19.³¹ However, there exists a theoretical risk of transmission through blood transfusion, and there are still many unknowns regarding the virus that causes COVID-19.³² Transmission primarily occurs through respiratory body fluids, but the virus that causes COVID-19 has been detected in blood samples from infected individuals, thereby raising questions about the possibility of transmission through blood transfusion from blood collected from an infected donor.³³ The potential of transmission through blood transfusion, although theoretical, necessitates some precautionary measures.

Blood centers and the American Red Cross issued specific guidance to potential blood donors regarding COVID-19, which was largely based on the FDA notices. Organizations representing

²⁸ FDA, "Important Information for Blood Establishments Regarding the Novel Coronavirus Outbreak," press release, February 4, 2020, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-information-blood-establishments-regarding-novel-coronavirus-outbreak>.

²⁹ FDA, "Updated Information for Blood Establishments Regarding the Novel Coronavirus Outbreak," press release, May 11, 2020, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-blood-establishments-regarding-novel-coronavirus-covid-19-outbreak>.

³⁰ Ibid.

³¹ Ibid.

³² Le Chang, Ying Yan, and Lunan Wang, "Coronavirus Disease 2019: Coronaviruses and Blood Safety," *Transfusion Medicine Reviews*, [Epub ahead of print] February 21, 2020.

³³ Wenling Wang, Yanli Xu, and Ruqin Gao, et al., "Detection of SARS-CoV-2 in Different Types of Clinical Specimens," *JAMA*, vol. 323, no. 18 (March 11, 2020), pp. 1843-1844.

the industry also issued press releases calling for individuals to schedule appointments for donation and reassuring them about the safety of donating blood.³⁴

The task force urged blood centers to contact state and local emergency management and public health agencies to request inclusion in emergency planning and response activities.³⁵ The task force recommended that blood centers share draft letters from HHS and the Federal Emergency Management Agency (FEMA) that highlight the importance of working with the blood centers during an emergency response.³⁶ The HHS letter was drafted prior to the COVID-19 pandemic. The FEMA letter was published on March 19, 2020, to specifically address the COVID-19 response.³⁷

FDA Guidance to Address COVID-19-Related Supply Issues

FDA issued four guidance documents on April 2, 2020, to address COVID-19-related blood supply issues. This new guidance did not mitigate the immediate need for blood in March 2020, but may increase the donor pool for supply shortages in the future as the country continues to respond to the COVID-19 pandemic. One document creates alternative procedures for blood collection, while the other three relax restrictions on donor eligibility intended to protect the blood supply.³⁸ FDA has traditionally issued guidance on reducing potential risks associated with blood donations. The new guidance documents alter donor deferral recommendations for potential donors regarding three areas of blood supply safety:

- Human Immunodeficiency Virus (HIV) transmission by blood and blood products (HIV guidance);³⁹
- transfusion-transmitted Malaria (Malaria guidance);⁴⁰ and
- transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease by blood and blood components (CJD guidance).⁴¹

These recommendations are intended to broaden the pool of potential donors while maintaining the safety of the blood supply.

The FDA guidance documents are expected to remain in effect for the duration of the public health emergency.⁴² Unlike the typical process for issuing new guidance, these guidance

³⁴ For an example of a call to donate, see <http://www.aabb.org/press/Pages/pr200312.aspx>.

³⁵ For more information, see <http://www.aabb.org/programs/disasterresponse/Pages/default.aspx#4>.

³⁶ HHS, “Raising Priority Status of Blood with State/Local Emergency Management Agencies,” April 10, 2019, <http://www.aabb.org/programs/disasterresponse/Documents/letterhhs.pdf>.

³⁷ FEMA, “Raising Priority Status of Blood with State/Local Emergency Management Agencies,” March 19, 2020, <http://www.aabb.org/programs/disasterresponse/Documents/FEMA-Letter.pdf>.

³⁸ FDA, “Coronavirus (COVID-19) Update: FDA Provides Updated Guidance to Address the Urgent Need for Blood During the Pandemic,” press release, April 2, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-updated-guidance-address-urgent-need-blood-during-pandemic>.

³⁹ FDA, “Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products,” Guidance for Industry, April 2, 2020, <https://www.fda.gov/media/92490/download>.

⁴⁰ FDA, “Revised Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria,” Guidance for Industry, April 2, 2020, <https://www.fda.gov/media/72243/download>.

⁴¹ FDA, “Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components,” Guidance for Industry, April 2, 2020, <https://www.fda.gov/media/124156/download>.

⁴² A public health emergency was first declared on January 27, 2020. It was renewed on April 26, 2020. HHS, “Renewal of Determination That a Public Health Emergency Exists,” press release, April 21, 2020,

documents were issued without a public comment period, in accordance with a notice published in the *Federal Register* that outlined a process for making available guidance documents related to COVID-19.⁴³ Under this process, FDA is accepting comments for the published guidance and is to consider the comments and potentially update the guidance to incorporate them. The only exception is the guidance related to CJD, which finalizes draft guidance from January 2020. FDA indicated that the HIV and Malaria guidance will continue to apply outside the context of the current public health emergency, subject to comments received on the interim final guidance. However, the alternative procedure guidance is to terminate when the public health emergency is terminated.

Alternative Procedure Guidance

FDA issued guidance titled “Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency; Guidance for Industry” (Alternative Procedure Guidance) on April 2, 2020, that creates exceptions to procedures included in the regulatory framework for determining donor eligibility and for storage of certain blood products during the COVID-19 emergency.⁴⁴ The changes are intended to expand the availability of blood products. Under typical circumstances, certain blood donations may be considered unsuitable because of a failure to follow procedures put in place to protect the health of the donor (e.g., a physical assessment to determine the potential donor’s blood pressure, pulse, weight, and donation frequency).⁴⁵ The guidance recommends using such blood donations, which would have previously been considered unsuitable because they might have adversely affected the health of the donor. This guidance does not eliminate the physical assessment requirement, but it allows collected blood to be used in the event that there was an error.

In addition, the emergency guidance increases the time in which blood centers must obtain omitted donor information—from within 24 hours of donation⁴⁶ to within 72 hours.⁴⁷ Lastly, the guidance decreases the recommended amount of time, from 60 to 45 calendar days that certain plasma donations must be quarantined prior to use.⁴⁸ Plasma from paid donors is quarantined before use to ensure that the donor meets all eligibility requirements.⁴⁹

HIV Transmission by Blood and Blood Products

Long-standing FDA guidance, first established in 1985, deferred men who have sex with men (MSM) from donating blood for life. This lifetime deferral applied to men who had sex with men even one time. The intent of the deferral was to reduce the risk of HIV transmission by blood and

<https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-21apr2020.aspx>.

⁴³ FDA, “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” 85 *Federal Register* 16949, March 5, 2020.

⁴⁴ FDA, “Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency,” Guidance for Industry, April 2, 2020, <https://www.fda.gov/media/136603/download>.

⁴⁵ 21 C.F.R. §630.10(f).

⁴⁶ 21 C.F.R. §630.10(c)(2).

⁴⁷ FDA, “Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency,” Guidance for Industry, April 2, 2020, p. 4, <https://www.fda.gov/media/136603/download>.

⁴⁸ FDA, “Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency,” Guidance for Industry, April 2, 2020, p. 3, <https://www.fda.gov/media/136603/download>. [21 C.F.R. § 640.69(f)].

⁴⁹ 21 C.F.R. §640.69(e).

blood products. In 1992, FDA issued a memo that reiterated the lifetime deferral for MSM. FDA revised its recommendations in 2015 to apply the deferral for 12 months rather than a lifetime.⁵⁰

The 12-month deferral period also applied to women who had sex with MSM, as well as to individuals who were tattooed or pierced, had sex in exchange for money or drugs, had engaged in nonprescription injection drug use, had received a blood transfusion, had come into contact with another individual’s blood, and/or had a history of syphilis or gonorrhea. The new guidance, issued in response to the COVID-19 pandemic, revises the recommended deferral period from 12 months to 3 months for each of these groups.⁵¹

Transfusion-Transmitted Malaria

Since 1994, FDA has recommended deferral of blood donors who have had malaria or have had possible exposure to malaria during travel to or residence in malaria-endemic countries.⁵² The occurrence of transfusion-transmitted malaria is relatively low in the United States,⁵³ and the recommendation contributes to thousands of deferrals every year. **Table 1** lists recommended deferral periods under the new and previous guidance for different travel scenarios.

Table 1. Malaria-Related Donor Deferral Recommendations Under Previous and Current FDA Guidance

Donor History	2013 Deferral Guidance	2020 Deferral Guidance
Travel to a malaria-endemic area (resident of a nonendemic country)	1 year	3 months
Resident of a malaria-endemic country	3 years	3 years
Travel to a malaria-endemic area (resident of a malaria-endemic country)—less than 3 consecutive years in nonendemic country	3 years	3 years
Travel to a malaria-endemic area (resident of a malaria-endemic country)—3 or more consecutive years in nonendemic country	1 year	3 months
Malaria diagnosis	3 years	3 years

Source: FDA, “Revised Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria,” Guidance for Industry, April 2, 2020, p. 12.

Transmission of Creutzfeldt-Jakob Disease by Blood and Blood Components

Recommended deferrals for individuals who may have been exposed to Creutzfeldt-Jakob Disease and variant-Creutzfeldt-Jakob Disease (commonly known as “mad cow disease”) were previously broad, including indefinite deferrals for individuals who spent five or more years in Europe since 1980 and certain military personnel and families that spent time on U.S. military bases in Europe.⁵⁴ The new guidance eliminates those deferrals but continues to recommend indefinite, lifetime deferrals for specified residency in some European countries (i.e., France, the United Kingdom, and Ireland).

⁵⁰ FDA, “Revised Recommendation for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products; Draft Guidance for Industry; Availability,” 80 *Federal Register* 27973-27976, May 15, 2015.

⁵¹ FDA, “Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products,” Guidance for Industry, April 2, 2020, pp. 8-9, <https://www.fda.gov/media/92490/download>.

⁵² FDA, “Revised Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria,” Guidance for Industry, April 2, 2020, p. 3, <https://www.fda.gov/media/72243/download>.

⁵³ *Ibid.*, p. 3.

⁵⁴ FDA, “Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components,” Guidance for Industry, April 2, 2020, pp. 16-17, <https://www.fda.gov/media/124156/download>.

CARES Act Section 3226

The Coronavirus Aid, Relief, and Economic Security Act (CARES Act; P.L. 116-136), enacted on March 27, 2020, included one provision related to the blood supply. Section 3226 of the CARES Act requires the Secretary to carry out a national campaign to improve awareness of, and support outreach to the public and health care providers about, the importance and safety of blood donation and the need for donations to the blood supply.

The provision requires the Secretary to consult with heads of relevant federal agencies, accrediting bodies, and representative organizations to carry out the campaign. In addition, the Secretary is authorized to contract with public and private nonprofit entities to carry out the campaign.

The provision requires the Secretary to submit a report to the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce not later than two years from enactment (i.e., March 27, 2022) that (1) describes the activities carried out, (2) describes trends in blood supply donations, and (3) evaluates the impact of the public awareness campaign.

Potential Use of U.S. Blood Supply to Treat COVID-19

To date, no therapeutics—drugs or biologics—have been approved to treat COVID-19. Although various drugs and biologics, including blood-derived therapies, are being studied to determine their capacity to treat or prevent COVID-19, the data regarding whether they can do so safely and effectively are still being generated. As described further below, FDA has used its existing authorities to expand access to unapproved products, including COVID-19 Convalescent Plasma (CCP).

Convalescent Plasma and Hyperimmune Globulin

FDA has identified two investigational blood-derived therapies for the treatment of COVID-19: convalescent plasma and hyperimmune globulin. Both are made from the blood plasma (the fluid portion of human blood) of a person who has recovered from the disease.⁵⁵ Individuals who recover from COVID-19 typically develop antibodies to the SARS-CoV-2 virus that causes the disease. There is evidence to suggest that these antibodies can be administered safely to treat critically ill patients with COVID-19.⁵⁶

Convalescent plasma refers to blood plasma that is collected from an individual who has recovered (i.e., “convalesced”) from a disease, in this case COVID-19, and then administered to a patient actively sick with COVID-19 for treatment. Convalescent plasma therapy has been

⁵⁵ FDA, “Coronavirus (COVID-19) Update: FDA Coordinates National Effort to Develop Blood-Related Therapies for COVID-19,” April 3, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-coordinates-national-effort-develop-blood-related-therapies-covid-19>.

⁵⁶ Ibid. C Shen, Z Wang, F Zhao, et al., “Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma,” *JAMA* (March 27, 2020). JD Roback and J Guarner, “Convalescent Plasma to Treat COVID-19 Possibilities and Challenges,” *JAMA* (March 27, 2020). FDA, Clinical Memorandum Regarding EUA 26382: Emergency Use Authorization (EUA) Request (original request 8/12/20; amended request 8/23/20) for COVID-19 Convalescent Plasma (CCP), <https://www.fda.gov/media/141480/download>.

studied in, although not approved for, the treatment of other viral respiratory diseases, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza.⁵⁷ Several steps are involved in using convalescent plasma as a treatment—including obtaining blood from a recovered donor, testing it for safety, isolating the plasma, and then transfusing it into a patient with COVID-19.⁵⁸ Some estimates indicate that one donor could treat two or three recipients.⁵⁹ Plasma transfusions are generally safe; however, they are not without risk and can cause allergic reactions and other side effects in some patients.⁶⁰ Data are limited regarding the effectiveness of convalescent plasma in treating COVID-19, but available evidence suggests the treatment may be safe and effective for some patients.⁶¹

A related therapy, *hyperimmune globulin*, is a manufactured biological product containing concentrated antibodies collected from convalescent plasma. Although convalescent plasma units vary in antibody types (e.g., IgG, IgM) and amount (titer) based on the plasma donor, hyperimmune globulin preparations are typically standardized.⁶² FDA has approved hyperimmune globulin therapies for several non-COVID-19 indications, including exposure to Hepatitis B and treatment of inhalational anthrax, among others.⁶³ According to one drug manufacturer currently in the process of developing hyperimmune globulin for COVID-19, manufacturing this product “will require plasma donation from many individuals who have fully recovered from COVID-19, and whose blood contains antibodies that can fight the novel coronavirus. Once collected, the ‘convalescent’ plasma would then be transported to manufacturing facilities where it undergoes proprietary processing, including effective virus inactivation and removal processes, and then is purified into the [hyperimmune globulin] product.”⁶⁴

Serological tests that detect COVID-19 antibodies may help identify the best treatment candidates, as well as potential plasma donors. However, questions remain regarding immunity to the SARS-CoV-2 virus, including whether antibodies confer immunity and if so, to what extent, reinfection, and the accuracy of available serological tests.⁶⁵

⁵⁷ FDA, “Investigational COVID-19 Convalescent Plasma,” Guidance for Industry, April 2020, <https://www.fda.gov/media/136798/download>. Y Cheng, R Wong, YO Soo, et al., “Use of convalescent plasma therapy in SARS patients in Hong Kong,” *Eur J Clin Microbiol Infect Dis*, vol. 24, no. 1 (January 2005). IF Hung, KK To, CK Lee, et al., “Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection,” *Clinical Infectious Diseases*, vol. 52, no. 4 (February 2011).

⁵⁸ A. Joseph, “Everything we know about coronavirus immunity and antibodies—and plenty we still don’t,” *STAT News*, April 20, 2020, <https://www.statnews.com/2020/04/20/everything-we-know-about-coronavirus-immunity-and-antibodies-and-plenty-we-still-dont/>.

⁵⁹ American Association of Hematology, “COVID-19 and Convalescent Plasma: Frequently Asked Questions,” updated April 10, 2020, <https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma>.

⁶⁰ FDA, “Investigational COVID-19 Convalescent Plasma - Emergency INDs Frequently Asked Questions,” April 3, 2020, <https://www.fda.gov/media/136470/download>.

⁶¹ *Ibid.*

⁶² JD Roback and J Guarner, “Convalescent Plasma to Treat COVID-19 Possibilities and Challenges,” *JAMA* (March 27, 2020).

⁶³ FDA, “Immune Globulins,” August 16, 2019, <https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins>.

⁶⁴ Takeda, “Global Plasma Leaders Collaborate to Accelerate Development of Potential COVID-19 Hyperimmune Therapy,” Newsroom, April 6, 2020, <https://www.takeda.com/newsroom/newsreleases/2020/global-plasma-leaders-collaborate-to-accelerate-development-of-potential-covid-19-hyperimmune-therapy/>.

⁶⁵ CRS In Focus IF11516, *COVID-19 Testing: Key Issues*. JD Roback and J Guarner, “Convalescent Plasma to Treat COVID-19 Possibilities and Challenges,” *JAMA* (March 27, 2020). A. Joseph, “Everything we know about coronavirus immunity and antibodies—and plenty we still don’t,” *STAT News*, April 20, 2020, <https://www.statnews.com/2020/04/>

FDA Regulation of Biologics

FDA regulates convalescent plasma and hyperimmune globulins as biological products (biologics)—therapeutics derived from or made in a living system.⁶⁶ Generally, a biologic may be provided to patients only if FDA has licensed (i.e., approved) it for marketing under a biologics license application (BLA), authorized its use in a clinical trial under an investigational new drug application (IND), or authorized its use through expanded access under an IND, including an emergency IND (eIND). Under certain emergency circumstances, FDA may issue an emergency use authorization (EUA) to allow the use of an unapproved medical product or the unapproved use of an approved product.

Licensure Under a Biologics License Application (BLA)

Most biologics available to patients are licensed under a BLA for marketing and use. For purposes of licensure, FDA requires data from clinical investigations—formally designed, conducted, and analyzed studies of human subjects—to provide evidence of a biologic’s safety, purity, and potency. Such investigations must be conducted under an IND, which is a request for FDA authorization to administer an investigational drug or biologic to humans.⁶⁷ An IND must include information about the investigational drug or biologic and its chemistry, manufacturing, and controls; the proposed clinical study design; completed animal test data; and the lead investigator’s qualifications, among other things.⁶⁸ The investigator also must provide assurance that an Institutional Review Board (IRB) will provide initial and continuous review and approval of each of the studies in the clinical investigation to ensure that participants are aware of the drug’s investigative status and that any risk of harm will be necessary, explained, and minimized.⁶⁹ FDA has 30 days to review an IND and, unless the agency objects, clinical testing may commence after that review. After completing clinical testing, the manufacturer may submit a BLA for licensure to FDA’s Center for Biologics Evaluation and Research. A BLA must contain certain information—for example, data from nonclinical laboratory and clinical studies—and licensure is based on a determination by FDA that the biologic and the facility in which it is manufactured, processed, packed, or held, meet standards to ensure that the product is safe, pure, and potent (effective).⁷⁰

Investigational Use and Expanded Access

Prior to or in absence of an effective BLA, a patient may access an investigational biologic under an IND by participating in a clinical trial. An individual who is not eligible for participation in a clinical trial (e.g., because they do not meet the study criteria, or because the trial is not enrolling

20/everything-we-know-about-coronavirus-immunity-and-antibodies-and-plenty-we-still-dont/.

⁶⁶ PHSa §351(i)(1) [21 U.S.C. §262(i)(1)] defines a biologic as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.” See CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*.

⁶⁷ FFDCa §505(i) [21 U.S.C. §355(i)]; PHSa §351(a)(3) [42 U.S.C. §262(a)(3)]; 21 C.F.R. Part 312.

⁶⁸ 21 C.F.R. §312.23.

⁶⁹ 21 C.F.R. §312.23(a)(1)(iv) and 21 C.F.R. Part 56.

⁷⁰ PHSa §351(a)(2)(C) [42 U.S.C. §262(a)(2)(C)]. FDA regulations at 21 C.F.R. §601.2(a) specify the required contents of a BLA.

new patients) may request access to an investigational therapy through an expanded access protocol, provided that an IND is in effect for the investigational therapy and

- the physician determines that the patient has no comparable or satisfactory alternative therapy, and that the probable risk from the investigational therapy is not greater than the probable risk from the disease or condition, and
- FDA determines there is sufficient evidence of safety and effectiveness and that provision of the investigational therapy will not interfere with “the initiation, conduct, or completion of clinical investigations to support marketing approval.”⁷¹

In cases where access to a clinical trial or the expanded access protocol is not available or feasible, a physician may request an eIND for an individual patient.⁷²

The provision of an investigational therapy in a clinical trial is intended to generate evidence of safety and effectiveness to support marketing approval of a therapeutic. In contrast, expanded access protocols are primarily intended to provide investigational therapies to patients who have exhausted all other options rather than to obtain safety and effectiveness data.

Emergency Use Authorization (EUA)

FDA also may enable access to unapproved medical products through EUA, if the HHS Secretary declares that circumstances exist to justify the emergency use of an unapproved product or an unapproved use of an approved medical product.⁷³ Following the HHS Secretary’s declaration, FDA, in consultation with the HHS Assistant Secretary for Preparedness and Response (ASPR), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC), may issue an EUA authorizing the emergency use of a specific medical product, provided that the following criteria are met:

- the agent that is the subject of the EUA can cause a serious or life-threatening disease or condition;
- based on the totality of the available scientific evidence, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such disease or condition, and that the known and potential benefits of the product outweigh its known and potential risks; and
- there is no adequate, approved, or available alternative to the product.⁷⁴

The standard of evidence for an EUA is different than that for approval. EUA issuance, as noted above, is based on FDA’s determination that the totality of the available scientific evidence suggests that a product *may be effective* in diagnosing, treating, or preventing a disease or condition and that the known and potential benefits of the product outweigh its known and potential risks. This is different from the standard required for FDA approval of a drug or

⁷¹ FFDCA §561(b) [21 U.S.C. §360bbb(b)].

⁷² 21 C.F.R. §312.310.

⁷³ FFDCA §564 [21 U.S.C. §360bbb-3]. For additional information about EUA, see CRS In Focus IF10745, *Emergency Use Authorization and FDA’s Related Authorities*, and CRS Report R46427, *Development and Regulation of Medical Countermeasures for COVID-19 (Vaccines, Diagnostics, and Treatments): Frequently Asked Questions*.

⁷⁴ FFDCA §564(c) [21 U.S.C. §360bbb-3(c)]. These criteria are explained in more detail in the FDA guidance *Emergency Use Authorization of Medical Products and Related Authorities*, January 2017, p. 7, <https://www.fda.gov/media/97321/download>.

biologic, which is based on *substantial evidence* of effectiveness derived from adequate and well-controlled studies.

FDA must impose certain conditions as part of an EUA to the extent practicable (e.g., distributing certain information to health care providers and patients) and may impose additional discretionary conditions where appropriate.⁷⁵

On February 4, 2020, the HHS Secretary determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves COVID-2019.⁷⁶ On the basis of this determination, the HHS Secretary declared that circumstances exist justifying the authorization of emergency use of unapproved drugs and biologics.⁷⁷ Pursuant to this declaration, on August 23, 2020, FDA issued an EUA for CCP for patients hospitalized with COVID-19.⁷⁸

FDA Treatment and Research Guidance for COVID-19

FDA has not approved a BLA for convalescent plasma for treatment of COVID-19 and, as such, considers it an investigational biologic. In April 2020, FDA issued guidance clarifying that administration of CCP by a health care provider must occur either in a clinical trial under an IND, under an expanded access IND, or under a single-patient eIND.⁷⁹

To facilitate patient access to investigational convalescent plasma for treatment of COVID-19, FDA, working with federal partners and academia, initiated an expanded access protocol for patients across the United States, the National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic. Access is limited to individuals with severe or life-threatening COVID-19, or to those who have been judged by the treating provider to be at high risk of progression to severe or life-threatening disease.⁸⁰ The EAP was designed to primarily provide patient access to CCP, with the secondary purpose of examining safety, and then efficacy within the limits of the study design (i.e., the EAP is not a randomized controlled trial [RCT]).⁸¹ In June 2020, the Mayo Clinic reported that CCP used in patients hospitalized with COVID-19 is safe, based on a diverse sample of 20,000 patients.⁸² The study did not establish efficacy. A pre-print paper published on August 12, 2020, using data from the EAP further reported that transfusion of CPP “with higher antibody levels to hospitalized COVID-19 patients [~35,000] significantly

⁷⁵ FFDC §564(e) [21 U.S.C. §360bbb-3(e)].

⁷⁶ HHS, “Emergency Use Declaration,” 85 *Federal Register* 13907, publication date March 10, 2020, effective date February 4, 2020.

⁷⁷ HHS, “Emergency Use Authorization Declaration,” 85 *Federal Register* 18250, publication date April 1, 2020, effective date March 27, 2020.

⁷⁸ FDA Letter of Authorization to Dr. Robert P. Kadlec, ASPR, August 23, 2020, <https://www.fda.gov/media/141477/download>.

⁷⁹ FDA, “Investigational COVID-19 Convalescent Plasma,” April 2020, updated May 1, 2020, <https://www.fda.gov/media/136798/download>. Also see Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19, <https://www.uscovidplasma.org/>.

⁸⁰ *Ibid.*

⁸¹ US COVID Plasma, “Comparing EAP vs. EUA: What you need to know,” August 24, 2020, <https://www.uscovidplasma.org/pdf/EAP%20vs%20EUA.pdf>.

⁸² R Nellis, “Mayo finds convalescent plasma safe for diverse patients with COVID-19,” June 18, 2020, <https://newsnetwork.mayoclinic.org/discussion/mayo-finds-convalescent-plasma-safe-for-diverse-patients-with-covid-19/>. M Joyner, K Bruno, S Klassen, et al., “Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients,” *Mayo Clinic Proceedings*, pre-proof, July 19, 2020.

reduced mortality compared to transfusions with low antibody levels.”⁸³ As of August 23, 2020, the EAP had enrolled more than 100,000 subjects.⁸⁴ While the Mayo Clinic has announced that it would discontinue enrollment to the EAP, eligible patients already enrolled would receive CCP.

In cases where access to a clinical trial or expanded access is not available, a physician may request an eIND for an individual patient—limited to those with severe or life-threatening COVID-19. FDA’s guidance further provides recommendations for collection and donation of CCP. To donate, an individual must be recovered, as specified; have a prior diagnosis of COVID-19 documented by a laboratory test; and meet other donor criteria.⁸⁵ For individuals who did not receive a diagnostic test at the time of illness, a serological test can help identify individuals previously infected with SARS-CoV-2 who have developed antibodies against the virus.

FDA has not approved a BLA for hyperimmune globulin for treatment of COVID-19 and considers it an investigational biologic. Although FDA’s convalescent plasma guidance does not address hyperimmune globulin specifically, patients may access investigational hyperimmune globulin under an IND by participating in a clinical trial or through expanded access. In addition, FDA is reportedly helping coordinate a study of hyperimmune globulin that will be conducted by the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH.⁸⁶ The Biomedical Advanced Research and Development Authority (BARDA) within HHS is also collaborating with various entities to facilitate the development of these investigational treatments. This collaboration includes working with the American Red Cross to recruit donors and collect, store, and distribute convalescent plasma, as well as expanding existing private-public partnerships. For example, through a partnership with BARDA, Emergent BioSolutions is to collect donated plasma and use its hyperimmune platform to develop and manufacture COVID-19 hyperimmune globulin.⁸⁷

EUA for Convalescent Plasma for COVID-19

On August 23, 2020, FDA issued an EUA to allow for the distribution and administration of investigational CCP in the United States to treat COVID-19 in hospitalized patients. The Mayo Clinic subsequently announced that it would discontinue enrollment to the EAP, but that eligible patients already enrolled would receive convalescent plasma.⁸⁸ Patients who do not qualify for access under the EUA can submit a request, through their physician, to FDA for expanded access via an IND or eIND, but not through the Mayo Clinic EAP.

⁸³ M Joyner, J Senefeld, S Klassen, et al., “Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience,” pre-print, August 12, 2020, <https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1>.

⁸⁴ C Gallagher, “Expanded Access Program for Convalescent Plasma discontinues enrollment as FDA authorizes its emergency use,” August 23, 2020, <https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/>.

⁸⁵ FDA, “Recommendations for Investigational COVID-19 Convalescent Plasma,” April 13, 2020, <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>.

⁸⁶ FDA Combatting COVID-19 with Therapeutics, updated April 9, 2020, <https://www.fda.gov/media/136832/download>.

⁸⁷ HHS, “HHS facilitates development of immunotherapies for COVID-19 patients,” April 13, 2020, <https://www.phe.gov/Preparedness/news/Pages/immunotherapies-COVID-13April20.aspx>.

⁸⁸ C. Gallagher, “Expanded Access Program for Convalescent Plasma discontinues enrollment as FDA authorizes its emergency use,” August 23, 2020, <https://newsnetwork.mayoclinic.org/discussion/expanded-access-program-for-convalescent-plasma-discontinues-enrollment-as-fda-authorizes-its-emergency-use/>.

The EUA letter to ASPR (the EUA requester) specifies that CCP must be obtained from registered or licensed blood establishments from U.S. donors in compliance with existing requirements, as well as that plasma donations be tested for relevant transfusion-transmitted infections and anti-SARS-CoV-2 antibodies. Current evidence suggests that the largest clinical benefit is associated with high titer units (i.e., those with a higher antibody content) given early in the course of disease.⁸⁹ As such, with respect to anti-SARS-CoV-2 antibodies, the EUA letter specifies at what value a CCP unit would qualify as “high titer,” but also allows health care providers to use low titer units provided they are labeled appropriately.

Some concern has been raised regarding FDA’s issuance of an EUA for CCP in the absence of evidence from RCTs, which are the gold standard for evaluating the effectiveness of therapies.⁹⁰ Some also have criticized FDA Commissioner Hahn’s characterization of the available data, which he addressed on social media.⁹¹

As mentioned, the level of evidence required for an EUA is lower than that required for full marketing approval.⁹² In the EUA letter, FDA states that it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks for the treatment of patients hospitalized with COVID-19. FDA further states in the letter and in a clinical memorandum that this determination was “[b]ased on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the ongoing National Convalescent Plasma Expanded Access Protocol (EAP).”⁹³ FDA also notes in the letter that the evidence used to support the EUA was not obtained from prospective, well-controlled RCTs, which are still needed, and that CCP “should not be considered a new standard of care for the treatment of patients with COVID-19.”⁹⁴

It is not clear the extent to which an EUA will increase access to convalescent plasma, as its availability is limited by donations. However, if patients are able to more readily access CCP through the EUA, participation in clinical trials may be hindered, making it more difficult to generate data regarding the effectiveness of convalescent plasma for COVID-19.

⁸⁹ FDA Letter of Authorization to Dr. Robert P. Kadlec, ASPR, <https://www.fda.gov/media/141477/download>. US COVID Plasma, “Comparing EAP vs. EUA: What you need to know,” August 24, 2020, <https://www.uscovidplasma.org/pdf/EAP%20vs%20EUA.pdf>.

⁹⁰ N Florko and L Facher, “As Covid-19 pressures mount, political newcomer Stephen Hahn struggles to protect an FDA under siege,” *STAT News*, August 24, 2020, <https://www.statnews.com/2020/08/24/newcomer-stephen-hahn-agency-seige/>. L Facher, “Is convalescent plasma safe and effective? We answer the major questions about the Covid-19 treatment,” *STAT News*, August 23, 2020, <https://www.statnews.com/2020/08/23/is-convalescent-plasma-safe-and-effective/>. S LaFraniere, S Fink, K Thomas and M Haberman, “F.D.A. Allows Expanded Use of Plasma to Treat Coronavirus Patients,” *New York Times*, published August 23, 2020, updated August 24, 2020, <https://www.nytimes.com/2020/08/23/us/politics/fda-plasma-coronavirus.html>.

⁹¹ Dr. Stephen M. Hahn @SteveFDA, “I have been criticized for remarks I made Sunday night about the benefits of convalescent plasma. The criticism is entirely justified. What I should have said better is that the data show a relative risk reduction not an absolute risk reduction.” August 24, 2020, 9:36 p.m., <https://twitter.com/SteveFDA/status/1298071603675373569>.

⁹² FDA, “Understanding the Regulatory Terminology of Potential Preventions and Treatments for COVID-19,” <https://www.fda.gov/consumers/consumer-updates/understanding-regulatory-terminology-potential-preventions-and-treatments-covid-19>.

⁹³ FDA Letter of Authorization to Dr. Robert P. Kadlec, ASPR, <https://www.fda.gov/media/141477/download>. See also FDA, Clinical Memorandum Regarding EUA 26382: Emergency Use Authorization (EUA) Request (original request 8/12/20; amended request 8/23/20) for COVID-19 Convalescent Plasma (CCP), <https://www.fda.gov/media/141480/download>.

⁹⁴ *Ibid.*

Given the therapeutic potential of blood-derived therapies, FDA encourages eligible individuals who have recovered from COVID-19 to donate their plasma.⁹⁵ To facilitate collection of CCP, more than 30 organizations have coalesced to form a national donor recruitment campaign, which aims to connect CCP donors with licensed blood and plasma donor centers.⁹⁶

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⁹⁵ FDA, "Donate COVID-19 Plasma," updated August 23, 2020, <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/donate-covid-19-plasma>.

⁹⁶ The Fight Is In Us, <https://thefightisinus.org/en-us#about>.