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An Old Drug for a New Emergency: FDA Issues New Guidance on the Use of Convalescent Plasma for COVID-19

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Following the issuance of the Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for the Treatment of COVID-19 in Hospitalized Patients on August 23, 2020, the FDA issued on September 2 a Guidance for Industry: "Investigational COVID-19 Convalescent Plasma." The Guidance provides insight on the use of convalescent plasma either via the EUA or as an investigational new drug (IND). The Guidance also provides a compliance policy for 90 days from the issuance of the Guidance for the use of convalescent plasma.

As background, convalescent plasma has been used to treat viral infections for which no vaccine or other treatment specific to the disease has been available for over a century. It was used for treatment during the Spanish influenza epidemic of 1918 and has been used more recently to treat Middle East respiratory syndrome coronavirus (MERS-CoV), H1N1, and H5N1 influenza. Convalescent plasma is collected from individuals who have recovered from a particular disease and have developed antibodies to it. Unlike a vaccine, which triggers an immune response and the formation of antibodies (active immunization), convalescent plasma therapy transfers already-formed antibodies to the patient (passive immunization).

The EUA

The EUA is closely mirrored and widely referenced in the Guidance. Under the EUA, convalescent plasma may be used for the treatment of COVID-19 under the following, nonexhaustive, list of conditions:

- The product is distributed for use in hospitals consistent with the authorization, including ensuring that the authorized labeling (e.g., fact sheets) accompanies the COVID-19 convalescent plasma and that the receiving hospitals are aware of the letter of authorization.
- The plasma is obtained from duly registered or licensed blood establishments.
- The plasma is obtained from donors in the United States or its territories.
- Donors must meet all donor eligibility requirements and qualifications, and blood establishments must operate in accordance with applicable regulations, policies, and procedures.
- The plasma must be tested by blood establishments using the Ortho VITROS SARS-CoV-2 IgG test and be high titer (found to have a signal-to-cutoff (S/C) value of 12 or greater) or low titer (S/C value below 12) units and used after an individualized risk-benefit assessment by the health care provider.

- The plasma must be accompanied by authorized labeling, which includes an indication of whether the plasma is low or high titer.
- The plasma must be stored at -18° C or colder. It may be kept refrigerated for up to five days after thawing.
- Blood establishments and hospitals must maintain records of the distribution of COVID-19 convalescent plasma and make records related to the EUA available to the FDA upon request.

The FDA based the decision to authorize the emergency use in part on the data generated during an Expanded Access Program (EAP) sponsored by the Mayo Clinic. The EAP discontinued enrollment on August 28 and is encouraging physicians to administer convalescent plasma under the EUA.

Though the EUA is intended to ensure ready access of high-titer convalescent plasma to hospitalized patients, the authorization acknowledges that additional data is needed and encourages the continuation and initiation of clinical trials.

The Guidance

The guidance provides recommendations for:

- The collection of COVID-19 convalescent plasma (defined in the Guidance as the convalescent plasma authorized under the EUA) and investigational convalescent plasma (defined in the Guidance as convalescent plasma that does not meet all the conditions of the EUA or is being used under an IND).
- The administration of COVID-19 convalescent plasma consistent with the EUA.
- The administration of investigational convalescent plasma.

Additionally, the Guidance announces the "FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma."

The recommendations for the collection of the COVID-19 convalescent plasma and the administration of convalescent plasma are entirely consistent with the requirements in the EUA.

Investigational Convalescent Plasma

The FDA acknowledges that this treatment "may be administered under the traditional IND regulatory pathway, a single-patient IND for emergency use, or an intermediate-size population expanded access IND." These routes of use are not unique to investigational convalescent plasma or even to treatments during a declared emergency.

The FDA is committed to engaging with sponsors and "reviewing such [IND] requests expeditiously. During the COVID-19 pandemic, INDs may be submitted via email to CBERDCC_eMailSub@fda.hhs.gov."

Health care providers treating patients who are not eligible for the EUA and who are not able to participate in a clinical trial but who otherwise have serious or immediately life-threatening COVID-19 may seek an expanded access IND.

Health care providers for such patients may also request single-patient INDs. However, since most patients within this category are likely to be hospitalized, the FDA anticipates that most providers will obtain COVID-19 plasma under the EUA instead of single-patient INDs because the EUA does not require a submission to the FDA, while a single-patient IND does. To request a single-patient IND, the Form FDA 3926 should be completed and emailed to CBER_eIND_Covid-19@FDA.HHS.gov.

Interim Compliance and Enforcement Policy

Recognizing that "investigational convalescent plasma collected prior to the EUA may not meet the Conditions of Authorization [in the EUA], specifically the requirement for testing plasma donations for anti-SARS-CoV-2 antibodies using the Ortho VITROS SARS-CoV-2 IgG as a manufacturing step to determine suitability before release, as well as qualifying the unit as high titer or low titer COVID-19 convalescent plasma, based on the results of this testing," and that it may take time to come within the conditions of authorization under the EUA, the FDA is permitting the use of plasma from donors with COVID-19 antibodies that does not meet the conditions of the EUA without the issuance of an IND if the following conditions are met:

- The convalescent plasma is intended for the treatment of COVID-19 in hospitalized patients.
- The patient or his or her legal representative provides informed consent. (The EUA itself is silent on informed consent.)
- The blood collection facility is registered, and the donors meet all eligibility requirements and qualifications.
- Labeling requirements are met.

The FDA further recommends that neutralizing antibody titers be measured.

The interim policy expires on December 1 (90 days from the September 2 date of issuance of the Guidance).

Background on EUAs

EUAs are authorized and regulated under Section 564 of the Federal Food, Drug, and Cosmetic Act (FFDCA). EUAs can be authorized if an emergency is declared by at least one of four federal entities, including the Department of Health and Human Services (HHS), the parent agency of the FDA, and the Secretary of HHS has determined that: (1) the "biological, chemical, radiological, or nuclear agent or agents [BCRNAs] … can cause a serious or life-threatening disease or condition"; (2) the available evidence suggests that "it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing" either "such disease or condition; or a serious or life-threatening disease or condition caused by a product authorized under [the FFDCA] for diagnosing, treating, or preventing such a disease or condition caused by such an agent"; (3) the benefits of the product outweigh the risks, taking into account the threat from the BRCNA; and (4) "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition."

The Public Readiness and Emergency Preparedness (PREP) Act authorizes the Secretary of HHS to issue a declaration that provides immunity from liability (except willful misconduct) "related to the manufacture, testing, development, distribution, administration and use of medical countermeasures against" BCRNAs. Covered medical countermeasures include:

- Qualified pandemic or epidemic products.
- Security countermeasures.
- Products authorized under an EUA.
- Approved products used consistent with their approval.
- Unapproved products held by a government agency, or its agent, and used only when authorized.

PREP Act protections are not afforded to products used under policies of compliance or enforcement discretion.

Conclusion

The FDA continues to expand the availability of medical countermeasures it believes are likely to aid in the response to the COVID-19 pandemic. As the FDA states in the EUA and the Guidance, however, there are substantial data gaps that require the generation of additional data. While the FDA has taken steps to ensure that this treatment option is available to hospitals during the public health emergency, such data would be required for use under a license or once the EUA expires or is withdrawn.

Alston & Bird has formed a multidisciplinary response and relief team to advise clients on the business and legal implications of the coronavirus (COVID-19). You can view all our work on the coronavirus across industries and subscribe to our future webinars and advisories.

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