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**Policy for Certain REMS
Requirements During the Tocilizumab
Shortage Related to the COVID-19
Public Health Emergency**

**Guidance for Industry and Health
Care Professionals**

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," available at <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and from the FDA webpage titled "Search for FDA Guidance Documents" available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

Additional copies of this guidance are also available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.

Questions

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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Guidance for Industry and Health Care Professionals

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to communicate its temporary policy with respect to certain risk evaluation and mitigation strategies (REMS) requirements for tocilizumab due to the shortage related to the COVID-19 public health emergency (PHE).^{1, 2} This guidance will remain in effect for the duration of the tocilizumab shortage. FDA is continually assessing the needs and circumstances related to this temporary policy. As relevant needs and circumstances evolve, FDA intends to update, modify, or withdraw this policy as appropriate.

¹ A PHE declaration lasts until the Secretary declares that the PHE no longer exists or upon the expiration of the 90-day period beginning on the date the Secretary declared a PHE exists, whichever occurs first. The Secretary may extend the PHE declaration for subsequent 90-day periods for as long as the PHE continues to exist, and may terminate the declaration whenever he determines that the PHE has ceased to exist.

<https://www.phe.gov/Preparedness/legal/Pages/phe-qa.aspx#faq7>.

² The HHS Public Health Emergency Declaration is available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>.

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The tocilizumab shortage was first posted on the FDA Drug Shortages webpage on August 17, 2021.³ In August 2021, Genentech, Inc.,⁴ issued press releases⁵ on the global tocilizumab shortage due to an unprecedented surge in worldwide demand and supply constraints currently driven by the COVID-19 PHE.

Given the tocilizumab shortage related to this PHE, and as discussed in the Notice in the Federal Register of March 25, 2020, titled “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency’s good guidance practices.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA’s guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a PHE related to COVID-19 and mobilized the Operating Divisions of HHS.⁶ In addition, on March 13, 2020, the President of the United States declared a National Emergency in response to COVID-19.⁷

³ FDA Drug Shortages:

https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Tocilizumab%20Injection&st=c. Note that Tocilizumab has been intermittently available, however, in limited quantities during the shortage due to the increased demand associated with COVID-19 use. Clinical sites are, or could have, difficulty receiving the amounts they order.

⁴ Genentech, Inc., is currently the only sponsor of an approved BLA for tocilizumab, or of tocilizumab authorized for emergency use under an EUA.

⁵ Genentech, Inc., press release: https://www.gene.com/media/statements/ps_081621.

⁶ Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued on Jan. 31, 2020, and subsequently renewed), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁷ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>. On February 24, 2021, there was a Presidential Declaration continuing the national emergency concerning the COVID-19 pandemic beyond March 1, 2021. See Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic (February 24, 2021), available at <https://www.federalregister.gov/documents/2021/02/26/2021-04173/continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic>.

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On June 24, 2021, FDA issued an Emergency Use Authorization (EUA) for tocilizumab for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).^{8, 9} As noted in section I of this guidance, in August 2021, Genentech, Inc., issued press releases on the global tocilizumab shortage, and FDA posted information about the tocilizumab shortage on the FDA Drug Shortages webpage.

Due to the tocilizumab shortage related to the COVID-19 pandemic, the Agency has received a number of queries concerning the REMS for chimeric antigen receptor (CAR) T cell immunotherapies, which include requirements for on-site, immediate access to tocilizumab, and the impact of these REMS requirements on patient access to CAR T cell immunotherapies during the tocilizumab shortage.

Section 505-1 of the FD&C Act (21 U.S.C. 355-1) authorizes FDA to require REMS for certain drugs¹⁰ if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.^{11, 12, 13}

A REMS may include a Medication Guide, a patient package insert, a communication plan, and/or certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose.¹⁴ FDA also may require certain *elements to assure safe use* (ETASU) as part of the REMS for a drug.¹⁵

ETASU may be required if the drug has been shown to be effective, but it is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labeling of the drug. ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.

Specifically, ETASU may include one or any combination of the following requirements¹⁶:

- Health care providers who prescribe the drug have particular training or experience, or are specially certified;

⁸ Letter of authorization dated June 24, 2021, is available at <https://www.federalregister.gov/documents/2021/08/05/2021-16705/authorizations-of-emergency-use-of-certain-biological-products-during-the-covid-19-pandemic?form=MY01SV&OCID=MY01SV>.

⁹ Fact Sheet for Healthcare Providers: Emergency Use Authorization For Actemra® (tocilizumab), is available at https://www.gene.com/download/pdf/actemra_eua_hcp_fact_sheet.pdf.

¹⁰ Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act and to applications submitted or approved under section 351 (i.e., biologics license applications) of the Public Health Service Act (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term drug refers to human prescription drugs, including those that are licensed as biological products (biologics).

¹¹ Public Law 110-85, September 27, 2007, available at <https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm>.

¹² Public Law 112-144, July 9, 2012, available at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>.

¹³ See Section 505-1(a) of the FD&C Act.

¹⁴ Section 505-1(e)(2)-(4) of the FD&C Act.

¹⁵ See Section 505-1(f)(1) of the FD&C Act.

¹⁶ See Section 505-1(f)(3) of the FD&C Act.

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- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
- The drug be dispensed to patients only in certain health care settings, such as hospitals;
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug be subject to monitoring; or
- Each patient using the drug be enrolled in a registry.

If a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements (e.g., development of a REMS-specific website or call center to facilitate enrollment; establishment of electronic databases of certified health care settings).¹⁷

III. DISCUSSION

The CAR T cell immunotherapies are all subject to REMS with ETASU, which require, among other things, that before infusion of the CAR T cell immunotherapy to a patient, a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours). Tocilizumab is licensed for several indications, including the treatment of adults and pediatric patients (2 years of age and older) who develop CAR T cell-induced severe or life-threatening cytokine release syndrome (CRS).

FDA recognizes that adherence to the REMS requirement for immediate access to tocilizumab, specifically the requirement that before infusion of the CAR T cell immunotherapy to a patient, a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours), may not be feasible because of the current tocilizumab shortage.

For CAR T cell immunotherapies subject to these REMS, FDA does not intend to object if health care providers prescribe, dispense, or administer these biological products when two doses of tocilizumab are not available, provided that all of the following circumstances are present:

- Before infusion of the CAR T cell immunotherapy to a patient, one dose of tocilizumab is available on-site for each patient for immediate administration (within 2 hours), and there is access to an additional dose of tocilizumab within 8 hours after each previous dose of tocilizumab administered to each patient, if needed.
- Health care providers use their best medical judgment in weighing the benefits and risks of treatment with the CAR T cell immunotherapy in the context of the tocilizumab shortage. There are limited data to support the use of alternative agents directed against interleukin (IL)-6 or other cytokines for CRS management in general, and in particular, as first-line therapy. Using their best medical judgment, health care providers may consider alternative agents inhibiting activities of IL-6 or other cytokines in managing CAR T cell immunotherapy-induced CRS.
- Health care providers communicate with their patients regarding these judgments, including the risks and benefits of treatment with CAR T cell immunotherapy in the

¹⁷ See Section 505-1(f)(4) of the FD&C Act.

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context of the tocilizumab shortage, and inform their patients about potential challenges in the treatment of CRS related to the tocilizumab shortage and potential use of alternative CRS management approaches.

Under the REMS for CAR T cell immunotherapies, certified hospitals and their associated clinics are required to maintain records that all processes and procedures are in place and are being followed, and to comply with audits carried out by the sponsor. Any noncompliance with the REMS requirements, including noncompliance consistent with the policy described above due to the tocilizumab shortage, must be reported by certified hospitals and their associated clinics to the sponsor. Specifically:

- In the event of not being able to comply with REMS requirements due to the tocilizumab shortage, certified hospitals and their associated clinics should maintain adequate records of patient-level data regarding use of CAR T cell immunotherapy consistent with this policy and must document and report any serious adverse events suggestive of CRS or neurological toxicity.

Additionally, sponsors are required under the REMS for CAR-T cell immunotherapies to maintain adequate records to demonstrate that REMS requirements have been met, including audits of REMS participants. Any noncompliance with the REMS requirements, including noncompliance consistent with the policy described above due to the tocilizumab shortage, must be reported by sponsors to FDA in REMS Assessment Reports. Specifically:

- The Sponsor must maintain records of certified hospitals and their associated clinics that were not able to comply with REMS requirements and instead provided CAR T cell immunotherapy in a manner consistent with this policy due to the tocilizumab shortage. The sponsor must document provision of CAR T cell immunotherapy under such circumstances, including regarding use of CAR T cell immunotherapy consistent with this policy and the associated outcomes, and any adverse events (AEs), particularly events of CRS and neurological toxicity. Sponsors must submit this information for all instances of noncompliance with the REMS to the FDA in the REMS Assessment Report.

Note that the REMS Supporting Document may be updated to reflect use of CAR T immunotherapies consistent with this policy and the associated outcomes.

As noted elsewhere in this guidance, there is an ongoing shortage of tocilizumab, as announced by Genentech, Inc., in August 2021. The shortage is due, at least in part, to increased demand for tocilizumab following the June 2021 EUA of tocilizumab for the treatment of certain hospitalized adult and pediatric patients with COVID-19, the cause of the ongoing PHE. Although all REMS requirements remain in effect during this time, FDA does not intend to take enforcement action against sponsors or others with respect to the REMS requirements relating to the access to tocilizumab imposed under sections 505-1(f)(3)(B) or (C) of the FD&C Act (21 U.S.C. 355-1(f)(3)(B) or (C)) during the tocilizumab shortage, provided that the circumstances described above are present.¹⁸ Manufacturers must document and summarize in their next REMS

¹⁸ This guidance is limited to our enforcement policy with respect to access to tocilizumab requirements.

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Assessment Reports steps that were taken to accommodate patient access to CAR T cell immunotherapy during the tocilizumab shortage, including providing patient-level data on specific steps taken and their outcomes and any adverse events, particularly events of CRS and neurological toxicity. Manufacturers must also document and report in their next REMS Assessment Reports occurrences when certified hospitals and their associated clinics employed the steps described in this guidance due to the tocilizumab shortage.