# Emergency Use Authorizations
# *COVID-19 Therapeutics*

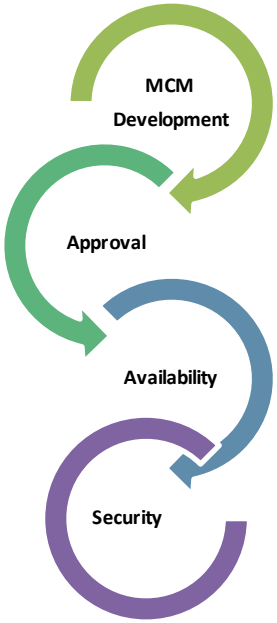
Andrew A. LeBoeuf, JD, MS
*Acting* Associate Director for Policy
Office of New Drug Policy
Office of New Drugs
Center for Drug Evaluation and Research

# General Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

# FDA's Public Health Emergency Response

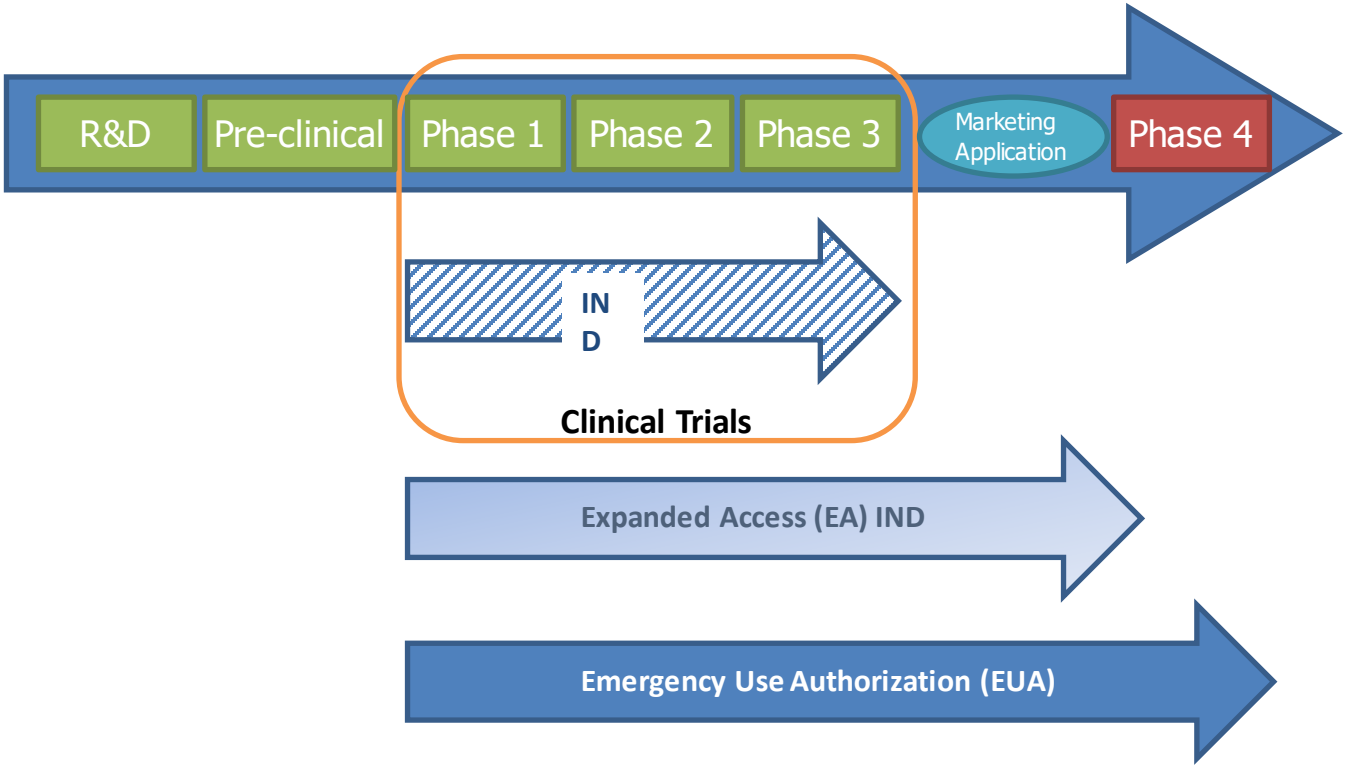
- Facilitating development of MCMs; approving, licensing, clearing, and regulating throughout product lifecycle
- Using legal mechanisms to facilitate emergency use to investigational products
- Preventing shortages
- Protecting blood supply & tissue for transplantation
- Ensuring consumer protection against fraud
- Monitoring MCM use for adverse events to ensure safety and efficacy of FDA-regulated products



# Coronavirus Treatment Acceleration Program (CTAP)


- Emergency program for potential coronavirus therapies created April 2020.
- Enabled FDA to leverage cross-agency scientific resources and expertise to facilitate COVID-19 therapeutic development and review.
- Facilitated fast, early, and frequent discussions between FDA and drug sponsors -- an essential element in expediting efficient development of therapies.
- Includes significant emphasis on providing timely FDA feedback to industry on clinical trial development – reinforcing the gold standard for assessing whether a particular therapeutic is safe and effective for its investigational use.

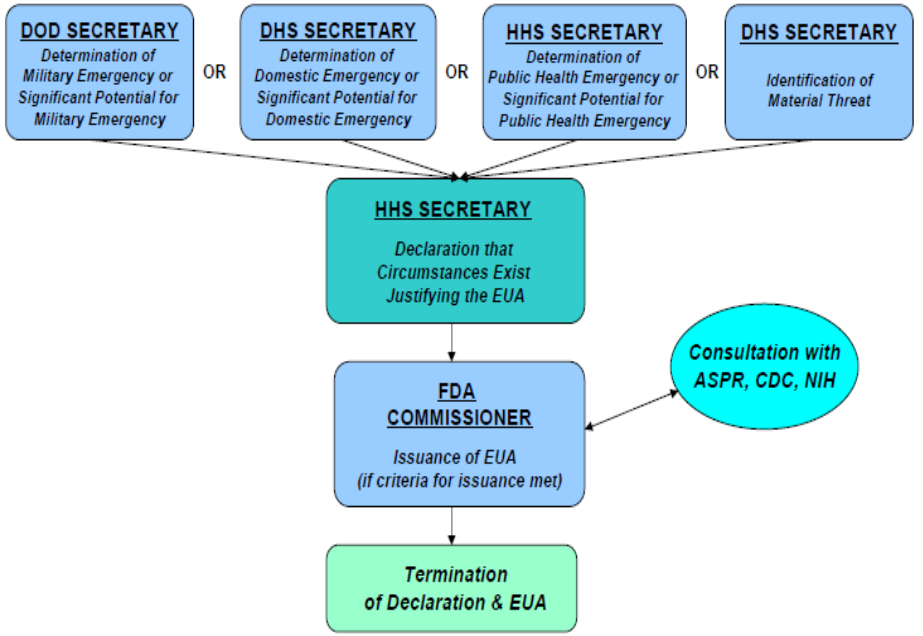
# Regulatory Mechanisms to Enable Access to Investigational Products




www.fda.gov/medicalcountermeasures

# Summary of Process for EUA Issuance

- Pursuant to a Declaration by the Secretary of Health and Human Services, the FDA *may* authorize an unapproved product or unapproved uses of an approved product for emergency use.
- Issuance of an EUA is discretionary.



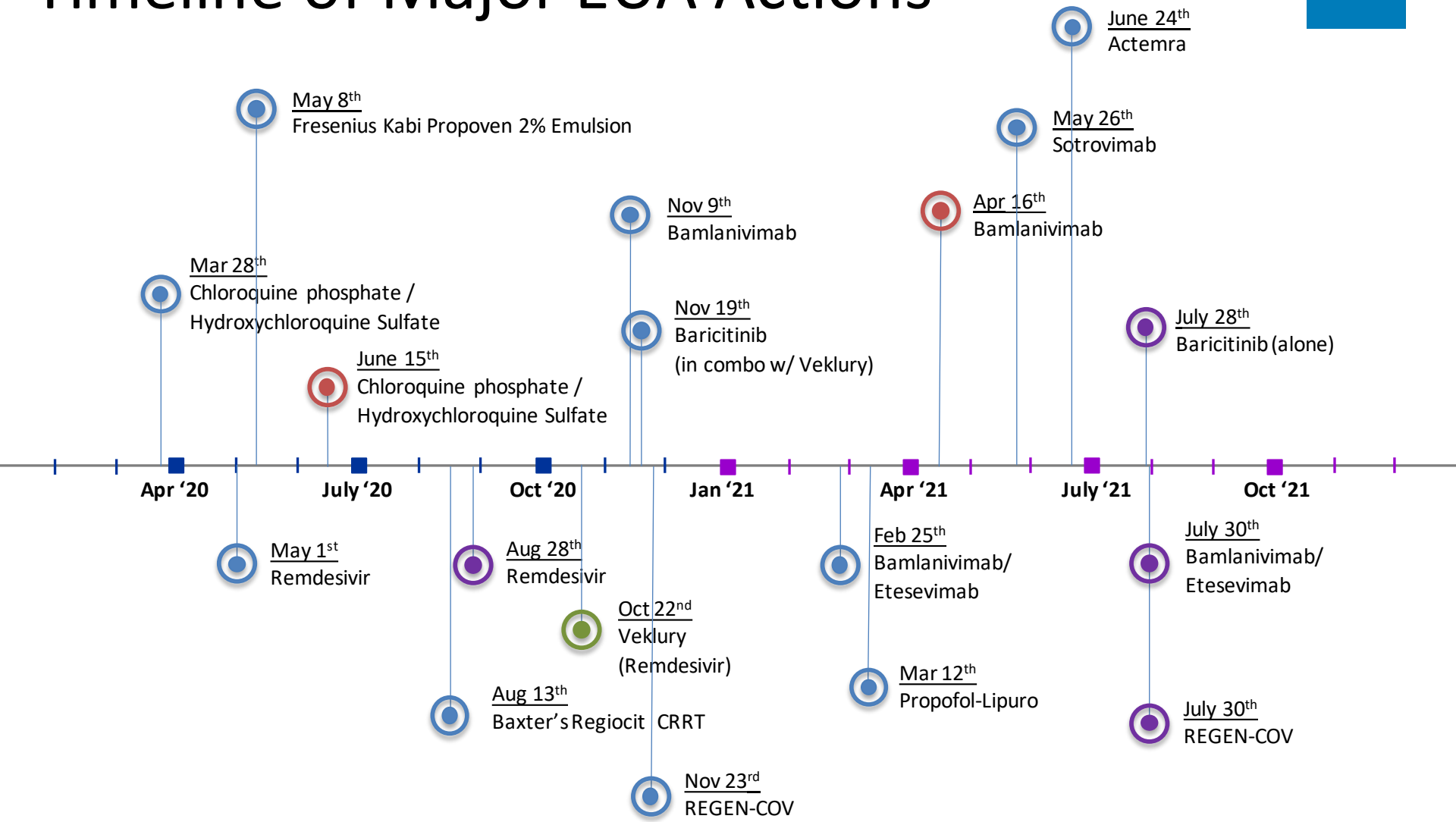
# Criteria for Issuance

- For FDA to issue an EUA, the chemical, biological, radiological, or nuclear agent(s) referred to in the HHS Secretary's EUA declaration must be capable of causing a serious or life-threatening disease or condition.
- *COVID-19 PHE:* Based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, that
  - It is reasonable to believe that the product *may be effective* in diagnosing, treating, or preventing such disease or condition caused by SARS-CoV-2, or a serious or life-threatening disease or condition caused by an FDA-regulated product that is used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
  - The known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved and available alternative to the product for diagnosing, treating, or preventing such disease or condition.

# Current Therapeutic EUAs

- tocilizumab
- sotrovimab
- REGEN-COV (casirivimab and imdevimab)
- bamlanivimab and etesevimab, administered together
- baricitinib
- Veklury (certain pediatric uses)
- convalescent plasma
- Propofol-Lipuro
- Propoven 2% Emulsion
- REGIOCIT
- Fresenius MultiBic Solutions

# Timeline of Major EUA Actions




**Key**

**Initial Authorization** **Revision** **Approved** **Revoked**

CRRT - Continuous Renal Replacement Therapy

# Conditions to EUA

- Shall establish conditions necessary or appropriate to protect the public health
- Examples:
  - Information to be shared with healthcare providers and patients (e.g., Fact Sheets)
  - Reporting of adverse events associated with the emergency use of the product
  - cGMPs and recordkeeping

# Examples of Conditions

**III. Conditions of Authorization**

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Genentech and Authorized Distributors[8]

A. Genentech and authorized distributor(s) will ensure that Actemra is distributed with the FDA-approved package insert and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers as described in Section II of this Letter of Authorization.

B. Genentech and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Genentech and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving Actemra. Genentech will provide to all relevant

[8] "Authorized Distributor(s)" are identified by Genentech as an entity or entities allowed to distribute Actemra for the use authorized in this letter.

# FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR ACTEMRA® (tocilizumab)

**HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)**
**These highlights of the EUA do not include all the information needed to use ACTEMRA under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for ACTEMRA.**

**ACTEMRA® (tocilizumab) injection, for intravenous use**
**Original EUA Authorized Date: 06/2021**

**----------EUA FOR ACTEMRA (tocilizumab)----------**
The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of ACTEMRA for the treatment of coronavirus disease 2019 (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). However, ACTEMRA is not FDA-approved for this use.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

**----------DOSAGE AND ADMINISTRATION----------**
The recommended dosage of ACTEMRA is a single 60-minute intravenous infusion as follows:

| | |
|---|---|
| Patients less than 30 kg weight | 12 mg/kg |
| Patients at or above 30 kg weight | 8 mg/kg |

If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

Maximum dosage in COVID-19 patients is 800 mg per infusion.

Preparation and Administration
- For patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

**----------DOSAGE FORMS AND STRENGTHS----------**
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)

**----------CONTRAINDICATIONS----------**
ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA (4)

**----------WARNINGS AND PRECAUTIONS----------**
- Serious Infections – do not administer ACTEMRA during any other concurrent active infection (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity – ACTEMRA treatment is not recommended in patients with elevated ALT or AST above 10 times the upper limit of the reference range. (5.3)
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, and liver function tests. (5.4)
- Hypersensitivity reactions, including anaphylaxis and death have occurred. (5.5)
- Live vaccines – avoid use with ACTEMRA. (5.8)

**----------ADVERSE REACTIONS----------**
Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension and nausea (6.1)

**You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to ACTEMRA (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Genentech at us_drug.safety@gene.com or call 1-888-835-2555 (6.2).**

**----------DRUG INTERACTIONS----------**
Interactions with CYP450 Substrates: Caution should be exercised when co-administering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable. (7)

**----------USE IN SPECIFIC POPULATIONS----------**
- Pregnancy: ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. (8.1)
- Lactation: Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19. (8.2)
- Pediatric Use: ACTEMRA is not authorized or approved for emergency use for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients less than 2 years of age. (8.4)

**See PATIENT AND PARENTS/CAREGIVER FACT SHEET.**

# Fact Sheet for Healthcare Providers

**Fact Sheet for Patients, Parents and Caregivers**
**Emergency Use Authorization (EUA) of ACTEMRA® (tocilizumab) for Coronavirus Disease 2019 (COVID-19)**

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you or your child with ACTEMRA for the treatment of coronavirus disease 2019 (COVID-19). Taking ACTEMRA may benefit certain people in the hospital with COVID-19 who are receiving corticosteroids and require supplemental oxygen, or a machine that helps with their breathing (ventilator) or a machine that adds oxygen to the blood outside the body (extracorporeal membrane oxygenation or ECMO). This Fact Sheet contains information to help you understand the risks and benefits of taking ACTEMRA you or your child have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make ACTEMRA available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). ACTEMRA is not FDA-approved for this use. Read this Fact Sheet for information about ACTEMRA. Talk to your or your child's healthcare provider about your options or if you have any questions. It is your choice for you or your child to take ACTEMRA or stop it at any time.

**What is COVID-19?**
COVID-19 is caused by a virus called a coronavirus. You or your child can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your or your child's other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

**What are the symptoms of COVID-19?**
The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your or your child's other medical conditions to become worse.

**What is ACTEMRA?**
ACTEMRA is a FDA-approved prescription medicine that is used to treat adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well, to treat adults with giant cell arteritis (GCA), for slowing the rate of decline in lung function in adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD), and to treat people aged 2 years and older with polyarticular juvenile idiopathic arthritis, systemic



# Fact Sheet for Patients, Parents and Caregivers

# Examples of Conditions

- Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
- Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the product to meet the established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

GSK will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, GSK must recall them.

If not included in its initial notification, GSK must submit information confirming that GSK has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate

# Examples of Conditions

O. GSK shall provide samples as requested of the authorized sotrovimab to the U.S. Department of Health and Human Services (HHS) for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized sotrovimab may include, but are not limited to, cell culture potency assays, protein binding assays, cell culture variant assays (pseudotyped virus-like particles and/or authentic virus), and *in vivo* efficacy assays.

P. GSK will submit to FDA all sequencing data assessing sotrovimab, including sequencing of any participant samples from the full analysis population from COMET-ICE that have not yet been completed no later than September 30, 2021. GSK will provide the Agency with a frequency table reporting all substitutions detected for all participants at all available timepoints at a frequency >1%.

Q. GSK will submit to FDA all SARS-CoV-2 viral shedding and viral load data, including quantitation of viral shedding and viral load for any participant samples from the full analysis population from COMET-ICE that have not yet been completed, no later than June 30, 2021.

# Revocation or Revision of EUA

- FDA will periodically review the circumstances and appropriateness of an EUA
  - The review will include a regular assessment based on additional information provided by the sponsor of the progress made with respect to the approval, licensure, or clearance of the unapproved product, or of the unapproved use of an approved product, for which an EUA was issued.
- Revision or Revocation
  - Circumstances warranting issuance are no longer in existence.
  - Criteria for issuance of the EUA are no longer met.
  - Other circumstances make such revision or revocation appropriate to protect the public health or safety.

# Example of Revision

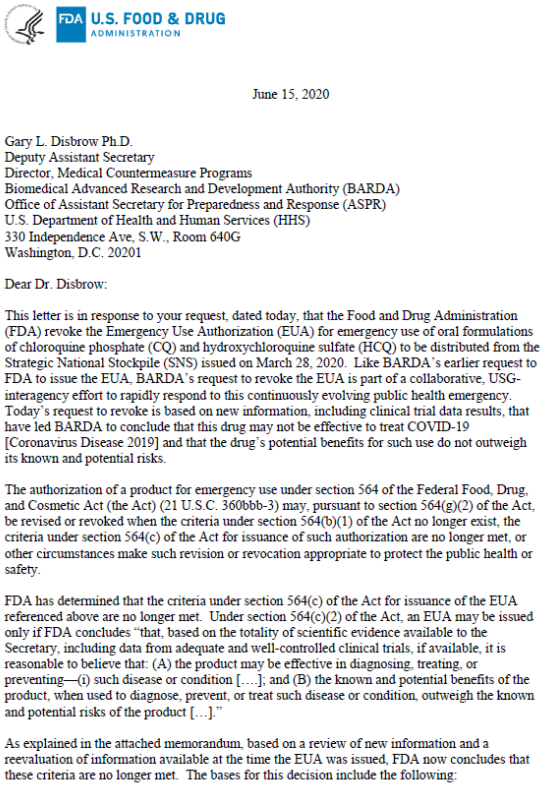
On August 28, 2020, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the May 1, 2020 letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers has been revised to provide updated clinical trial results and supporting data.[5]

# Example of Revision

On February 3, 2021, FDA reissued the November 21, 2020 letter.[4] Thereafter, on February 25, 2021, FDA reissued the February 3, 2021 letter.[5] Thereafter, on June 3, 2021, FDA reissued the February 25, 2021 letter.[6]

On July 30, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the June 3, 2021 letter in its entirety, to also authorize REGEN-COV for emergency use as post-exposure prophylaxis in certain adults and pediatric individuals. Clarifying revisions to the conditions on good manufacturing practices as well as advertising and promotion have also been incorporated.

# Example of Revocation – CQ/HCQ



FDA U.S. FOOD & DRUG ADMINISTRATION

June 15, 2020

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
U.S. Department of Health and Human Services (HHS)
330 Independence Ave, S.W., Room 640G
Washington, D.C. 20201

Dear Dr. Disbrow:

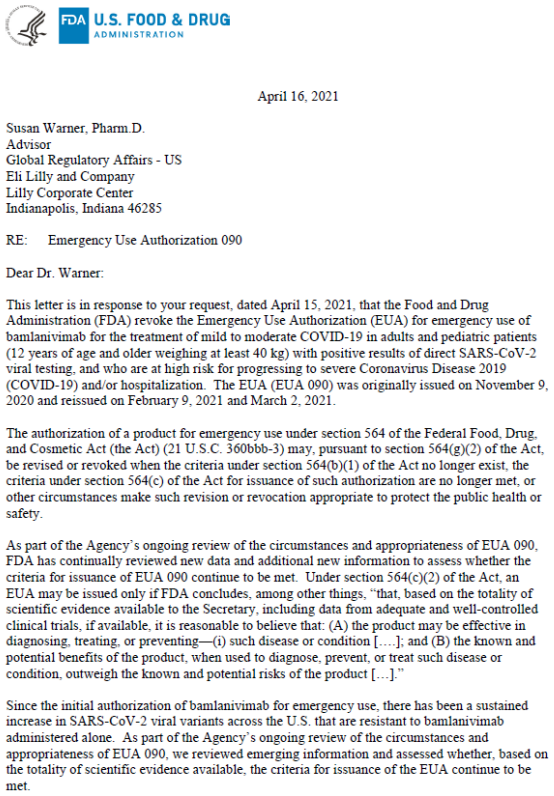
This letter is in response to your request, dated today, that the Food and Drug Administration (FDA) revoke the Emergency Use Authorization (EUA) for emergency use of oral formulations of chloroquine phosphate (CQ) and hydroxychloroquine sulfate (HCQ) to be distributed from the Strategic National Stockpile (SNS) issued on March 28, 2020. Like BARDA's earlier request to FDA to issue the EUA, BARDA's request to revoke the EUA is part of a collaborative, USG-interagency effort to rapidly respond to this continuously evolving public health emergency. Today's request to revoke is based on new information, including clinical trial data results, that have led BARDA to conclude that this drug may not be effective to treat COVID-19 [Coronavirus Disease 2019] and that the drug's potential benefits for such use do not outweigh its known and potential risks.

The authorization of a product for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3) may, pursuant to section 564(g)(2) of the Act, be revised or revoked when the criteria under section 564(b)(1) of the Act no longer exist, the criteria under section 564(c) of the Act for issuance of such authorization are no longer met, or other circumstances make such revision or revocation appropriate to protect the public health or safety.

FDA has determined that the criteria under section 564(c) of the Act for issuance of the EUA referenced above are no longer met. Under section 564(c)(2) of the Act, an EUA may be issued only if FDA concludes "that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) the product may be effective in diagnosing, treating, or preventing—(i) such disease or condition [….]; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product […]."

As explained in the attached memorandum, based on a review of new information and a reevaluation of information available at the time the EUA was issued, FDA now concludes that these criteria are no longer met. The bases for this decision include the following:

# Example of Revocation - Bamlanivimab



U.S. FOOD & DRUG ADMINISTRATION

April 16, 2021

Susan Warner, Pharm.D.
Advisor
Global Regulatory Affairs - US
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

RE: Emergency Use Authorization 090

Dear Dr. Warner:

This letter is in response to your request, dated April 15, 2021, that the Food and Drug Administration (FDA) revoke the Emergency Use Authorization (EUA) for emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe Coronavirus Disease 2019 (COVID-19) and/or hospitalization. The EUA (EUA 090) was originally issued on November 9, 2020 and reissued on February 9, 2021 and March 2, 2021.

The authorization of a product for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3) may, pursuant to section 564(g)(2) of the Act, be revised or revoked when the criteria under section 564(b)(1) of the Act no longer exist, the criteria under section 564(c) of the Act for issuance of such authorization are no longer met, or other circumstances make such revision or revocation appropriate to protect the public health or safety.

As part of the Agency's ongoing review of the circumstances and appropriateness of EUA 090, FDA has continually reviewed new data and additional new information to assess whether the criteria for issuance of EUA 090 continue to be met. Under section 564(c)(2) of the Act, an EUA may be issued only if FDA concludes, among other things, "that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) the product may be effective in diagnosing, treating, or preventing—(i) such disease or condition [….]; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product […]."

Since the initial authorization of bamlanivimab for emergency use, there has been a sustained increase in SARS-CoV-2 viral variants across the U.S. that are resistant to bamlanivimab administered alone. As part of the Agency's ongoing review of the circumstances and appropriateness of EUA 090, we reviewed emerging information and assessed whether, based on the totality of scientific evidence available, the criteria for issuance of the EUA continue to be met.

# Public Transparency


- Transparency is critical to public confidence in the Agency's scientific review process.
- Scientific reviews that underpin our decisions to issue, revise or revoke an EUA are made public on our website.*
- There may be delays in such release as we engage with the sponsor on what must be protected from disclosure.



* https://www.fda.gov/drugs/coronavirus-covid-19-drugs/cder-scientific-review-documents-supporting-emergency-use-authorizations-drug-and-biological