



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Commentary

COVID-19: Regulatory Landscape of Medicinal and Medical Device Products for Human Use



Paul Beninger, MD, MBA

Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

ABSTRACT

Against the backdrop of the COVID pandemic, the scientific and medical communities are working with all deliberate speed with state-of-the-art technologies to develop diagnostic and therapeutic products that can identify, treat, and prevent infection with SARS-CoV-2. These activities may only be legally conducted with the necessary statutes and regulations in place to facilitate the timely development, manufacturing, evaluation, and distribution of products that meet quality standards. The present regulatory landscape for medicinal and medical products for human use has been shaped by nearly 12 decades of statutory history that followed in reaction to disasters and tragedies. Five distinct, closely woven threads of statutory history have led to the regulatory infrastructure we have in place: (1) standardized processes for routine development of medicinal and medical device products for human use; (2) processes for expedited development to shorten time frames and expand patient populations; (3) mechanisms of Expanded Access to make medicinal products available to patients prior to approval of the US Food and Drug Administration; (4) Emergency Use Authorization during public health emergencies; and (5) the development of pathways for bringing generic drugs and biosimilar biologics to market. These mechanisms are being brought to bear to facilitate the defeat of infection with SARS-CoV-2. (*Clin Ther.* 2020;42:1444–1450) © 2020 Elsevier Inc.

Key words: emergency use authorization, expanded access, expedited drug development.

On May 1, 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for remdesivir, intended for use in the treatment of adults and children with suspected or laboratory-confirmed COVID-19 infection and *severe disease*, defined as an SpO₂ of 94% on room air and requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.¹ Given the medical community's general lack of familiarity with the regulatory mechanism Emergency Use Authorization, a useful description of the statute and its use would be helpful. Such a description is best considered in the context of nearly 12 decades of statutory history promulgated in response to major disasters and tragedies that have led to the development of our present regulatory landscape. There are 5 distinct, closely woven threads of statutory history that have come to form our present regulatory framework for making medicinal and medical products available to patients under varying clinical and societal conditions and pressures: (1) standardized processes for the routine development of medicinal and medical device products for human use; (2) processes for expedited development to shorten time frames and expand patient populations; (3) Expanded Access to medicinal products prior to FDA approval; (4) Emergency Use Authorization (EUA) during public health emergencies; and (5) the development of pathways for bringing generic drugs and biosimilar biologics to market. Although of fiscal importance to federal and state programs and of financial importance to

Accepted for publication June 19, 2020

<https://doi.org/10.1016/j.clinthera.2020.06.014>

0149-2918/\$ - see front matter

© 2020 Elsevier Inc.

company and family budgets, this fifth series of statutory developments has been discussed elsewhere and will not be discussed further.^{2,3}

INTRODUCTION

Relevant historical events that led to the eventual regulation of medicinal products, including drugs, biologics, and vaccines, include the following: the Biologics Control Act of 1902, which established the concepts of tolerability, purity, and potency standards for biologics⁴; the Pure Food and Drug Act of 1906, which established the concepts of adulteration and misbranding of drugs⁴; the Food, Drug, and Cosmetic Act of 1938, which created a safety standard for drugs that must be met prior to entering the market and which also developed the concepts of the Investigational New Drug exemption (IND) and the New Drug Application (NDA)¹; and the Kefauver-Harris Drug Amendments of 1962, which established an efficacy standard for drugs that must be met prior to entering the market.¹ Important populations of patients that have been specifically addressed through statutes and enabling regulations include patients with orphan diseases⁵ and children.⁶

There is a parallel series of statutes that directed the regulation of medical device products, including scalpels, personal protective equipment, orthopedic and cardiovascular implants, heart–lung pumps, and *in vitro* diagnostic tests. These include the Medical Device Amendments of 1976, which created a risk-based classification system and accompanying controls to ensure safe use; the Safe Medical Devices Act of 1990, which established requirements for adverse-events reporting⁴; and the Unique Device Identification system for tracking implantable devices.⁷

Important events that have occurred in the current era of regulation include the quinquennially renewed User Fee Acts, which began in 1992.⁸ This was a sea change in how funding for premarket and postmarket regulatory science would be sourced, shifting from wholly congressionally budgeted funding to partially congressionally budgeted funding that is augmented by user fees obtained from regulated industries seeking market access. In fiscal year 2020, the FDA's budget is 5.94 billion USD, of which 2.67 billion USD (45%) is expected to come from user fees.⁹ User fee-augmented budgets have been successful in having the intended effects of

facilitating product-development activities and of reducing standard NDA review times to a goal of 10 months, and priority NDA review times to a goal of 6 months. Five-year review of accompanying legislation has had the further effect of offering regularly scheduled opportunities for legislating innovation and other prospectively considered concerns, issues, and activities that might otherwise be limited to statutory remedies in response to disasters and tragedies. Similar benefits have followed the adoption of user fees for medical devices.¹⁰

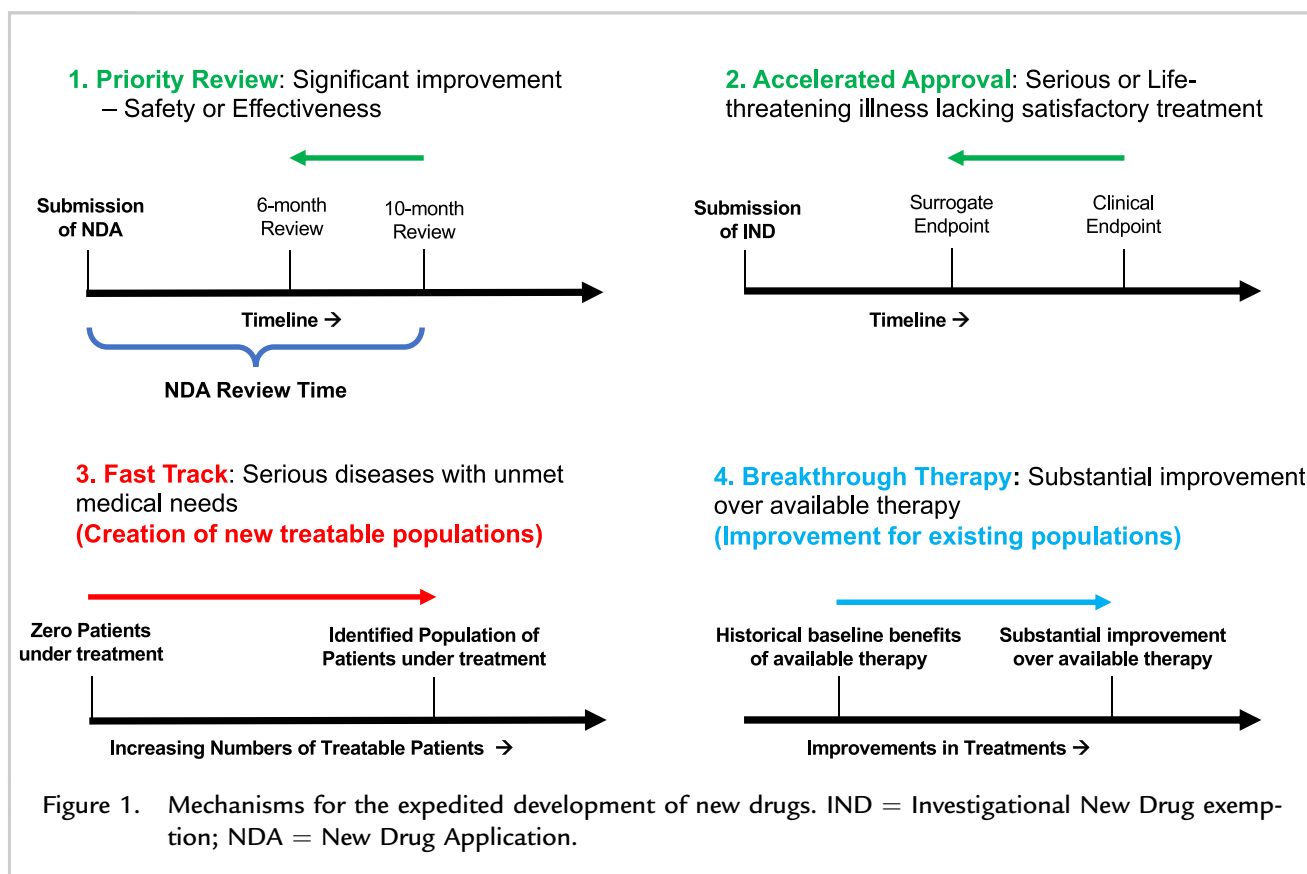
REGULARIZED DRUG DEVELOPMENT

Regulatory processes for the routine development of medicinal and medical device products were gradually standardized over the first 8 decades of the 20th century¹¹ to meet the medical and scientific communities' expectations of the majority of products, although improvements in timeliness would have to await the enactment of user fees in the 1990s to address business expectations. The HIV epidemic that began in the early 1980s had laid bare weaknesses in the standardized routine model of drug development in responding to the urgent pressures of expedited development of new drugs and in facilitating the availability of promising drugs to large numbers of patients without alternatives during company preparation of NDAs and FDA reviews of applications. These experiences acute attention to the need for expedited development processes and Expanded Access approaches to medicinal products prior to FDA approval.

EXPEDITED DEVELOPMENT

Figure 1 shows the 4 basic mechanisms of expediting the development of new drugs: Priority Review, Accelerated Development, Fast Track, and Breakthrough Therapy.

Drugs that provide significant improvements in tolerability or effectiveness in the treatment, diagnosis, or prevention of serious conditions when compared to standard applications may be granted a Priority Review designation, which shortens the anticipated review time from 10 months to 6 months.¹² Drugs in development that have recently been given a Priority Review designation include capmatinib for patients with certain non–small cell lung cancers, and belantamab mafodotin for patients with relapsed or refractory multiple myeloma.¹³



There was a total of 48 approvals for New Drug Applications and 13 approvals for Biologics License Applications given the Priority Review designation in the calendar year of 2018, the last year of available cumulative information.¹⁴

An Accelerated Development designation relies on the use of surrogate laboratory markers as primary end points that may significantly shorten the study duration, rather than on clinical end points, for drugs intended for use in the treatment of serious or life-threatening illnesses that lack satisfactory treatments.¹⁵ Recently approved drugs that were granted an Accelerated Development designation include golodirsen for patients with Duchenne muscular dystrophy, and voxelotor for patients with sickle cell disease. There was a cumulative total of 208 approvals for all products given the Accelerated Development designation by CDER through December 2019.¹⁶

The Fast Track designation addresses a broad range of products developed for use in the treatment of

serious diseases with unmet medical needs, which creates whole new populations of treatable patients.¹⁷ Recently approved drugs that were granted the Fast Track designation include triclabendazole for patients with fascioliasis, and esketamine for patients with treatment-resistant major depression. There was a cumulative total of 29 approvals for all products given a Fast Track designation through December 2019.¹⁸

The Breakthrough Therapy designation directs the expedited development and review of products that can provide substantial improvement over available therapy, which expands the benefits that patients experience over prior treatments.¹⁹ Products approved in 2020 that were granted a Breakthrough Therapy designation include avapritinib for patients with gastrointestinal stromal tumor, and nintedanib for patients with chronic fibrosing interstitial lung diseases. There was a cumulative total of 156 approvals for all products given the Breakthrough Therapy designation by CDER through December 2019.²⁰

The 21st Century Cures Act established a new expedited option for certain eligible biologic products, the designation of Regenerative Medicine Advanced Therapy, as well as a Breakthrough Devices program.²¹ Gene and cell therapy products recently approved include onasemnogene abeparvovec-xioi for patients with spinal muscular atrophy, and talimogene laherparepvec for patients with recurrent melanoma. There was a cumulative total of 17 approvals for all gene and cell therapy products given the Regenerative Medicine Advanced Therapy designation by the FDA's Center for Biologics Evaluation and Research through December 2019.²²

EXPANDED ACCESS

A patchwork of Expanded Access (Compassionate Use) regulations for individual patient use or emergency use, treatment IND, and parallel track were consolidated into a Final Rule in 2009 and subsequently accompanied by a guidance document.^{23,24} The 3 categories of Expanded Access are individual use, including emergency use; use in intermediate-sized populations of patients; and widespread use. Expanded Access provides access to drugs, including biologics, by patients when a use is not primarily intended for the collection of information about the tolerability or effectiveness of an investigational agent. Between 1992 and 2017, there were 92 FDA approvals of drugs, including biologics, with the Expanded Access designation, half of which were for use in patients with cancer.²⁵

EMERGENCY USE AUTHORIZATION

Prior to September 11, 2001, there was only 1 statute that addressed preparedness and public health emergencies: the Public Health Threats and Emergencies Act of 2000.²⁶ Since 9/11, Congress has enacted an additional nine statutes to enhance preparedness for the full gamut of circumstances: emerging infectious diseases; threats stemming from chemical, biological, radiologic, and nuclear sources; and agents of war.²⁷ One of these provisions is the EUA, established as part of the Project Bioshield Act of 2004.²⁸ With this provision, the secretaries of the US departments of Defense, Homeland Security, and Health and Human Services (HHS) are empowered to make a determination of need, that is, that a military/

domestic/public health emergency, or a significant potential for an emergency, exists. The secretary of HHS declares that the described circumstance justifies an EUA, and the FDA commissioner evaluates the request using the four criteria necessary for supporting the issuance of an EUA, namely that: (1) there is a serious or life-threatening illness/condition caused by the identified agent(s); (2) there is reasonable belief that the product may be effective in preventing, diagnosing, or treating a serious or life-threatening disease or condition caused by the agent(s); (3) the known or potential benefits outweigh the known or potential risks; and (4) there is no adequate, approved, and available alternative to the product.

COVID-19

With this description of the regulatory framework that is in place for the development of medicinal and medical device products for human use, we can begin to understand how regulations support and contextualize responses to the COVID-19 pandemic.

To diagnose SARS-CoV-2 infection in the population of interest, there must be an *in vitro* diagnostic kit that has received either FDA 510(k) clearance or premarket approval. However, in a public health emergency, the HHS secretary can make a determination of need and declare that a public health emergency exists, and the FDA commissioner can issue Emergency Use Authorizations of specific *in vitro* diagnostic test kits. The same process may serve for the issuance of EUAs for serologic test kits used for measuring antibody levels in convalescence. Thus far, 81 individual EUAs for molecular diagnostic tests have been issued, as well as an umbrella EUA for molecular diagnostic tests for use in laboratories that are CLIA-certified to perform 37 high-complexity nucleic acid tests, an individual EUA for antigen diagnostic tests, 20 individual EUAs for serologic tests, an umbrella EUA for an independently validated serologic test, and an individual EUA for a test for the management of COVID-19–infected patients.^{29,30} Forty-one EUAs have also been issued for personal protective equipment,³¹ and 66 EUAs for ventilators.³² EUAs will be withdrawn after there is adequate supply of 510(k)-cleared or approved products on the market and the emergency has abated.

To treat patients with acute SARS-CoV-2–induced disease, physicians are generally limited to prescribing off-label, FDA-approved antiviral drugs indicated for use in the treatment of other viral diseases. New antiviral drugs specifically targeting SARS-CoV-2 will have to undergo premarket evaluation under an IND for the generation of data for use in supporting an NDA for submission to the FDA, which will likely take years. New, SARS-CoV-2–targeted drugs will be given a Priority Review designation, and will likely be given the Fast Track designation, which is accompanied by close collaboration between the developer and the FDA to speed development, review, and approval.

To prevent new infections and to end the pandemic quickly, vaccine candidates are being evaluated through the IND mechanism. Expedited development and FDA review mechanisms will likely be applied, including possibly a Regenerative Medicine Advanced Therapy designation.

To employ the Expanded Access mechanism, both acute antiviral treatments and prophylactic vaccines can be expected to be widely distributed under a treatment IND as soon as a manufactured product is available and evaluated by the FDA.

It is likely that each manufacturer of drug products, including biologics, or vaccine products will have short- and long-term postmarketing commitments to ensure the continuation of collecting postmarketing efficacy data, as well as to consider special populations and issues (eg, pediatric and elderly populations, patients with hepatic or renal insufficiency, and patients with a risk for drug–drug interactions) in the further evaluation of the product. To maintain the safety profile of marketed products, adverse-events reports on all products will be passively collected.

Finally, EUAs may be issued for antiviral drug products as well as for anti-inflammatory drug/biologic medicinal products as they are identified and directed toward specific patient populations, possibly as early as Phase II for new products and possibly any time after a repurposed product is considered potentially effective. EUAs may also play a role in making vaccines available. We have also seen EUA withdrawals in the cases of chloroquine and hydroxychloroquine after the FDA determined that they were “unlikely to be effective in treating COVID-19 for the authorized uses in the EUA”.³³

SUMMARY

The EUA that was issued for remdesivir is a part of a well-developed landscape of regulatory infrastructure intended for meeting the needs of patients in the face of the broad range of societal and environmental demands of routine development, expedited development, Expanded Access, and public health emergencies or threats. To that end, the long historical experience with disasters and tragedies has not been in vain.

ACKNOWLEDGMENTS

The author states that no other parties contributed to the content, review, edit, or revision of the article.

DISCLOSURES

In 2019 and 2020, the author received consultant's fees from a pharmaceutical company, subject-matter–expert fees from a nonprofit company Americal Association for the Advancement of Science (AAAS), and fees for his role as topics editor for *Clinical Therapeutics*. The author was employed by the FDA from 1987 to 1995. The author has indicated that he has no conflicts of interest with regard to the content of this article.

REFERENCES

1. Fact sheet for healthcare providers: emergency use authorization of remdesivir [FDA website]. Available at: <https://www.fda.gov/media/137566/download>. Accessed June 17, 2020.
2. Nesvisky M. How generic drugs, patents, and price controls affect markets [national bureau economic research website]. Available at: <https://www.nber.org/digest/jan15/w20532.html>. Accessed June 17, 2020.
3. Mehr R, Brook RA. Factors influencing the economics of biosimilars in the US. *J Med Econ*. 2017;20:1268–1271.
4. Food and Drug Administration (FDA). US dept of health and human services. Milestones in US Food and Drug Law History [FDA website]. Available at: <https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history>. Accessed June 17, 2020.
5. Food and Drug Administration (FDA). US dept of health and human services. The Story Behind the Orphan Drug Act [FDA website]. Available at: <https://www.fda.gov/industry/orphan-products-development-events/story-behind-orphan-drug-act>. Accessed June 17, 2020.

6. Food and Drug Administration (FDA). US dept of health and human services. Best pharmaceuticals for children Act and pediatric research equity Act [FDA website]. Available at: <https://www.fda.gov/science-research/pediatrics/best-pharmaceuticals-children-act-and-pediatric-research-equity-act>. Accessed June 17, 2020.
7. Food and Drug Administration (FDA). US dept of health and human services. Unique Device Identifier [FDA website]. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/unique-device-identifier-system-frequently-asked-questions-vol-1>. Accessed June 17, 2020.
8. Food and Drug Administration (FDA). US dept of health and human services. Prescription Drug User Fee Amendments [FDA website]. Available at: <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments>. Accessed June 17, 2020.
9. Food and Drug Administration (FDA). US dept of health and human services. 2020 Budget Summary [FDA website]. Available at: <https://www.fda.gov/about-fda/budgets/2020-budget-summary>. Accessed June 17, 2020.
10. Food and Drug Administration (FDA). US dept of health and human services. Medical device user fee Amendments [FDA website]. Available at: <https://www.fda.gov/industry/fda-user-fee-programs/medical-device-user-fee-amendments-mdufa>. Accessed June 17, 2020.
11. Food and Drug Administration (FDA). US dept of health and human services. The Drug Development Process [FDA website]. Available at: <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process>. Accessed June 17, 2020.
12. Food and Drug Administration (FDA). US dept of health and human services. Priority Review [FDA website]. Available at: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review>. Accessed June 17, 2020.
13. Keown A. FDA speeds up examination of 5 drugs with priority review [biospace online]. Available at: <https://www.biospace.com/article/5-companies-secure-priority-review-designation-from-the-fda-this-week>. Accessed June 17, 2020.
14. Food and Drug Administration (FDA). US dept of health and human services. Priority NDA and BLA Approvals [FDA website]. Available at: <https://www.fda.gov/drugs/nda-and-bla-approvals/priority-nda-and-bla-approvals>. Accessed June 17, 2020.
15. Food and Drug Administration (FDA). US dept of health and human services. Accelerated Review [FDA website]. Available at: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval>. Accessed June 17, 2020.
16. Food and Drug Administration (FDA). US dept of health and human services. Accelerated Approvals [FDA website]. Available at: <https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals>. Accessed June 17, 2020.
17. Food and Drug Administration (FDA). US dept of health and human services. Fast track [FDA website]. Available at: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track>. Accessed June 16, 2020.
18. Food and Drug Administration (FDA). US dept of health and human services. Fast track approvals [FDA website]. Available at: <https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals>. Accessed June 17, 2020.
19. Food and Drug Administration (FDA). US dept of health and human services. Breakthrough Therapy [FDA website]. Available at: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>. Accessed June 17, 2020.
20. Food and Drug Administration (FDA). US dept of health and human services. Breakthrough Approvals [FDA website]. Available at: <https://www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals>. Accessed June 17, 2020.
21. Food and Drug Administration (FDA). US dept of health and human services. 21st Century Cures Act [FDA website]. Available at: <https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act>. Accessed June 17, 2020.
22. Food and Drug Administration (FDA). US dept of health and human services. Cellular and gene therapy products [FDA website]. Available at: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>. Accessed June 17, 2020.
23. Federal Register. Expanded Access to Investigational Drugs for Treatment Use [FDA website]. Available at: <https://www.federalregister.gov/documents/2009/08/13/E9-19005/expanded-access-to-investigational-drugs-for-treatment-use>. Accessed June 17, 2020.
24. Food and Drug Administration (FDA), US dept of health and human services. Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers. Guidance to Industry [FDA website]. Updated October 2017.
25. Pithumana J, Miller JE, Kim J, Ross JS. Availability of investigational medicines through the US Food and Drug Administration's expanded access and compassionate use

- programs. *JAMA Netw Open*. 2018;1, e180283.
26. S. Rept. 106-505. Public health threats and emergencies Act [US congress website]. Available at: <https://www.congress.gov/congressional-report/106th-congress/senate-report/505/1>. Accessed June 17, 2020.
 27. Food and Drug Administration (FDA). US dept of health and human services. MCM-related counterterrorism legislation [FDA website]. Available at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/mcm-related-counterterrorism-legislation>. Accessed June 17, 2020.
 28. Food and Drug Administration (FDA). US dept of health and human services. Project Bioshield overview [medical countermeasures website]. Available at: <https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview>. Accessed June 17, 2020.
 29. Food and Drug Administration (FDA). US dept of health and human services. Corona disease 2019 (COVID-19) emergency use Authorizations for medical devices [FDA website]. Available at: <https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices>. Accessed June 17, 2020.
 30. Food and Drug Administration (FDA). US dept of health and human services. In vitro diagnostics EUAs [FDA website]. Available at: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas>. Accessed June 17, 2020.
 31. Food and Drug Administration (FDA). US dept of health and human services. Personal Protective Equipment EUAs [FDA website]. Available at: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/personal-protective-equipment-euas>. Accessed June 17, 2020.
 32. Food and Drug Administration (FDA). US dept of health and human services. Ventilator EUAs [FDA website]. Available at: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/ventilators-and-ventilator-accessories-euas>. Accessed June 17, 2020.
 33. Food and Drug Administration (FDA). US dept of health and human services. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine [FDA website]. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and>. Accessed June 17, 2020.

Address correspondence to: Paul Beninger, MD, MBA, Public Health & Community Medicine, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, 02111, USA. E-mail: paul.beninger@tufts.edu