



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-N-3224]

Authorization of Emergency Use of an Injectable Treatment for Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the issuance of an Emergency Use Authorization (EUA) (the Authorization) for an injectable treatment for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning. FDA issued this Authorization under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as requested by the U.S. Centers for Disease Control and Prevention (CDC). The Authorization contains, among other things, conditions on the emergency use of the authorized injectable treatment. The Authorization follows the April 11, 2017, determination by the Department of Health and Human Services (HHS) Secretary that there is a significant potential for 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 nerve agents or certain insecticides (organophosphorus and/or carbamate). On the basis of such determination, the HHS Secretary declared on April 11, 2017, that circumstances exist justifying the authorization of emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning, subject to the terms of any authorization issued under the FD&C Act.

The Authorization, which includes an explanation of the reasons for issuance, is reprinted in this document.

DATES: The Authorization is effective as of April 11, 2017.

ADDRESSES: Submit written requests for single copies of the EUA to the Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, rm. 4338, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the Authorization may be sent. See the SUPPLEMENTARY INFORMATION section for electronic access to the Authorization.

FOR FURTHER INFORMATION CONTACT: Carmen Maher, Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, rm. 4347, Silver Spring, MD 20993-0002, 301-796-8510.

SUPPLEMENTARY INFORMATION:

#### I. Background

Section 564 of the FD&C Act (21 U.S.C. 360bbb-3) as amended by the Project BioShield Act of 2004 (Pub. L. 108-276) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (Pub. L. 113-5) allows FDA to strengthen the public health protections against biological, chemical, nuclear, and radiological agents. Among other things, section 564 of the FD&C Act allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product in certain situations. With this EUA authority, FDA can help assure that medical countermeasures may be used in emergencies to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by biological, chemical, nuclear, or radiological agents when there are no adequate, approved, and available alternatives.

Section 564(b)(1) of the FD&C Act provides that, before an EUA may be issued, the Secretary of HHS must declare that circumstances exist justifying the authorization based on one of the following grounds: (1) A determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a biological, chemical, radiological, or nuclear agent or agents; (2) a determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to U.S. military forces of attack with a biological, chemical, radiological, or nuclear agent or agents; (3) a determination by the Secretary of HHS that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of U.S. citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents; or (4) the identification of a material threat by the Secretary of Homeland Security under section 319F-2 of the Public Health Service (PHS) Act (42 U.S.C. 247d-6b) sufficient to affect national security or the health and security of U.S. citizens living abroad.

Once the Secretary of HHS has declared that circumstances exist justifying an authorization under section 564 of the FD&C Act, FDA may authorize the emergency use of a drug, device, or biological product if the Agency concludes that the statutory criteria are satisfied. Under section 564(h)(1) of the FD&C Act, FDA is required to publish in the Federal Register a notice of each authorization, and each termination or revocation of an authorization, and an explanation of the reasons for the action. Section 564 of the FD&C Act permits FDA to authorize the introduction into interstate commerce of a drug, device, or biological product intended for use when the Secretary of HHS has declared that circumstances exist justifying the

authorization of emergency use. Products appropriate for emergency use may include products and uses that are not approved, cleared, or licensed under sections 505, 510(k), or 515 of the FD&C Act (21 U.S.C. 355, 360(k), and 360e) or section 351 of the PHS Act (42 U.S.C. 262). FDA may issue an EUA only if, after consultation with the HHS Assistant Secretary for Preparedness and Response, the Director of the National Institutes of Health, and the Director of the CDC (to the extent feasible and appropriate given the applicable circumstances), FDA<sup>1</sup> concludes: (1) That an agent referred to in a declaration of emergency or threat can cause a serious or life-threatening disease or condition; (2) that, based on the totality of scientific evidence available to FDA, 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; or (ii) a serious or life-threatening disease or condition caused by a product authorized under section 564, approved or cleared under the FD&C Act, or licensed under section 351 of the PHS Act, for diagnosing, treating, or preventing such a disease or condition caused by such an agent; 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, taking into consideration the material threat posed by the agent or agents identified in a declaration under section 564(b)(1)(D) of the FD&C Act, if applicable; (3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition; and (4) that such other criteria as may be prescribed by regulation are satisfied.

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<sup>1</sup> The Secretary of HHS has delegated the authority to issue an EUA under section 564 of the FD&C Act to the Commissioner of Food and Drugs.

No other criteria for issuance have been prescribed by regulation under section 564(c)(4) of the FD&C Act. Because the statute is self-executing, regulations or guidance are not required for FDA to implement the EUA authority.

## II. EUA Request for an Injectable Treatment for Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

On April 11, 2017, under section 564(b)(1)(C) of the FD&C Act, the Secretary of HHS determined that there is a significant potential for 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 nerve agents or certain insecticides (organophosphorus and/or carbamate). On April 11, 2017, under section 564(b)(1) of the FD&C Act, and on the basis of such determination, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning, subject to the terms of any authorization issued under section 564 of the FD&C Act. Notice of the determination and declaration of the Secretary was published in the Federal Register on April 17, 2017 (82 FR 18152). On March 9, 2017, CDC requested, and on April 11, 2017, FDA issued, an EUA for the 2 mg Rafa Atropine Auto-Injector, manufactured by Rafa Laboratories Ltd., subject to the terms of the Authorization.

## III. Electronic Access

An electronic version of this document and the full text of the Authorization are available on the Internet at <https://www.regulations.gov>.

## IV. The Authorization

Having concluded that the criteria for issuance of the Authorization under section 564(c) of the FD&C Act are met, FDA has authorized the emergency use of an injectable treatment for

nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning subject to the terms of the Authorization. The Authorization in its entirety (not including the authorized versions of the fact sheets and other written materials) follows and provides an explanation of the reasons for its issuance, as required by section 564(h)(1) of the FD&C Act.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

April 11, 2017

Anne Schuchat, M.D. (RADM, USPHS)  
Acting Director  
Centers for Disease Control and Prevention  
1600 Clifton Rd, MS D-14  
Atlanta, GA 30333

Dear Dr. Schuchat:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of the Rafa Laboratories Ltd. (Rafa) Atropine Auto-Injector for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population (as described in the Scope of Authorization section of this letter (Section II)), pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).<sup>1</sup>

On April 11, 2017, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of Health and Human Services (HHS) determined that there is a significant potential for 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 nerve agents or certain insecticides (organophosphorus and/or carbamate).<sup>2</sup> Pursuant to section 564(b)(1) of the Act (21 U.S.C. § 360bbb-3(b)(1)), and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning, subject to the terms of any authorization issued under 21 U.S.C. § 360bbb-3(a).<sup>3</sup>

The Centers for Disease Control and Prevention (CDC) requested this EUA so that the Rafa Atropine Auto-Injector, which is not FDA-approved, may be distributed and held by CDC,

<sup>1</sup> At the time of issuance of this Emergency Use Authorization (EUA), the Rafa Atropine Auto-Injector was approved in at least one country (i.e., Israel) but not approved in the U.S. This EUA, including its Conditions of Authorization in Section IV, applies only to Rafa Atropine Auto-Injector product that is manufactured and distributed by Rafa and its authorized agent(s) specifically for U.S. Government procurement and further distribution, stockpiling, and use during an emergency as set forth in this authorization.

<sup>2</sup> As amended by the Pandemic and All-Hazards Preparedness Reauthorization Act, Pub. L. No. 113-5, under section 564(b)(1)(C) of the Act, the Secretary may make a determination of a public health emergency, or of a significant potential for a public health emergency.

<sup>3</sup> U.S. Department of Health and Human Services (HHS). *Determination of a Significant Potential for a Public Health Emergency and Declaration that Circumstances Exist Justifying an Authorization Pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. April 11, 2017.

Page 2 – Dr. Schuchat, CDC

emergency response stakeholders, and DoD for preparedness purposes in advance of an actual nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning event, with the intent that it may be administered by healthcare providers or caregivers, or be self-administered, during an event or post-event for treatment of the muscarinic symptoms of poisoning caused by exposure to these agents.<sup>4</sup> An EUA is needed to facilitate CDC, emergency response stakeholder, and DoD pre-event planning and preparedness activities related to the use of this unapproved product to enable activities to support rapid administration of treatment during an actual emergency event involving nerve agents or certain insecticides (organophosphorus and/or carbamate) (e.g., distribution and use of fact sheets about the product, pre-event distribution and stockpiling of an unapproved product, administration of an unapproved product without a prescription, and administration by individuals who are not licensed professionally to administer the product). This EUA is important for emergency response purposes because it enables rapid initiation of treatment with the Rafa Atropine Auto-Injector during a nerve agent or insecticide emergency without FDA and CDC, emergency response stakeholders, or DoD having to take further action with respect to otherwise applicable requirements under federal law.

Other atropine auto-injectors previously have been approved by FDA to treat nerve agent and insecticide poisoning in adults and children. However, at the time of issuance of this EUA, FDA-approved atropine auto-injectors for the treatment of nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning were not available to replenish the Department's Strategic National Stockpile inventory when the products in the current inventory expire.<sup>5</sup> This EUA will help to facilitate the fulfillment of national preparedness and stockpiling requirements and needs for new atropine auto-injectors.

Having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(c)) are met, I am authorizing the emergency use of the Rafa Atropine Auto-Injector (as described in the Scope of Authorization section of this letter (Section II)) in the specified population (as described in the Scope of Authorization section of this letter (Section II)) for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate), subject to the terms of this authorization.

This EUA applies in all circumstances when CDC, emergency response stakeholders, and/or DoD reasonably believe that there is a need to store, distribute, and/or administer the authorized Rafa Atropine Auto-Injector without an individual prescription in an emergency because of their constituents' known, suspected, or likely imminent exposure to nerve agents or certain insecticides (organophosphorus and/or carbamate).<sup>6</sup>

<sup>4</sup> For purposes of this EUA, the term "emergency response stakeholders" refers to CHEMPACK stakeholders (as defined by the Centers for Disease Control and Prevention (CDC)/Division of Strategic National Stockpile (SNS) under the CHEMPACK program), and to other public health, emergency response, and/or other government agencies that receive the authorized Rafa Atropine Auto-Injector through CDC, and that have legal responsibility and authority for responding to an incident, based on political or geographical boundaries (e.g., city, county, tribal, territorial, State, or Federal), or functional range or sphere of authority (e.g., law enforcement, public health, military health) to prescribe, administer, deliver, distribute, hold, or dispense a medical product during an emergency situation.

<sup>5</sup> Regarding the SNS, see 42 U.S.C. § 247d-6b(a).

<sup>6</sup> For purposes of this EUA, the terms "administer" and "administration" refer to administration of the authorized Rafa Atropine Auto-Injector by healthcare providers and caregivers (as defined later in this letter) and by individuals administering the authorized Rafa Atropine Auto-Injector to themselves (i.e., self-administration) when healthcare

Page 3 – Dr. Schuchat, CDC

### **I. Criteria for Issuance of Authorization**

I have concluded that the emergency use of the Rafa Atropine Auto-Injector for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population (as described in the Scope of Authorization section of this letter (Section II)) meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

1. Susceptible nerve agents and certain insecticides (organophosphorus and/or carbamate) can cause muscarinic symptoms of poisoning, a serious or life-threatening disease or condition to humans exposed to these agents or insecticides;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that the Rafa Atropine Auto-Injector, when used in accordance with the Scope of Authorization, may be effective for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate), and that the known and potential benefits of the Rafa Atropine Auto-Injector for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) outweigh the known and potential risks of such product; and
3. There is no adequate, approved, and available alternative to the emergency use of the Rafa Atropine Auto-Injector for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate).<sup>7</sup>

### **II. Scope of Authorization**

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized Rafa Atropine Auto-Injector by CDC, emergency response stakeholders, and DoD for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population (see below). The emergency use of the authorized Rafa Atropine Auto-Injector product under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.

#### **The Authorized Rafa Atropine Auto-Injector:**

I am authorizing the use of the 2 mg Rafa Atropine Auto-Injector. The 2 mg Rafa Atropine Auto-Injector is a combination product (drug/device) to provide initial treatment of the muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in adults and children (weighing over 41 kg (90 lbs) (generally over 10 years of age)) following an intentional terrorism-related or unintentional event.<sup>8</sup> CDC may request the authorization of additional strengths (e.g., 0.5 mg and/or 1 mg) of

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providers and caregivers are not available to administer the authorized Rafa Atropine Auto-Injector.

<sup>7</sup> No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

<sup>8</sup> Treatment and management of nerve agent and insecticide (organophosphorus and/or carbamate) poisoning include decontamination, supportive measures, and repeated administration of antidotes. Atropine is an antimuscarinic

Page 4 – Dr. Schuchat, CDC

the Rafa Atropine Auto-Injector, which may be authorized by FDA in consultation with, and with concurrence of, the Division of Neurology Products (DNP)/Office of Drug Evaluation 1 (ODE1)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER), the Counter-Terrorism and Emergency Coordination Staff (CTECS)/Office of the Center Director (OCD)/CDER, and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC).<sup>9</sup>

The authorized Rafa Atropine Auto-Injector is a self-contained unit specially designed for automatic healthcare provider,<sup>10</sup> caregiver,<sup>11</sup> or individual (i.e., self) administration. Each pre-filled auto-injector provides a single dose of atropine. When activated, the authorized 2 mg Rafa Atropine Auto-Injector dispenses 1.67 mg atropine base (equivalent to 2 mg atropine sulfate) in 0.7 mL of sterile pyrogen-free solution through a single needle for rapid intramuscular (IM) administration.

The authorized 2 mg Rafa Atropine Auto-Injector, and any other strengths that are authorized at a later time under this EUA, are authorized to be distributed by CDC, emergency response stakeholders, and DoD for pre-event storage and further redistribution, if appropriate, and for post-event storage, distribution, and administration, when packaged in the authorized manufacturer packaging and with the authorized labeling (e.g., the labels on each auto-injector and box carton, including expiration date, National Drug Code, National Stock Number if needed, bar code, and lot number; and fact sheets), despite the fact that they may not contain information on the prescription label that otherwise would be required under section 503(b)(2) of the Act (21 U.S.C. § 353(b)(2)) (e.g., name and address of dispenser; serial number; date of prescription or of its filling; name of prescriber; name of patient, if stated on prescription;

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agent that antagonizes the muscarine-like actions of acetylcholine and other choline esters. Atropine inhibits the muscarinic actions of acetylcholine on structures innervated by postganglionic cholinergic nerves, on smooth muscles, which respond to endogenous acetylcholine but are not so innervated, and on brain. As with other antimuscarinic agents, the major action of atropine is a competitive or surmountable antagonism, which can be overcome by increasing the concentration of acetylcholine at receptor sites of the effector organ (e.g., by using anticholinesterase agents, which inhibit the enzymatic destruction of acetylcholine). When atropine and pralidoxime (2-PAM) are co-administered, survival is improved due to their synergistic effects.

<sup>9</sup> On the date of issuance of this EUA, the 0.5 mg Rafa Atropine Auto-Injector and 1 mg Rafa Atropine Auto-Injector were not authorized for use under this EUA. However, CDC may request authorization under this EUA of the 0.5 mg and 1 mg strengths at a later time. If FDA authorizes use of the 0.5 mg and 1 mg strengths based on a review of the scientific data, communication about such authorization will be posted on FDA's EUA website at the time of amendment of this EUA (e.g., through a memorandum and updated EUA Fact Sheets).

<https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.

<sup>10</sup> For purposes of this EUA, the term "healthcare provider" includes (i) healthcare professionals who are acting within their professional scope of practice; (ii) healthcare professionals who might otherwise be acting outside of their professional scope of practice in administering the authorized Rafa Atropine Auto-Injector (e.g., physicians not licensed in the state; certain emergency medical technicians, paramedics, physician assistants, nurses, pharmacists, etc.); and (iii) other responders (e.g., firefighters). To the extent feasible and appropriate, healthcare providers should be acting under the authority of the applicable emergency response stakeholder's authority and official emergency response plans when administering the authorized product.

<sup>11</sup> For purposes of this EUA, the term "caregiver" includes individuals who are not healthcare providers as defined in this EUA (e.g., public health agency staff, military service members, volunteers, agents, contractors, family members, co-workers, bystanders, etc.), but who might be the only available individual to administer the Rafa Atropine Auto-Injector to an individual exhibiting symptoms of nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning (e.g., if the demand for patient care exceeds the capacity of available healthcare providers during an emergency response). To the extent feasible and appropriate, caregivers should be acting under the authority of the applicable emergency response stakeholder's official emergency response plans when receiving and administering the authorized product.

Page 5 – Dr. Schuchat, CDC

directions for use and cautionary statements, if contained in the prescription).

The authorized Rafa Atropine Auto-Injector is authorized to be administered without a prescription and by healthcare providers, caregivers, and individuals (i.e., to oneself) under this EUA, despite the fact that it does not meet certain requirements otherwise required by federal law.

The authorized Rafa Atropine Auto-Injector is authorized to be accompanied by the authorized manufacturer's labeling (e.g., the labels on each auto-injector and box carton) developed in consultation with FDA and CDC. The authorized Rafa Atropine Auto-Injector is also authorized to be accompanied by the following information pertaining to the emergency use, which is authorized to be made available to healthcare providers, caregivers, and individuals/patients<sup>12</sup> to facilitate understanding of nerve agent and certain insecticide (organophosphorus and/or carbamate) poisoning, the risks and benefits of the Rafa Atropine Auto-Injector, and proper medication administration:

- Fact Sheet for Healthcare Providers: Use of the 2 mg Rafa Atropine Auto-Injector for Initial Treatment of Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning
- Fact Sheet for Patients and Caregivers: Use of the 2 mg Rafa Atropine Auto-Injector for Initial Treatment of Nerve Agent or Certain Insecticide (Organophosphorus and/or Carbamate) Poisoning

Other Fact Sheets developed by CDC and/or by DoD (e.g., specifically for DoD purposes) in consultation with, and with concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC may be authorized to accompany the above described Rafa Atropine Auto-Injector and to be made available to healthcare providers, caregivers, and individuals/patients, as appropriate.

As described in Section IV below, CDC and DoD are also authorized to make available additional information relating to the emergency use of the authorized Rafa Atropine Auto-Injector that is reasonably consistent with, and does not exceed, the terms of this letter of authorization.

Authorized Rafa Atropine Auto-Injectors are authorized to have their manufacturer labeled expiry dating extended by DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC based on scientific data supporting such an extension.

I have concluded, pursuant to section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of the authorized Rafa Atropine Auto-Injector in the specified population, when used for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) and used consistently with the Scope of Authorization of this letter (Section II), outweigh the known and

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<sup>12</sup> The authorized Fact Sheet for Patients and Caregivers includes information for (i) patients to whom the authorized Rafa Atropine Auto-Injector is administered by healthcare providers or caregivers, (ii) individuals who may need to self-administer the authorized Rafa Atropine Auto-Injector, and (iii) caregivers who may need to administer the authorized Rafa Atropine Auto-Injector to individuals.

Page 6 – Dr. Schuchat, CDC

potential risks of such a product.

I have concluded, pursuant to section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that the authorized Rafa Atropine Auto-Injector may be effective in the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate), when used consistently with the Scope of Authorization of this letter (Section II), pursuant to section 564(c)(2)(A) of the Act.

FDA has reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, and concludes that the authorized Rafa Atropine Auto-Injector, when used for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population (as described in the Scope of Authorization of this letter (Section II)), meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of the authorized Rafa Atropine Auto-Injector under this EUA must be consistent with, and may not exceed, the terms of this letter, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section IV). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the Rafa Atropine Auto-Injector described above is authorized for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population.

This EUA will cease to be effective when the HHS declaration that circumstances exist to justify the EUA is terminated under section 564(b)(2) of the Act or when the EUA is revoked under section 564(g) of the Act.

### **III. Waiver of Certain Requirements**

This letter authorizes use of Rafa Atropine Auto-Injectors as previously manufactured by Rafa under U.S. Government contract as of the date of this letter, as well as authorized Rafa Atropine Auto-Injectors that may be manufactured by Rafa under U.S. Government contract after such date, insofar as the informational visit and testing completed on production quality products provide reasonable assurance that the methods used in, and the facilities and controls used for, the manufacturing, processing, labeling, and packing of the authorized Rafa Atropine Auto-Injector are adequate to preserve its identity, strength, quality, and purity for use of the product under this EUA.

The authorized Rafa Atropine Auto-Injector should be held in accordance with the manufacturer's labeled and appropriate product storage conditions for the product (i.e., ambient temperature, 25°C (77°F), with excursions permitted to 15°C-30°C (59°F-86°F)). In addition, the USP allows for a brief excursion to higher temperatures (i.e., up to 24 hours at up to 40°C (104°F)). However, to ensure the delivery and availability of the authorized Rafa Atropine Auto-Injector in the event of a nerve agent or certain insecticide (organophosphorus and/or carbamate) emergency and a decision on the part of CDC, an emergency response stakeholder(s), or DoD to distribute and administer the product under the terms of this EUA, the authorized Rafa Atropine Auto-Injector may require transportation and/or temporary storage for rapid

Page 7 – Dr. Schuchat, CDC

administration without the capacity to maintain labeled storage conditions in the midst of the response. During such scenarios, the authorized Rafa Atropine Auto-Injector may be stored with temperature excursions up to 40°C (104°F) for a total period of up to 7 days. Significant excursions from the labeled storage conditions should be documented to the extent practicable given the circumstances of an emergency.

#### **IV. Conditions of Authorization**

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

##### **CDC**

- A. CDC will distribute the authorized Rafa Atropine Auto-Injector under its direction to the extent such decisions are consistent with and do not exceed the terms of this letter, including distribution with the authorized labeling.
- B. Through a process of inventory control, CDC will maintain records regarding distribution under its direction of the authorized Rafa Atropine Auto-Injector (i.e., lot numbers, quantity, receiving site, receipt date).
- C. CDC will ensure that the terms of this EUA are made available to emergency response stakeholders and DoD through appropriate means.<sup>13</sup> CDC will provide authorized emergency response stakeholders and DoD a copy of this letter of authorization, and communicate to emergency response stakeholders and DoD any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (e.g., Fact Sheets).
- D. CDC will make available to emergency response stakeholders and DoD through appropriate means the authorized Rafa Atropine Auto-Injector Fact Sheet for Healthcare Providers, the authorized Rafa Atropine Auto-Injector Fact Sheet for Patients and Caregivers, and any other Fact Sheets for emergency response stakeholders that FDA may authorize, as well as any authorized amendments thereto.
- E. CDC may request changes to the authorized Rafa Atropine Auto-Injector Fact Sheet for Healthcare Providers and the authorized Rafa Atropine Auto-Injector Fact Sheet for Patients and Caregivers and may request the development of additional Fact Sheets. Such requests will be made by CDC in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC.
- F. CDC is authorized to issue additional recommendations and instructions related to the emergency use of the authorized Rafa Atropine Auto-Injector as described in this letter of authorization, to the extent that additional recommendations and instructions are necessary to meet public health needs during an event involving susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) and are reasonably consistent with the authorized emergency use of the product.

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<sup>13</sup> For example, through hard copy, web posting, and/or mass media.

Page 8 – Dr. Schuchat, CDC

- G. CDC may request changes to the authorized manufacturer’s labeling (e.g., the labels on each auto-injector and carton) for the authorized Rafa Atropine Auto-Injector, or to the manufacturing, labeling, and packaging processes of Rafa or its authorized agent(s) for the authorized product. Such requests will be made by CDC in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC.
- H. CDC may request the authorization of additional strengths (e.g., 0.5 mg and 1 mg) of the authorized Rafa Atropine Auto-Injector under this EUA. Such requests will be made by CDC in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC.
- I. CDC will inform emergency response stakeholders about the need to have a process in place for performing adverse event monitoring and compliance activities designed to ensure that adverse events and all medication errors associated with the use of the authorized Rafa Atropine Auto-Injector are reported to FDA, to the extent practicable given emergency circumstances, as follows: complete the MedWatch FDA Form 3500 online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), by using a postage-paid MedWatch Form 3500 (available at <https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>), or by calling 1-800-FDA-1088. Submitted reports should state that the Rafa Atropine Auto-Injector was used under an EUA and should provide the strength (e.g., 2 mg) that was administered. CDC will conduct any follow-up requested by FDA regarding adverse events, to the extent feasible given the emergency circumstances.
- J. CDC will ensure that the authorized Rafa Atropine Auto-Injector is distributed for use under its direction within the expiry dating on the manufacturer’s labeling. If FDA authorizes any expiry dating extensions of the authorized Rafa Atropine Auto-Injector under this EUA, CDC will inform emergency response stakeholders and DoD receiving the authorized Rafa Atropine Auto-Injector of such extensions and any conditions related to such extensions under this EUA. CDC will maintain adequate records regarding the expiry dates by which authorized Rafa Atropine Auto-Injectors may be used.
- K. CDC will make available to FDA upon request any records maintained in connection with this EUA.

**Emergency Response Stakeholders to Whom the Authorized Rafa Atropine Auto-Injector Is Distributed**

- L. Emergency response stakeholders will inform their applicable healthcare providers<sup>14</sup> of this letter of authorization, including the terms herein, and of any subsequent amendments that might be made to this letter of authorization and its authorized

<sup>14</sup> As defined earlier, for purposes of this EUA, the term “healthcare provider” includes (i) healthcare professionals who are acting within their professional scope of practice; (ii) healthcare professionals who might otherwise be acting outside of their professional scope of practice in administering the Rafa Atropine Auto-Injector (e.g., physicians not licensed in the state; certain emergency medical technicians, paramedics, physician assistants, nurses, pharmacists, etc.); and (iii) other responders (e.g., firefighters). To the extent feasible and appropriate, healthcare providers should be acting under the authority of the applicable emergency response stakeholder’s authority and official emergency response plans when administering the authorized product.

Page 9 – Dr. Schuchat, CDC

accompanying materials (e.g., Fact Sheets), through appropriate means.

- M. Emergency response stakeholders will inform their applicable healthcare providers that the authorized Rafa Atropine Auto-Injector may be used only for the initial treatment of the muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population.
- N. Emergency response stakeholders will ensure that their applicable healthcare providers administering the authorized Rafa Atropine Auto-Injector will abide by any procedures regarding drug accountability issued by CDC and/or their respective institutions.
- O. Through a process of inventory control, emergency response stakeholders will maintain records of product usage (i.e., lot number, quantity, receiving site, receipt date, and administration date), product storage, and disposition of the authorized product and will maintain records regarding further distribution (if permissible) under their direction of the authorized Rafa Atropine Auto-Injector product.
- P. Emergency response stakeholders will, consistent with any applicable CDC and/or jurisdictional procedures, be responsible for authorizing their applicable healthcare providers to administer the authorized Rafa Atropine Auto-Injector in accordance with the terms of this letter of authorization, including instructing their applicable healthcare providers about the terms of this letter of authorization with regard to pre-event storage and distribution and post-event storage, distribution, and administration, and for instructing them about the means through which they are to obtain the authorized Rafa Atropine Auto-Injector.<sup>15</sup>
- Q. Emergency response stakeholders will include with the authorized Rafa Atropine Auto-Injector the authorized Fact Sheet for Healthcare Providers, the authorized Fact Sheet for Patients and Caregivers, and any other Fact Sheets for emergency response stakeholders that FDA may authorize, as well as any authorized amendments thereto. Under exigent circumstances, these Fact Sheets may be disseminated through other appropriate means (e.g., web posting, mass media). With the exception of DoD-specific Fact Sheets (see Condition FF), changes to the authorized Fact Sheets may be made only by CDC in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC.
- R. Emergency response stakeholders will train their applicable healthcare providers on the use of the authorized Rafa Atropine Auto-Injector in accordance with this EUA and any applicable institutional procedures or protocols. In the event of an emergency during which the authorized Rafa Atropine Auto-Injector may need to be administered by caregivers and/or be self-administered, emergency response stakeholders will inform such caregivers and individuals about the use of the authorized product (e.g., by providing them with the Fact Sheet for Patients and Caregivers and/or just-in-time

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<sup>15</sup> An emergency response stakeholder may also, if permitted by CDC, distribute the authorized product to other public or private entities acting as the agents or delegates of the emergency response stakeholder as part of a public health or medical response. If such distribution occurs, the emergency response stakeholder will be responsible for ensuring that the authorized agents and/or delegates adhere to the emergency response stakeholder conditions and any applicable healthcare provider conditions provided in this letter of authorization.

Page 10 – Dr. Schuchat, CDC

training, instructing healthcare providers how to inform patients and caregivers, etc.), to the extent feasible given the emergency circumstances.<sup>16</sup>

- S. Emergency response stakeholders will track adverse events and report to FDA in accordance with the Fact Sheet for Healthcare Providers (i.e., complete the MedWatch FDA Form 3500 online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), by using a postage-paid MedWatch Form 3500 (available at <https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>), or by calling 1-800-FDA-1088; submitted reports should state that the Rafa Atropine Auto-Injector was used under an EUA and should provide the strength (e.g., 2 mg) that was administered), to the extent feasible given the emergency circumstances. Emergency response stakeholders will conduct any follow-up requested by FDA and/or CDC regarding adverse events, to the extent feasible given the emergency circumstances.
- T. Emergency response stakeholders will track and communicate, to the extent appropriate, any expiry dating extensions of the authorized Rafa Atropine Auto-Injector that FDA may authorize, and that CDC may communicate, under this EUA and any conditions related to such extensions under this EUA. Emergency response stakeholders will maintain adequate records regarding the expiry dates by which authorized Rafa Atropine Auto-Injector may be used.
- U. Emergency response stakeholders will ensure that any records associated with this EUA are maintained until notified by CDC and/or FDA. Such records will be made available to FDA and/or CDC for inspection upon request.

**Healthcare Providers Conducting Activities under the Direction of Emergency Response Stakeholders with Respect to the Authorized Rafa Atropine Auto-Injector<sup>17</sup>**

- V. Healthcare providers conducting activities under the direction of emergency response stakeholders with respect to the authorized Rafa Atropine Auto-Injector will be aware of this letter, including the terms and any authorized amendments thereto. Healthcare providers will read the authorized Fact Sheet for Healthcare Providers prior to administering the authorized Rafa Atropine Auto-Injector, to the extent feasible given the emergency circumstances.
- W. Healthcare providers administering the authorized Rafa Atropine Auto-Injector will ensure that the authorized Fact Sheet for Patients and Caregivers has been made available to patients and/or caregivers through appropriate means, to the extent feasible given the emergency circumstances. In the event of an emergency during which the authorized Rafa Atropine Auto-Injector may need to be administered by caregivers and/or be self-administered, healthcare providers will inform such caregivers and individuals about the use of the authorized product (e.g., by providing them with the Fact Sheet for Patients

<sup>16</sup> As described earlier in this letter of authorization, it is contemplated during some response scenarios that the authorized Rafa Atropine Auto-Injector may need to be administered by caregivers or be self-administered.

<sup>17</sup> The Conditions of Authorization for healthcare providers conducting activities under the direction of emergency response stakeholders with respect to the authorized Rafa Atropine Auto-Injector do not apply to DoD. DoD-specific Conditions of Authorization are provided below.

Page 11 – Dr. Schuchat, CDC

and Caregivers, just-in-time training, etc.), to the extent feasible given the emergency circumstances.

- X. Healthcare providers will administer the authorized Rafa Atropine Auto-Injector only for the initial treatment of the muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population following an intentional terrorism-related or unintentional event.
- Y. Healthcare providers will track adverse events and report to FDA in accordance with the Fact Sheet for Healthcare Providers (i.e., complete the MedWatch FDA Form 3500 online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), by using a postage-paid MedWatch Form 3500 (available at <https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>), or by calling 1-800-FDA-1088; submitted reports should state that the Rafa Atropine Auto-Injector was used under an EUA and should provide the strength (e.g., 2 mg) that was administered), to the extent feasible given the emergency circumstances. Healthcare providers will conduct any follow-up requested by FDA and/or CDC regarding adverse events, to the extent feasible given the emergency circumstances.
- Z. Healthcare providers will ensure that any records associated with the use of this product under this EUA are maintained, to the extent feasible given the emergency circumstances, until notified by FDA and/or CDC. Such records will be made available to FDA and/or CDC for inspection upon request.

#### **DoD**

- AA. DoD may distribute the authorized 2 mg Rafa Atropine Auto-Injector product under its direction to DoD components to the extent such decisions are consistent with and do not exceed the terms of this letter, including distribution with the authorized labeling.
- BB. DoD will ensure that the terms of this EUA are made available to applicable DoD components through appropriate means. DoD will provide applicable DoD components a copy of this letter of authorization, and communicate to such components any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (e.g., Fact Sheets for DoD-only use).
- CC. DoD will inform applicable DoD components that the authorized Rafa Atropine Auto-Injector may be used only for the initial treatment of the muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) in the specified population.
- DD. Through a process of inventory control, DoD will maintain records regarding distribution and use under its direction of the authorized Rafa Atropine Auto-Injector (i.e., lot number, quantity, receiving site, receipt date, and administration date), product storage, and disposition of the authorized product, to the extent feasible given the emergency circumstances.

Page 12 – Dr. Schuchat, CDC

- EE. DoD will make available through applicable DoD communication channels and procedures the authorized Rafa Atropine Auto-Injector Fact Sheets and/or authorized DoD-specific Rafa Atropine Auto-Injector Fact Sheet(s), as well as any authorized amendments thereto. Under exigent circumstances, other appropriate means for disseminating these Fact Sheets may be used.
- FF. DoD may request the development and use of a Fact Sheet(s) for DoD-specific purposes for the authorized 2 mg Rafa Atropine Auto-Injector. Such requests will be made by DoD in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC. DoD will inform CDC of such requests. Changes to any authorized DoD-specific Rafa Atropine Auto-Injector Fact Sheets may be made only by DoD in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC. DoD will also inform CDC of such changes. Such DoD-specific Rafa Atropine Auto-Injector Fact Sheets will not be used by non-DoD emergency response stakeholders.
- GG. DoD will be responsible for authorizing components acting as part of a DoD response to administer the authorized Rafa Atropine Auto-Injector in accordance with the terms of this EUA, including instructing such components about the terms of this EUA with regard to pre-event storage and distribution and post-event storage, distribution, and administration, and for instructing them about the means through which they are to obtain and use the authorized Rafa Atropine Auto-Injector.
- HH. DoD is authorized to issue additional recommendations and instructions related to the DoD-specific emergency use of the authorized Rafa Atropine Auto-Injector as described in this letter of authorization, to the extent that additional recommendations and instructions are necessary to meet military needs during an event involving susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate) and are reasonably consistent with the authorized emergency use of the product.
- II. DoD will train applicable DoD components and/or personnel on the use of the authorized Rafa Atropine Auto-Injector in accordance with this EUA and any applicable DoD procedures or protocols.
- JJ. DoD, through applicable DoD components, will track adverse events and report to FDA (e.g., by completing the MedWatch FDA Form 3500 online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), by using a postage-paid MedWatch Form 3500 (available at [https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting\\_home](https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting_home)), or by calling 1-800-FDA-1088; submitted reports should state that the Rafa Atropine Auto-Injector was used under an EUA and should provide the strength (i.e., 2 mg) that was administered), to the extent feasible given the emergency circumstances. DoD will conduct any follow-up requested by FDA and/or CDC regarding adverse events, to the extent feasible given the

Page 13 – Dr. Schuchat, CDC

emergency circumstances.

- KK. DoD will ensure that the authorized Rafa Atropine Auto-Injector is distributed for use under its direction within the expiry dates on the manufacturer’s labeling. If FDA authorizes any expiry dating extensions of the authorized Rafa Atropine Auto-Injector under this EUA, DoD will inform DoD components receiving the authorized Rafa Atropine Auto-Injector of such extensions and any conditions related to such extensions under this EUA. DoD will maintain adequate records regarding the expiry dates by which authorized Rafa Atropine Auto-Injector may be used.
- LL. DoD will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to FDA for inspection upon request.

**Rafa**

- MM. Rafa is authorized to have Shalon Chemical Industries Ltd. as its authorized agent under this EUA. Rafa may request an additional authorized agent(s) related to its production and/or distribution of the authorized Rafa Atropine Auto-Injector under this EUA. Such requests will include the name, address, phone number, and role of any proposed authorized agent(s) and will be made to FDA by CDC and/or Rafa in consultation with, and require concurrence of, DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC. Rafa will also notify FDA and CDC before beginning to use such agent(s) as may be authorized by FDA.
- NN. Rafa will post on its website the following statement: “For information about the FDA-authorized emergency use of the Rafa Atropine Auto-Injector, please see: <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm>.” Rafa will ensure that any website references to the authorized Rafa Atropine Auto-Injector by its authorized agent(s) will include the same statement.
- OO. Rafa will distribute the authorized Rafa Atropine Auto-Injector under this EUA only under U.S. Government contract to CDC and/or CDC’s designee(s) and subject to terms of this letter.
- PP. Rafa will contact CDC for CDC to request FDA review and concurrence before any changes are made to the manufacturer’s labeling (e.g., the labels on each auto-injector and carton) for the authorized product, and before any changes are made to its manufacturing, labeling, and packaging processes, or any such processes of its authorized agent(s), for the authorized product (see Condition G).
- QQ. Rafa may submit additional data to FDA through CDC to support the authorization of additional strengths of the Rafa Atropine Auto-Injector. Upon

Page 14 – Dr. Schuchat, CDC

review of this data and DNP/ODE1/OND/CDER, CTECS/OCD/CDER, and OCET/OCS/OC concurrence (as described above in Condition H), Rafa and its authorized agent(s) will be authorized to manufacture and distribute under U.S. Government contract the additional strengths of the Rafa Atropine Auto-Injector subject to the terms set forth in this letter of authorization and any subsequent amendments to this letter.

- RR. Rafa will promptly notify FDA and CDC of any suspected or confirmed quality, manufacturing, distribution, and/or other issues with the authorized Rafa Atropine Auto-Injector, including such issues associated with its authorized agent(s), of which it becomes aware.
- SS. Rafa will make available to FDA and, as reasonably appropriate, to CDC upon request any records maintained in connection with this letter. Upon request, Rafa will report to FDA and/or, as reasonably appropriate, to CDC information on the authorized Rafa Atropine Auto-Injector (e.g., with respect to the quality, manufacturing, distribution, emergency use, etc. of the authorized product, including activities related to its authorized agent(s)).

**Conditions Related to Advertising and Promotion**

- TT. All advertising and promotional descriptive printed matter relating to the use of the authorized Rafa Atropine Auto-Injector shall be consistent with the Fact Sheets, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.
- UU. All advertising and promotional descriptive printed matter relating to the use of the authorized Rafa Atropine Auto-Injector shall clearly and conspicuously state that:
- This product has not been FDA approved or cleared;
  - This product has been authorized by FDA under an EUA for use by CDC, emergency response stakeholders, and DoD;
  - This product has been authorized only for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate), not for any other agents, viruses, or pathogens; and
  - This product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

No advertising or promotional descriptive printed matter relating to the use of the authorized Rafa Atropine Auto-Injector may represent or suggest that this product is safe or effective for

Page 15 – Dr. Schuchat, CDC

the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate).

The emergency use of the authorized Rafa Atropine Auto-Injector as described in this letter of authorization must comply with the conditions and all other terms of this authorization.

**V. Duration of Authorization**

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of injectable treatments for nerve agent or certain insecticide (organophosphorus and/or carbamate) poisoning is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Sincerely,



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Stephen M. Ostroff, M.D.  
Acting Commissioner of Food and Drugs

Enclosures

Dated: June 26, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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