DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

November 19, 2009

Thomas R. Frieden, MD, MPH
Director
Centers for Disease Control and Prevention
1600 Clifton Rd, MS D-14
Atlanta, GA 30333

Dear Dr. Frieden:

On October 23, 2009, a letter was issued authorizing the emergency use of the unapproved drug peramivir in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for the emergency use of peramivir administered intravenously for treatment of 2009 H1N1 influenza virus (hereafter "2009 H1N1") in certain adult and pediatric patients, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3). FDA has received inquiries related to the recommended dosing for patients with renal impairment. The purpose of this letter is to amend the Fact Sheet for Health Care Providers to provide additional clarification regarding the dosing recommendations for IV peramivir in patients with severe renal impairment, including those who require continuous renal replacement therapy or hemodialysis. The amended authorized version of the Fact Sheet for Health Care Providers is enclosed with this letter. In addition, this version of the letter includes minor editorial changes. The letter of authorization, as amended, appears below in its entirety:

This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for the emergency use of the unapproved drug peramivir administered intravenously for treatment of 2009 H1N1 influenza virus (hereafter "2009 H1N1") in certain adult and pediatric patients, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 360bbb-3).

On April 26, 2009, pursuant to section 564(b)(1)(C) of the Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the then Acting Secretary of the Department of Health and Human Services (HHS) determined that a public health emergency exists involving Swine Influenza A (now referred to as "2009 H1N1") that affects or has significant potential to affect national security. The Secretary has renewed the determination. Pursuant to section 564(b) of the Act (21 U.S.C. § 360bbb-3(b)), and on the basis of such determination, the Secretary of HHS declared an emergency justifying the authorization of the emergency use of the antiviral peramivir, accompanied by emergency use information, subject to the terms of any authorization issued under section 564(a) of the Act (21 U.S.C. § 360bbb-3(a)).

Having consulted with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), and having concluded that the criteria for issuance of this authorization under section 564(c) of the Act (21 U.S.C. § 360bbb-3(b)) are met, I am

authorizing the emergency use of peramivir[1] administered intravenously for treatment of 2009 H1N1 in certain adult and pediatric patients, subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of peramivir administered intravenously for treatment of 2009 H1N1 in certain adult and pediatric patients meets the criteria for issuance of an authorization under section 564(c) of the Act, because I have concluded that:

(1) 2009 H1N1 can cause influenza, a serious or life-threatening disease or condition;

(2) based on the totality of scientific evidence available to FDA, it is reasonable to believe that peramivir may be effective when administered intravenously for the treatment of 2009 H1N1 in certain adult and pediatric patients, and that the known and potential benefits of peramivir, when administered intravenously for the treatment of 2009 H1N1 in certain adult and pediatric patients, outweigh the known and potential risks of peramivir; and

(3) there is no adequate, approved, and available alternative to the emergency use of peramivir administered intravenously for the treatment of 2009 H1N1 in certain adult and pediatric patients.[2]

Therefore, I have concluded that the emergency use of peramivir administered intravenously for the treatment of 2009 H1N1 in certain adult and pediatric patients meets the above statutory criteria for issuance of an authorization.

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 emergency use of authorized peramivir for the treatment of 2009 H1N1 in certain adult and pediatric patients. The emergency use of authorized peramivir 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.

Peramivir (a neuraminidase inhibitor) is an unapproved drug that it is currently being studied in clinical investigations. Peramivir is not currently approved by FDA for any use in the United States.

<u>The authorized peramivir is as follows:</u>

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[1] FDA is authorizing the emergency use of peramivir administered intravenously for treatment of 2009 H1N1 in certain adult and pediatric patients as described in the scope section of this letter (Section II of this letter). For ease of reference, this letter of authorization will also use the term "authorized peramivir."

[2] No other criteria of issuance have been prescribed by regulation under section 564(c)(4) of the Act.

- Peramivir injection: 200mg/20mL (10 mg/mL) single use vial manufactured for BioCryst Pharmaceuticals, Inc. (BioCryst). (See Section IV.D.3. of this letter).

1. The above peramivir product is authorized only for intravenous (IV) administration.

2. The above peramivir product is authorized for the treatment of certain patients with suspected or laboratory confirmed 2009 H1N1 infection or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Specifically, the peramivir product is authorized only for the following patients who are admitted to a hospital and under the care or consultation of a licensed clinician (skilled in the diagnosis and management of patients with potentially life-threatening illness and the ability to recognize and manage medication-related adverse events):
   a. Adult patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:
      (i) patient not responding to either oral or inhaled antiviral therapy, or
      (ii) drug delivery by a route other than IV (e.g., enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or
      (iii) the clinician judges IV therapy is appropriate due to other circumstances.
   b. Pediatric patients for whom an IV agent is clinically appropriate because:
      (i) patient not responding to either oral or inhaled antiviral therapy, or
      (ii) drug delivery by a route other than IV (e.g., enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.

3. The above peramivir product may only include product distributed from Strategic National Stockpile (SNS), in which case such product is authorized only to be labeled with the enclosed label.

4. The above peramivir product is authorized to be accompanied by the following written information pertaining to the emergency use, which is enclosed and authorized to be made available to health care providers and patients (and parents/caregivers):

- Fact Sheet for Health Care Providers
- Fact Sheet for Patients and Parents/Caregivers

CDC, hospitals, and health care providers receiving authorized peramivir are also authorized to make available additional written information relating to the emergency use of authorized peramivir that is consistent with and does not exceed the terms of this letter of authorization (including the above referenced facts sheets).

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 authorized peramivir, when used for the treatment of H1N1 in certain adult and pediatric patients, outweigh the known and potential risks of such 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 peramivir may be effective for the treatment of 2009 H1N1 in certain adult and pediatric patients pursuant to section 564(c)(2)(A) of the Act. FDA has reviewed the scientific information available, including the information supporting the conclusions described in Section I of this letter above,

and concludes that the authorized peramivir when used for the treatment of 2009 H1N1 in certain adult and pediatric patients, meets the criteria set forth in section 564(c) of the Act concerning safety and potential effectiveness.

Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under section 564(b)(1), the peramivir described above is authorized for the treatment of 2009 H1N1 in certain adult and pediatric patients.

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

III. Current Good Manufacturing Practice

This letter covers authorized peramivir as previously manufactured for BioCryst as of the date of this letter as well as authorized peramivir that may be manufactured for BioCryst after such date, insofar as FDA has determined that the methods used in, and the facilities and controls used for, the manufacturing, processing and packing of authorized peramivir are adequate to preserve its identity, strength, quality and purity.

Authorized peramivir should be held in accordance with its labeled and appropriate product storage conditions (ambient temperature, 15°C-30°C or 59°F-86°F). However, in order to ensure the delivery and availability of authorized peramivir, I am waiving current good manufacturing practice (CGMP) requirements with respect to proper storage conditions of temperature during the shipment and holding of authorized peramivir by CDC and/or its designees for a maximum of 90 days (consecutive or non-consecutive) from the date of shipment to CDC and/or its designees. Significant excursions from labeled storage conditions should be documented to the extent practicable given the circumstances of the emergency, and need not be supported by additional testing by CDC or its designees.

IV. Conditions of Authorization

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

A. CDC

A.1. CDC will decide how authorized peramivir will be distributed under its direction to Hospitals upon request by licensed treating clinicians at the Hospitals to the extent such decisions are consistent with and do not exceed the terms of this letter; except that CDC will ensure that authorized peramivir will be distributed to Hospitals as soon as possible within 24 hours of CDC's decision to distribute such product, to the extent practicable given the circumstances of the emergency.

A.2. CDC will maintain adequate records regarding distribution under its direction of authorized peramivir (i.e., lot numbers, quantity, receiving site, receipt date, unique identifier(s) (e.g., Peramivir Request number(s))).

A.3. CDC will notify FDA on a weekly basis (unless otherwise specified by FDA) of the quantity of and to which Hospitals authorized peramivir is distributed under its direction. CDC will also include in the notification the unique identifier(s) (e.g., Peramivir Request number(s)).

A.4. CDC will ensure that authorized peramivir is distributed for use under its direction only within the expiry dates identified by FDA. CDC will inform Hospitals receiving authorized peramivir under its direction of the expiry dates by which authorized peramivir is to be used if authorized peramivir is nearing expiry. CDC will maintain adequate records regarding the expiry dates by which authorized peramivir is to be used.

A.5. CDC will ensure that Hospitals receiving authorized peramivir under its direction are informed of this letter, including the terms and conditions as well as any authorized amendments thereto.

A.6. CDC will make available through appropriate means to the Hospitals receiving authorized peramivir under its direction the authorized Fact Sheet for Health Care Providers and Fact Sheet for Patients and Parents/Caregivers as well as any authorized amendments thereto.

A.7. CDC will perform adverse event monitoring and compliance activities (e.g., follow-up surveys) designed: (1) to ensure that selected adverse events and all medication errors associated with the use of authorized peramivir are reported to FDA as follows: the MedWatch FDA Form 3500 must be completed either online at www.fda.gov/medwatch/report.htm **or** by using a postage-paid FDA Form 3500 (available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf) and returning by fax (1-800-FDA-0178) **or** by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787). If there is no online internet access such reports must be made by calling 1-800-FDA-1088; (2) to ensure that such reports include in the description section of the MedWatch Form 3500 the words "Peramivir EUA" and include unique identifier(s) (e.g., Peramivir Request number(s)), and (3) to ensure that such reports are made within seven calendar days from the onset of the event. CDC will report such information to FDA upon request.

A.8. CDC will only make available additional written information relating to the emergency use of authorized peramivir to the extent that it is consistent with and does not exceed the terms of this letter (including the facts sheets referenced in Section II of this letter).

A.9. CDC will make available to FDA upon request any records maintained in connection with this letter.

B. Hospitals to Which Authorized Peramivir is Distributed

B.1 Such Hospitals will make available through appropriate means to relevant health care providers this letter, including the terms and conditions as well as any authorized amendments thereto.

B.2. Such Hospitals will make available through appropriate means to relevant health care providers and patients and/or parents/caregivers the authorized Fact Sheet for Health Care Providers and Fact Sheet for Patients and Parents/Caregivers as well as any authorized amendments thereto.

B.3. Such Hospitals will ensure that relevant health care providers abide by the institutional procedures regarding drug accountability. Such Hospitals will maintain adequate records showing receipt, use, and disposition of authorized peramivir.

B.4. Such Hospitals will ensure that the emergency use of authorized peramivir is limited to patients who are under the care or consultation of a licensed clinician (e.g., skilled in the diagnosis and management of patients with systemic illness, including recognition and management of medication-related adverse events).

B.5. Such Hospitals will conduct any follow-up requested by FDA and/or CDC regarding medication errors and adverse events.

B.6. Such Hospitals will only make available additional written information relating to the emergency use of authorized peramivir to the extent that it is consistent with and does not exceed the terms of this letter of authorization (including the facts sheets referenced in Section II of this letter).

B.7. Such Hospitals will make available to FDA and/or CDC upon request any records maintained in connection with this letter. Upon request, such Hospitals will report to FDA and/or CDC information with respect to the emergency use of authorized peramivir.

C. Health Care Providers Conducting Activities With Respect to Authorized Peramivir[3]

C.1. Health Care Providers will be aware of this letter, including the terms and conditions as well as any authorized amendments thereto. Health Care Providers will read the Fact Sheet for Health Care Providers, including the sections on Mandatory Requirements for Peramivir Administration Under Emergency Use Authorization and Considerations Prior to Peramivir Use Under EUA as well as any amendments thereto. (See Fact Sheet for Health Care Providers).

C.2. Health Care Providers prescribing and/or administering authorized peramivir will ensure that the authorized Fact Sheet for Patients and Parents/Caregivers, as well as any authorized amendments thereto, have been made available to patients and/or parents/caregivers through appropriate means. Such Health Care Providers (to the extent practicable given the circumstances of the emergency) will document in the patient's

[3] The activities with respect to authorized peramivir refer to requesting, preparing, prescribing, and/or administering authorized peramivir, unless otherwise specified.

medical record that: (a) patients/caregivers have been given the Fact Sheet for Patients and Parents/Caregivers, (b) patients/caregivers have been informed of the alternatives to receiving authorized peramivir, and (c) patients/caregivers have been informed that peramivir is an unapproved drug that is authorized for use under Emergency Use Authorization.

C.3. Prescribing Health Care Providers (or their designees) will ensure that: (1) selected adverse events and all medication errors associated with the use of authorized peramivir are reported as follows: the MedWatch FDA Form 3500 must be completed either online at www.fda.gov/medwatch/report.htm **or** by using a postage-paid FDA Form 3500 (available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf) and returning by fax (1-800-FDA-0178) **or** by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787). If there is no online internet access such reports must be made by calling 1-800-FDA-1088; (2) that such reports include in the description section of the MedWatch Form 3500 the words "Peramivir EUA" and include unique identifier(s) (e.g., Peramivir Request number(s)); and (3) that such reports are made within seven calendar days from the onset of the event. Such Health Care Providers or their designees will conduct any follow-up requested by FDA and/or CDC.

C.4. Health Care Providers will prescribe and/or administer authorized peramivir only for the treatment of certain patients with suspected or laboratory confirmed 2009 H1N1 infection or infection due to nonsubtypable influenza A virus suspected to be 2009 H1N1 based on community epidemiology. Specifically, peramivir is authorized only for the following patients who are admitted to a hospital and under the care or consultation of a licensed clinician (skilled in the diagnosis and management of patients with potentially life-threatening illness and the ability to recognize and manage medication-related adverse events):

a. Adult patients for whom therapy with an IV agent is clinically appropriate, based upon one or more of the following reasons:
   (i) patient not responding to either oral or inhaled antiviral therapy, or
   (ii) drug delivery by a route other than IV (e.g., enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible, or
   (iii) the clinician judges IV therapy is appropriate due to other circumstances.

b. Pediatric patients for whom an IV agent is clinically appropriate because:
   (i) patient not responding to either oral or inhaled antiviral therapy, or
   (ii) drug delivery by a route other than IV (e.g., enteral oseltamivir or inhaled zanamivir) is not expected to be dependable or is not feasible.

C.5. Health Care Providers will ensure that patients with known or suspected renal insufficiency have creatinine clearance determined prior to peramivir dose calculation and first administration. (See Fact Sheet For Health Care Providers; Dosage and Administration for Impaired Renal Function Dosing).

C.6. Health Care Providers prescribing and/or administering authorized peramivir will ensure that patients with history of severe allergic reaction to any other neuraminidase inhibitor

(zanamivir or oseltamivir) or any ingredient of peramivir will not receive authorized peramivir. (See Fact Sheet for Health Care Providers; Product Description.)

C.7. Health Care Providers will only make available additional written information relating to the emergency use of authorized peramivir to the extent that it is consistent with and does not exceed the terms of this letter of authorization (including the facts sheets referenced in Section II of this letter).

C.8. Heath Care Providers will make available to FDA and/or CDC upon request any records maintained in connection with this letter. Upon request, Health Care Providers will report to FDA and/or CDC information with respect to the emergency use of authorized peramivir.

D. BioCryst

D.1. BioCryst will post on its website the following statement: "For information about the FDA-authorized emergency use of peramivir, please see www.cdc.gov/h1n1flu/eua."

D.2. BioCryst will distribute authorized peramivir only to CDC and/or its designees subject to the terms and conditions of this letter.

D.3 BioCryst will contact FDA concerning the need for any FDA review and approval before any changes are made to the manufacturing, packaging, and labeling processes authorized as of the date of this letter.

D.4. BioCryst (or anyone acting on behalf of BioCryst) will not represent authorized peramivir in a promotional context or otherwise promote authorized peramivir.

D.5. BioCryst will make available to FDA and (as reasonably appropriate) CDC upon request any records maintained in connection with this letter. Upon request, BioCryst will report to FDA and/or (as reasonably appropriate) CDC information with respect to the emergency use of authorized peramivir.

The emergency use of authorized peramivir as described in this letter of authorization must comply with the conditions above and all other terms of this authorization.

V. Duration of Authorization

This EUA will be effective until the declaration of emergency is terminated under section 564(b)(2) of the Act or the EUA is revoked under section 564(g) of the Act.

Joshua M. Sharfstein

Joshua M. Sharfstein, M.D.
Principal Deputy Commissioner
Food and Drugs