from his nephrologist explaining that he has ''chronic kidney disease with unknown oetiology [*sic*].'' Also included in his petition was a press release issued by the WTC–CHEST Program at Icahn School of Medicine at Mount Sinai (Mount Sinai) describing a forthcoming study by Mary Ann McLaughlin and others, finding a ''significant link between a high level of exposure to particulate matter by first responders at Ground Zero and the increased level of the protein albumin in their urine.'' [3] The anticipated study findings are described in an abstract supplement to the *Journal of the American Society of Nephrology*.[4]

C. Administrator's Determination on Petition 003

The Administrator has established a methodology for evaluating whether to add non-cancer health conditions to the List of WTC-Related Health Conditions.[5] A health condition may be added to the List if published, peer-reviewed epidemiologic evidence provides substantial support for a causal relationship between 9/11 exposures and the health condition in 9/11-exposed populations.[6] If the epidemiologic evidence provides modest support for a causal relationship between 9/11 exposures and the health condition, the Administrator may then evaluate studies of associations between the health condition and 9/11 agents.[7] If that additional assessment establishes substantial support for a causal relationship between a 9/11 agent or agents and the health condition, the health condition may be added to the List.

In accordance with § 3312(a)(6)(B) of the PHS Act and 42 CFR 88.17, described above, the Administrator has reviewed the evidence presented in Petition 003. The Administrator has also conducted a search of the existing scientific/medical literature for evidence that could establish a causal relationship between 9/11 exposure and kidney damage/disease. He did not find any peer-reviewed, published epidemiologic studies of 9/11-exposed populations supporting such an relationship. While the information reported in the McLaughlin *et al.* abstract is an important first step in scientific inquiry, the Administrator finds that an abstract is insufficient to serve as the scientific basis for adding an entire class of health conditions—chronic kidney damage/disease—to the List.

Because the McLaughlin *et al.* abstract is found to be insufficient to scientifically support the further consideration of kidney damage/disease and because it is clear to the Administrator that the scientific literature on 9/11 exposed-populations does not support a causal relationship between that exposure and kidney damage/disease, the Administrator has determined that requesting a recommendation from the STAC (pursuant to PHS Act, § 3312(a)(6)(B)(i) and 42 CFR 88.17(a)(2)(i)) is unwarranted. In prior actions, the Administrator requested a recommendation from the STAC when he determined that it would assist his evaluation; such as when, for example, the Administrator is in need of an interpretation of conflicting or inconclusive published scientific evidence.

Similarly, the Administrator has determined that insufficient evidence exists to take further action, including either proposing the addition of kidney damage/disease to the List (pursuant to PHS Act, § 3312(a)(6)(B)(ii) and 42 CFR 88.17(a)(2)(ii)) or publishing a determination not to publish a proposed rule in the **Federal Register** (pursuant to PHS Act, § 3312(a)(6)(B)(iii) and 42 CFR 88.17(a)(2)(iii)). In order to publish such a proposed addition or a determination not to propose a rule, the Administrator would first need to find that enough scientific evidence is available to analyze whether 9/11 exposures are associated with the health condition. Since the Administrator is unable to identify sufficient evidence to conduct an analysis of whether to add the health condition, the Administrator (pursuant to PHS Act, § 3312(a)(6)(B)(iv) and 42 CFR 88.17(a)(2)(iv)) is publishing a determination that he cannot take any of the other statutory and regulatory actions.

For the reasons discussed above, the request made in Petition 003 to add kidney damage/disease to the List of WTC-Related Health Conditions is denied.

Dated: March 24, 2014.

John Howard,

Administrator, World Trade Center Health Program and Director, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.

[FR Doc. 2014–06906 Filed 3–28–14; 8:45 am]

BILLING CODE 4163–18–P

[3] Mount Sinai Hospital [November 9, 2013]. Kidney Damage in First Responders Linked to September 11. *http://www.mountsinai.org/about-us/newsroom/press-releases/kidney-damage-in-first-responders-linked-to-september-11*.

[4] McLaughlin MA, Sanghavi S, Maceda C, Woodward M, Crowley LE, Wyatt CM [2013]. New Evidence that Particulate Matter Exposure at Ground Zero is Associated with Kidney Damage.'' J Am Soc Nephrol 24:663A. See *http://www.asn-online.org/education/kidneyweek/archives/*.

[5] This methodology, ''Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions,'' is available on the WTC Health Program Web site, at *http://www.cdc.gov/wtc/policies.html*.

[6] The substantial evidence standard is met when the Program assesses all of the available, relevant information and determines with high confidence that the evidence supports its findings regarding a causal association between the 9/11 exposure(s) and the health condition.

[7] The modest evidence standard is met when the Program assesses all of the available, relevant information and determines with moderate confidence that the evidence supports its findings regarding a causal association between the 9/11 exposure(s) and the health condition.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 110

RIN 0906–AA79

Countermeasures Injury Compensation Program: Pandemic Influenza Countermeasures Injury Table

AGENCY: Health Resources and Services Administration (HRSA), HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Public Readiness and Emergency Preparedness Act (PREP Act) directs the Secretary of Health and Human Services (the Secretary), to establish a Countermeasures Injury Compensation Program (the Program) to provide ''timely, uniform, and adequate compensation'' to eligible individuals who sustain serious physical injuries or to certain survivors of individuals who die as a direct result of the use or administration of covered countermeasures identified by the Secretary in declarations issued under the PREP Act. The Secretary has delegated authority to administer the Program to the Health Resources and Services Administration (HRSA). Through this regulation, the Secretary proposes a Table for pandemic influenza covered countermeasures identified by the Secretary in several PREP Act declarations. This regulation also includes proposed Table time intervals for the first symptom or manifestation of onset of injury, Table injury definitions, and requirements which define the terms and conditions included on the Table. These are considered part of the proposed Table.

DATES: Written comments must be submitted on or before May 30, 2014. Subject to consideration of the comments received, the Secretary intends to publish a final regulation.

ADDRESSES: You may submit comments in one of three ways, as listed below.

Please submit your comments in only *one* of these ways to minimize the receipt of duplicate submissions. The first is the preferred method.

1. Federal eRulemaking Portal. You may submit comments electronically to *www.regulations.gov*. Click on the link ''[S]ubmit electronic comments on HRSA regulations with an open comment period.'' You may submit attachments to your comments in any file format accepted by Regulations.gov.

2. By regular, express, or overnight mail. You may mail written comments to the following address only: Health Resources and Services Administration, Department of Health and Human Services, Attention: HRSA Regulations Officer, Parklawn Building, Room 14–101, 5600 Fishers Lane, Rockville, MD 20857. Please allow sufficient time for mailed comments to be received before the close of the comment period.

3. Delivery by hand (in person or by courier). If you prefer, you may deliver your written comments before the close of the comment period to the same address: Parklawn Building, Room 14–101, 5600 Fishers Lane, Rockville, MD 20857. Please call in advance to schedule your arrival with one of our HRSA Regulations Office staff members at telephone number (301) 443–1785. This is not a toll-free number.

Because of staffing and resource limitations, and to ensure that no comments are misplaced, the Program cannot accept comments by facsimile (FAX) transmission. When commenting by any of the above methods, please refer to file code: #0906–AA79. Comments received on a timely basis will be available for public inspection as they are received, beginning approximately three weeks after publication of this notice, online at *www.regulations.gov* or in person at: Parklawn Building, Room 14–101 of the Health Resources and Services Administration's offices at 5600 Fishers Lane, Rockville, MD on Monday through Friday of each week from 8:30 a.m. to 5 p.m. (excluding Federal holidays). Phone: (301) 443–1785. This is not a toll-free number.

FOR FURTHER INFORMATION CONTACT: Please visit the Countermeasures Injury Compensation Program's Web site, *http://www.hrsa.gov/cicp/*, or contact Dr. Vito Caserta, Director, Countermeasures Injury Compensation Program, Healthcare Systems Bureau, HRSA, Parklawn Building, Room 11C–06, 5600 Fishers Lane, Rockville, MD 20857. Phone calls can be directed to (855) 266–2427. This is a toll-free number.

SUPPLEMENTARY INFORMATION: The President encourages Federal agencies through Executive Order 13563 to develop balanced regulations by encouraging broad public participation in the regulatory process and an open exchange of ideas. The Department of Health and Human Services accordingly urges all interested parties to examine this regulatory proposal carefully and to share your views with us, including any data to support your positions. If you have questions before submitting comments, please see the ''For Further Information'' box below for the names and contact information of subject matter experts involved in this proposal's development. We must consider all written comments received during the comment period before issuing a final rule.

If you are a person with a disability and/or a user of assistive technology who has difficulty accessing this document, please see the ''For Further Information'' box below for the names and contact information to obtain this information in an accessible format. Please visit *http://www.HHS.gov/regulations* for more information on HHS rulemaking and opportunities to comment on proposed and existing rules.

The PREP Act (Pub. L. 109–148) directs the Secretary to establish, through regulations, a Covered Countermeasures Injury Table (Table) identifying serious physical injuries that are presumed to be directly caused by the administration or use of covered countermeasures identified in PREP Act declarations issued by the Secretary. The Secretary may only add injuries to a Table if it is determined based on ''compelling, reliable, valid, medical and scientific evidence'' that the administration or use of the covered countermeasure directly causes such covered injuries.[1] Such a Table informs the public about serious physical injuries supported by medical and scientific evidence known to be directly caused by covered countermeasures. In addition, such a Table creates a rebuttable presumption of causation, for compensation purposes, for eligible individuals whose injuries are listed on a Table and meet the requirements of a Table.

Background

The Public Readiness and Emergency Preparedness Act of 2005 (PREP Act), part of the ''Department of Defense, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006,'' Public Law 109–148, establishes liability protections for certain covered persons and authorizes the payment of benefits to eligible individuals injured by covered countermeasures. Both liability protections and compensation are available under the PREP Act based on the terms of the PREP Act declarations (hereafter declarations or Secretarial declarations) issued by the Secretary of Health and Human Services (the Secretary).

The purpose of a Secretarial declaration is to identify a disease, health condition, or a threat to health that is currently, or may in the future constitute, a public health emergency. In addition, the Secretary, through a declaration, may recommend and encourage the development, manufacturing, distribution, dispensing, and administration or use of one or more covered countermeasures to treat, prevent, or diagnose the disease, condition, or threat specified in the declaration.[2]

This notice of proposed rulemaking (NPRM) concerns only the compensation program authorized by the PREP Act, not the liability protections set forth therein. Specifically, the PREP Act authorizes the Secretary to establish and administer this program to provide timely, uniform, and adequate compensation to certain individuals who develop serious physical injuries or to certain survivors of individuals who die as a direct result of the use or administration of a covered countermeasure identified in a Secretarial declaration.[3] The Secretary delegated responsibility for establishing and administering the Program to HRSA, within the Department of Health and Human Services (HHS).

The PREP Act authorizes the Secretary to publish regulations to establish and administratively implement the Program. Specifically, the PREP Act authorizes the Secretary to determine Program eligibility, the process to apply for benefits, the methods of payments and amounts of compensation, and the process for further review of Requests for Benefits submitted by, or on behalf of, requesters. To be considered for compensation for any serious physical injury or death, an individual must

[1] Section 319F–4(b)(5)(A) of the Public Health Service Act, as amended (42 U.S.C. 247d–6e(b)(5)(A)).

[2] Section 319F–3(b) of the PHS Act (42 U.S.C 247d–6d(b)).

[3] Section 319F–4(a) of the PHS Act (42 U.S.C. 247d–6e(a)).

submit a Request for Benefits with the required information.

The Secretary published the interim final rule implementing the Program on October 15, 2010.[4] This rule, which was published as a final rule on October 7, 2011, explains the Program's policies, procedures, and requirements. Title 42 of the Code of Federal Regulations (CFR) § 110.20(a) states that individuals must establish that a covered injury occurred in order to be eligible for benefits under the Program. A covered injury is death or a serious injury determined by the Secretary to be: (1) An injury meeting the requirements of a Covered Countermeasures Injury Table, which is presumed to be the direct result of the administration or use of a covered countermeasure unless the Secretary determines there is another more likely cause; or (2) an injury (or its health complications) that is the direct result of the administration or use of a covered countermeasure. This includes serious aggravation caused by a covered countermeasure of a pre-existing condition. 42 CFR 110.3(g).

Serious injury means serious physical injury. Physical biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, be considered serious injuries. As a general matter, only injuries that warranted hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability (whether or not hospitalization was warranted) will be considered serious injuries. 42 CFR 110.3(z).

Through this NPRM, the Secretary proposes adding subpart K to 42 CFR part 110, which had been reserved for the purpose of creating an Injury Table for covered countermeasures. These countermeasures are identified in Secretarial declarations relating to pandemic influenza, including influenza caused by the 2009 H1N1 pandemic influenza virus (hereafter referred to as the 2009 H1N1 virus), and other potential pandemic strains, such as H5N1 avian influenza.

The Table proposed in this notice is limited to pandemic influenza covered countermeasures. Future Countermeasure Injury Tables (Tables) may be created for other countermeasures relating to threats to health that pose or constitute public health emergencies, since the PREP Act mandates the establishment of a Program Table identifying covered injuries that may be presumed to be directly caused by the administration or use of a covered countermeasure. To date, declarations have been issued with respect to countermeasures against pandemic influenza A viruses, anthrax, botulism, smallpox, and acute radiation syndrome. The Secretary may publish Tables in the **Federal Register** through separate amendments to 42 CFR part 110 in the future.

The 2009 H1N1 virus outbreak quickly emerged into an influenza pandemic in the spring of 2009. An influenza pandemic is a worldwide epidemic of the disease and occurs when: (1) A new influenza virus appears against which the human population has no or very limited immunity; and (2) the virus can spread easily from person-to-person in a sustained manner.

The 2009 H1N1 virus was a new recombinant influenza A virus of swine origin that was first recognized as causing human illness with transmission from person to person in Mexico and the United States in the early spring of 2009. The first documented case in the United States was confirmed by laboratory testing at the Centers for Disease Control and Prevention (CDC) on April 15, 2009. The virus then spread rapidly throughout the world and it was determined that the human population had very limited immunity to this novel influenza A virus.

The virus has been reported to cause a wide range of influenza-like symptoms, including fever, cough, sore throat, body aches, headaches, chills, fatigue, nausea, vomiting, and/or diarrhea. Most infections have been mild and self-limiting; however, serious illnesses including pneumonia and death have occurred.

Due to the novel nature of the 2009 H1N1 virus and the increasing number of CDC-confirmed cases indicating rapid spread, the Acting Secretary of HHS issued a public health emergency determination, under section 319 of the Public Health Service (PHS) Act[5] on April 26, 2009, titled ''Determination that a Public Health Emergency Exists.'' This determination stated that a public health emergency was in existence nationwide involving the pandemic 2009 H1N1 influenza virus because it affected, or had significant potential to affect, national security. More information is available at *http://www.flu.gov/planning-preparedness/federal/h1n1emergency042609.html#*. This declaration was renewed by the Secretary on July 24, 2009; October 1, 2009; December 28, 2009; and March 23, 2010. Each renewal, titled ''Renewal of Determination that a Public Health Emergency Exists,'' focused specifically on the 2009 H1N1 influenza pandemic. HHS did not further renew this determination, which resulted in the expiration of the Secretary's 2009 H1N1 influenza public health emergency determination on June 23, 2010, under section 319 of the PHS Act.[6] However, HHS still encourages individuals to continue to practice flu prevention techniques (*http://www.flu.gov/prevention-vaccination/index.html#*).

Definition of Covered Countermeasure

The Secretary has issued several PREP Act declarations concerning pandemic influenza covered countermeasures, pursuant to section 319F–3(b) of the PHS Act.[7] ''Covered countermeasure'' is defined in the PREP Act and includes three categories.[8] The first category, consisting of ''qualified pandemic or epidemic product[s],'' is defined in section 319F–3(i)(7) of the PHS Act.[9] This category includes products (drugs, biologics, and devices) manufactured, used, designed, developed, modified, licensed, or procured to diagnose, mitigate, prevent, treat, or cure a pandemic or epidemic or to limit the harm such pandemic or epidemic might otherwise cause. The category also extends to products used to diagnose, mitigate, prevent, treat, or cure a serious or life-threatening disease or condition caused by a ''qualified pandemic or epidemic product.'' [10] To qualify, a drug, biologic, or device must be: (1) Approved or cleared under the Federal Food, Drug, and Cosmetic Act (FD&C Act) or licensed under the PHS Act; (2) the subject of research for possible use and subject to an exemption under sections 505(i) or 520(g) of the FD&C Act; or (3) authorized for emergency use in accordance with section 564, 564A, or 564B of the FD&C Act.

The second category includes ''security countermeasure[s].'' A security countermeasure, defined in section 319F–2(c)(1)(B) of the PHS Act,[11] is a drug, biologic, or device that the Secretary determines: (1) Is a priority to diagnose, mitigate, prevent, or treat harm either from an agent identified as a material threat or from a condition that may result in injuries or deaths, and may be caused by administering a drug, biologic, or device against such an agent; (2) is a necessary

[4] 42 CFR part 110.

[5] 42 U.S.C. 247d.

[6] 42 U.S.C. 247d.

[7] 42 U.S.C. 247d–6d(b).

[8] Section 319F–3(i)(1) of the PHS Act (42 U.S.C. 247d–6d(i)(1)).

[9] 42 U.S.C. 247d–6d(i)(7).

[10] Section 319F–3(i)(7)(A)(ii) of the PHS Act (42 U.S.C. 247d–6d(i)(7)(A)(ii)).

[11] 42 U.S.C. 247d–6b(c)(1)(B).

countermeasure; and (3) is approved or cleared under the FD&C Act or licensed under the PHS Act or will likely be approved, cleared, or licensed within ten years or is authorized for emergency use under section 564 of the FD&C Act.

The final category consists of drugs,[12] biologics,[13] or devices [14] that are authorized for emergency use in accordance with section 564, 564A, or 564B of the FD&C Act.

To be eligible for the liability protections of the PREP Act or to receive benefits under the compensation provisions of the PREP Act, a covered countermeasure must meet one of these three categories and must also be described by the Secretary in a declaration.

Covered Countermeasures

In this section, we provide an overview of the covered countermeasures subject to Secretarial declarations that will be included on the proposed Table.

Pandemic Influenza Vaccine Declarations

The Secretary published a declaration covering pandemic influenza A H5N1 vaccines on January 26, 2007.[15] This declaration was amended on November 21, 2007, with the effective date of November 30, 2007, adding influenza vaccines caused by subtypes H7 and H9.[16] The January 26, 2007, declaration was further amended on October 10, 2008, to add influenza caused by subtypes H2 and H6 and covering vaccines to prevent these diseases.[17] A fourth amendment was signed by the Secretary on June 15, 2009, which specified that pandemic H1N1 influenza and vaccines are covered.[18] The June 15, 2009, declaration also republished the amended January 26, 2007, declaration in its entirety and stated that the 2009 H1N1 virus and resulting disease constituted a public health emergency. The June 15, 2009, republished declaration was amended on September 28, 2009, adding provisions regarding the H5N1, H2, H6, H7, H9 subtypes and 2009 H1N1 vaccines.[19] The declaration was amended on February 26, 2010, which republished the June 15, 2009, declaration with amendments.[20]

This February 26, 2010, amended declaration widened the scope of the previous declarations to extend to vaccines against pandemic influenza A viruses with pandemic potential and to associated adjuvants.[21]

The declaration was further amended on February 29, 2012. This amendment extended the effective time period, reformatted the declaration, modified or clarified terms, and republished the February 26, 2010, declaration with amendments.[22]

Although the ''determination that a public health emergency exists'' under section 319 of the PHS Act [23] expired, the PREP Act declarations remain effective as described above.

Diagnostics, Personal Respiratory Protection Devices, and Respiratory Support Devices Declarations

On December 17, 2008, the Secretary signed a PREP Act declaration concerning pandemic influenza diagnostics, personal respiratory protection devices, and respiratory support devices.[24]

Pandemic influenza diagnostics are defined in section IX of the declaration as ''diagnostics to identify avian or other animal influenza A viruses that pose a pandemic threat, or to otherwise aid in the diagnosis of pandemic influenza, when (1) [l]icensed under section 351 of the Public Health Service Act; (2) approved under section 505 or section 515 of the FD&C Act; (3) cleared under section 510(k) of the FD&C Act; (4) authorized for emergency use under section 564 of the FD&C Act; (5) used under section 505(i) of the FD&C Act or section 351(a)(3) of the PHS Act and 21 CFR part 312; or (6) used under section 520(g) of the FD&C Act and 21 CFR part 812.'' [25]

Pandemic influenza personal respiratory protection devices are defined in section IX of the declaration as being ''for use by the general public to reduce wearer exposure to pathogenic biological airborne particulates during public health medical emergencies, such as an influenza pandemic, when (1) [l]icensed under section 351 of the Public Health Service Act; (2) approved under section 505 or section 515 of the FD&C Act; (3) cleared under section 510(k) of the FD&C Act; (4) authorized for emergency use under section 564 of the FD&C Act; (5) used under section 505(i) of the FD&C Act or section 351(a)(3) of the PHS Act and 21 CFR part 312; or (6) used under section 520(g) of the FD&C Act and 21 CFR part 812.'' [26]

Pandemic influenza respiratory support devices are defined in section IX of the declaration as, ''devices to support respiratory function for patients infected with highly pathogenic influenza A H5N1 viruses or other influenza viruses that pose a pandemic threat when (1) [l]icensed under section 351 of the Public Health Service Act; (2) approved under section 505 or section 515 of the FD&C Act; (3) cleared under section 510(k) of the FD&C Act; (4) authorized for emergency use under section 564 of the FD&C Act; (5) used under section 505(i) of the FD&C Act or section 351(a)(3) of the PHS Act and 21 CFR part 312; or (6) used under section 520(g) of the FD&C Act and 21 CFR part 812.'' [27]

Antiviral Medication Declarations

The Secretary signed a PREP Act declaration on October 10, 2008, adding the influenza antiviral drugs Tamiflu and Relenza as pandemic influenza covered countermeasures.[28] This declaration was amended on April 26, 2009, to expand the category of covered diseases to all animal influenza A viruses that are or may be capable of developing into a pandemic strain.[29]

In addition, the Secretary signed a September 28, 2009, PREP Act declaration for the antiviral drug, peramivir, when used to treat influenza caused by the pandemic 2009 H1N1 virus.[30]

General Information

The effective dates for the above-referenced declarations vary, and the Secretary has the authority to amend the declarations at any time. The declarations, including amendments to

[12] As defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)).

[13] As defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)).

[14] As defined in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[15] 72 FR 4710 (Feb. 1, 2007)); *http://www.gpo.gov/fdsys/pkg/FR-2007-02-01/pdf/E7-1635.pdf.*

[16] 72 FR 67731 (Nov. 30, 2007); *http://www.gpo.gov/fdsys/pkg/FR-2007-11-30/pdf/07-5884.pdf.*

[17] 73 FR 61871 (Oct. 17, 2008); *http://www.gpo.gov/fdsys/pkg/FR-2008-10-17/pdf/E8-24736.pdf.*

[18] 74 FR 30294 (June 25, 2009); *http://www.gpo.gov/fdsys/pkg/FR-2009-06-25/pdf/E9-14948.pdf.*

[19] 74 FR 51153 (Oct. 5, 2009); *http://www.gpo.gov/fdsys/pkg/FR-2009-10-05/pdf/E9-23844.pdf.*

[20] 75 FR 10268 (March 5, 2010); *http://www.gpo.gov/fdsys/pkg/FR-2010-03-05/pdf/2010-4644.pdf.*

[21] 75 FR 10268.

[22] 77 FR 13329 (March 6, 2012); *http://www.gpo.gov/fdsys/pkg/FR-2012-03-06/pdf/2012-5312.pdf.*

[23] 42 U.S.C. 247d.

[24] 73 FR 78362 (Dec. 22, 2008)); *http://edocket.access.gpo.gov/2008/pdf/E8-30510.pdf.*

[25] 73 FR 78362.

[26] 73 FR 78362.

[27] 73 FR 78362.

[28] 73 FR 61861 (Oct. 17, 2008)); *http://www.gpo.gov/fdsys/pkg/FR-2008-10-17/pdf/E8-24733.pdf.*

[29] 74 FR 29213 (June 19, 2009)); *http://www.gpo.gov/fdsys/pkg/FR-2009-06-19/pdf/E9-14412.pdf.*

[30] 74 FR 50968 (Oct. 2, 2009)); *http://www.gpo.gov/fdsys/pkg/FR-2009-10-02/pdf/E9-23761.pdf.*

the declarations, are published in the **Federal Register**.

In addition to the above-referenced declarations, the Secretary also has issued declarations for countermeasures to the security threats of anthrax, smallpox, botulism, and acute radiation syndrome. Injury Tables for these covered countermeasures may be published at a later date.

As noted above, the PREP Act authorized the Secretary to create Tables for each covered countermeasure identified in a declaration if there is compelling, reliable, valid, medical and scientific evidence that the countermeasure directly causes a covered injury. In this NPRM, the Secretary proposes a Table for injuries directly resulting from the use or administration of pandemic influenza covered countermeasures identified in the above-referenced declarations. The proposed Table lists serious physical injuries that have been demonstrated by compelling, reliable, valid, medical and scientific evidence to be directly caused by the administration or use of the covered countermeasures.[31] Only injuries supported by this type of evidence are proposed for inclusion on the Table.

For each countermeasure, the proposed Table will include the covered injuries and/or conditions directly caused by such countermeasure and the applicable time intervals for the first symptom or manifestation of onset of injuries. The Program's statute directs that covered injuries presumed to be caused by the administration or use of a covered countermeasure must be included on a Table.[32] The Secretary proposes also to note on the Table if no injuries or conditions qualify for a Table presumption for a particular countermeasure at this time. This is done to reflect that she considered the possibility of Table injuries for these covered countermeasures. Claims related to any injuries alleged to be caused by these countermeasures will be considered on a case-by-case basis.

General information about applying for compensation/benefits under the Program is outside the scope of this NPRM, but is available in 42 CFR part 110.40 or on the Program's Web site, *www.hrsa.gov/gethealthcare/conditions/countermeasurescomp/howtofile.html.* The implementing regulations for this Program can also be found at: *www.gpo.gov/fdsys/pkg/FR–2011–10–07/pdf/2011–25858.pdf.*

Summary of Proposed Regulation

This NPRM proposes to amend the Program's implementing regulations [33] and, if adopted, would establish a table of injuries resulting from the administration or use of pandemic influenza covered countermeasures. Certain conditions of interest that are currently not being proposed for inclusion on the Table also are discussed in this NPRM.

General Requirement of Serious Physical Injuries or Deaths

By statute, only serious physical injuries or deaths directly resulting from the use or administration of a covered countermeasure may be compensable under the Program.[34] The serious physical injury or death may be compensable regardless of whether the injury is a Table injury or a non-Table injury. Because this requirement of a serious physical injury applies to all Requests for Benefits filed with the Program, the Secretary considered this requirement while drafting the proposed Table included in this NPRM.

In general, only injuries or significant aggravation of injuries that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability will be considered serious physical injuries.[35] It is recognized that the term ''disability'' can be defined in many ways, and there are several definitions used by the Federal government specific to various programs and services. To provide further clarity as to the type of disability that would qualify as a serious injury for the Program, under this proposed rule, the term ''disability'' is defined as ''a physical or mental impairment that substantially limits one or more major life activities of an individual.'' This definition corresponds with the first listed definition of disability in the Americans with Disabilities Act, 42 U.S.C. 12102(1)(A). This definition was chosen because it is consistent with the Program's existing authorities and adds further guidance by using a widely accepted definition familiar to the general public.

In addition, pursuant to 42 CFR 110.3(z), ''physical biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, be considered serious physical injuries.'' According to the preamble to the interim final rule, serious physical injuries also include ''instances in which there may be no measurable anatomic or structural change in the affected tissue or organ, but there is an abnormal functional change. For example, many psychiatric conditions are caused by abnormal neurotransmitter levels in key portions of the central nervous system. Thus, it is possible that certain serious psychiatric conditions may qualify as serious physical injuries if the psychiatric conditions are a manifestation of a physical biochemical abnormality in neurotransmitter level or type caused by a covered countermeasure. One way of determining that an abnormal physical change in neurotransmitter level is causing the injury would be a clinical challenge that demonstrates a positive clinical response to a medication that is designed to restore the balance of appropriate neurotransmitters necessary for normal function in an injured countermeasure recipient.'' [36]

Only serious physical injuries believed to have a direct causal relationship with the use or administration of a covered countermeasure based on compelling, reliable, valid, medical and scientific evidence may be included on the Table.

Minor injuries do not meet the definition of a serious physical injury. For example, covered injuries do not include common and expected skin reactions (such as localized swelling or warmth that is not of sufficient severity to warrant hospitalization and does not lead to significant loss of function or disability). Expected minor reactions, such as headaches and body aches, commonly occur with influenza vaccinations. However, if a minor injury leads to a serious physical injury, and the minor injury was directly caused by a covered countermeasure, the Program may compensate the individual for the serious physical injury. The injury's causal link to the countermeasure must be based on compelling, reliable, valid, medical and scientific evidence. The Program will consider such claims on a case-by-case basis.

Serious Aggravation of Pre-Existing Conditions

Injuries covered under the Program may include serious aggravations of pre-existing conditions if such aggravations were caused by a covered countermeasure (i.e., any disorder that is proven to the satisfaction of the Secretary to have been made significantly more severe as the direct

[31] Section 319F–4(b)(5)(A) of the PHS Act (42 U.S.C. 247d–6e(b)(5)(A)).

[32] Section 319F–4(b)(5)(A) of the PHS Act (42 U.S.C. 247d–6e(b)(5)(A)).

[33] 42 CFR part 110.

[34] Section 319F–4(a), (e)(3) of the PHS Act (42 U.S.C. 247d–6e(a), (e)(3)).

[35] 42 CFR 110.3(z).

[36] 75 FR 63661.

result of the administration or use of the covered countermeasure). The serious aggravation of the pre-existing condition must be supported by compelling, reliable, valid, medical and scientific evidence and show a direct causal link between the aggravation or worsening of the pre-existing condition and the countermeasure. The Program will consider claims involving serious aggravations of pre-existing conditions on a case-by-case basis.

Table Time Intervals

The proposed Table includes time intervals, per covered injury, describing the time interval between the administration or use of the covered countermeasure and the first symptom or manifestation of onset of injury after the administration or use of the countermeasure. In addition to meeting the requirements of the Table injury, the symptom or manifestation of onset of injury must be evident within the time period described on the Table. The time intervals are biologically sound time intervals based on medical and scientific evidence in which nearly all of the cases of injury are known to appear when the injury is actually caused by the covered countermeasure. As is the case for non-Table injuries, Table injuries not meeting the Table time intervals may be compensated based on adequate demonstration of compelling, reliable, valid, medical and scientific evidence supporting that the countermeasure had a causal role.

Table Definitions and Requirements

The proposed Table also includes definitions of the terms and conditions included on the Table which sets forth the requirements necessary to establish the Table injuries. For this reason, the Table definitions and requirements are considered part of the Table. To receive compensation for a Table injury, the individual must meet the time interval, Table definition, and any other Table requirements, in addition to the other Program requirements.

Presumption Created for Table Injuries

For purposes of this Program, a rebuttable presumption exists that a Table injury was directly caused by the administration or use of a covered countermeasure if the first symptom or manifestation of onset of an injury listed on the Table occurred within the time period indicated, and the Table's definitions and requirements are satisfied. By statute, this presumption only applies to Table injuries.[37] An individual may obtain this presumption of causation by submitting medical documents demonstrating that the covered injury occurred, that it began within the time interval specified on the Table after administration or use of a covered countermeasure, that there was not another more likely cause, and that all other applicable Table requirements and Table definitions are met.

Nevertheless, the presumption is not conclusive. It may be rebutted if, based on review of the relevant medical and scientific evidence, the Secretary determines that the Table injury was more likely caused by other factors and not directly caused by the countermeasure.

Non-Table Injuries

Compensation may be available for individuals who develop an injury not included on the Table, or an injury that is included on the Table but where the injury begins outside the allotted time interval provided by the Table, or the injury does not satisfy the definition or requirements included on the Table with respect to such injury. In these cases, the requester does not receive the presumption of causation for a Table injury and must demonstrate that the use or administration of the covered countermeasure directly caused the injury. The regulation administratively implementing the Program includes more information about the requirements for such an injury.[38] For example, a temporal association between the administration or use of a covered countermeasure and onset of the injury (i.e., the injury occurs a certain time after the administration or use of the countermeasure) alone is not sufficient to show that an injury is the direct result of a covered countermeasure.[39] Proof of a causal association for the non-Table injury must still be based on compelling, reliable, valid, medical and scientific evidence.

***Sequelae* (Health Complications) of Table and Non-Table Injuries**

A requester who demonstrates a Table injury may be entitled to benefits related to *sequelae* (health complications), including death, if the Program determines that the *sequelae* resulted from the Table injury. This is also applicable to a requester who develops *sequelae* from a non-Table injury, but only if the non-Table injury is shown to be directly caused by a covered countermeasure, and the evidence shows a causal relationship based on compelling, reliable, valid, medical and scientific evidence. The Program will consider compensation for *sequelae* that develop from Table and non-Table injuries on a case-by-case basis.

Injuries Sustained as a Result of a Pandemic Influenza Virus

An individual will not have suffered a covered injury if a covered countermeasure is ineffective in diagnosing, preventing, or treating the underlying disease for which the countermeasure was administered or used, and the individual sustains an injury caused by the disease and not by the covered countermeasure. An injury sustained as the direct result of a disease (or health condition or threat to health), e.g., 2009 H1N1 influenza infection, for which the Secretary recommended the administration or use of a covered countermeasure in a declaration, is not a covered injury. This is because the injury results from the disease itself and not from the administration or use of a covered countermeasure. For more information, see 42 CFR 110.20(d).

Amendments to the Proposed Table of Injuries

The Secretary has the discretion to modify the Table in the future. For example, the Secretary may amend the Table by adding or removing injuries, modifying the governing time intervals, and/or revising the Table definitions and requirements. The Secretary will monitor new studies and evolving medical and scientific evidence concerning any causal relationships between covered countermeasures and injuries or death. The Secretary may amend the Table at any time while the Program remains operational. Changes to the Table will be accomplished as amendments to 42 CFR part 110 and will be published in the **Federal Register**.

The Table in Effect at the Time a Claim Is Filed

The version of the Table that applies to a requester is the one that is in effect on the filing date of his/her Request for Benefits unless a subsequent one is published that may provide greater benefit to the requester. If a new Table or an amendment to an existing Table would benefit a requester, as described in the following section, the requester may have an additional opportunity to file a Request for Benefits.

Filing Deadlines and Table Additions or Amendments

In accordance with 42 CFR 110.42(f), in the event that the Secretary issues a

[37] Section 319F–4(b)(5)(A) of the PHS Act (42 U.S.C. 247d–6e(b)(5)(A)).

[38] 42 CFR 110.20(c).

[39] 42 CFR 110.20(c).

new Covered Countermeasure Injury Table or amends a previously published Table, requesters may have an extended filing deadline based on the effective date of the Table amendment. This extended filing deadline will apply only if the Table amendment enables a requester who could not establish a Table injury before the amendment to establish such an injury. For example, if the Table proposed in this NPRM is adopted, any person who meets the Table requirements for an injury of anaphylaxis after receiving the monovalent 2009 H1N1 vaccine (2009 H1N1 vaccine) would have one year from the effective date of the Table's adoption to file a Request for Benefits. This filing deadline applies regardless of whether the requester previously filed a request form with the Program.

Individuals may seek compensation for one or more injuries stemming from a single administration of a covered countermeasure. However, if individuals have previously received compensation for an injury through the Program, they may not re-file a claim for compensation if the same injury is later added to a Table. The inability for individuals to re-file their claim avoids such individuals having the opportunity to receive additional compensation for the same serious physical injury. However, this does not preclude filing a Request for Benefits for an injury or aggravation of an injury, resulting from the subsequent administration or use of the same type of covered countermeasure. It also does not preclude subsequent Requests for Benefits for an injury, or an aggravation of an injury, resulting from the administration or use of a different covered countermeasure or a different injury from the same countermeasure.

The filing deadline provided under 42 CFR 110.42(f) is an additional filing period to the one afforded to all potential requesters under 42 CFR 110.42(a). Therefore, persons who would be eligible to use the filing deadline described in § 110.42(f) could rely on the deadline provided under § 110.42(a) or § 110.42(f).

It is important to note that the additional filing deadline described in 42 CFR 110.42(f) is only available to persons who meet the requirements of: (1) A new Table or an amendment(s) to a Table; (2) the Table time interval(s); (3) Table definitions; and (4) any other Table requirements. In this case, such persons may be eligible for the presumption of causation. Persons who sustained injuries not included on the Table, or those who do not meet all of the requirements for such a Table injury but may prove causation of the injury through other means, will not be afforded an additional one-year filing deadline based on the Table change. Because the Table change would not enable such individuals to establish a Table injury, they would be subject to the standard filing deadline described in 42 CFR 110.42(a) (i.e., one year from the date of administration or use of the covered countermeasure).

Overview of the Proposed Table

Through this NPRM, as authorized by statute, the Secretary is proposing a Table for several covered countermeasures listing serious physical injuries (i.e., illnesses, disabilities, conditions, etc.). The serious physical injuries included on the Table are injuries that are supported by compelling, reliable, valid, medical and scientific evidence showing that the administration or use of the covered countermeasures directly causes such covered injuries. The Table lists the serious injuries directly caused by a specific countermeasure, if any, the time interval within which the first symptom or manifestation of onset of adverse effects must appear, and the definition of the injury. Table definitions are included to further explain each covered injury and the level of severity necessary to qualify as a Table injury. However, as discussed above, individuals with injuries not meeting these requirements of the Table injury may still pursue their claims as non-Table injuries under the Program.

The injuries included on the proposed Table and the time intervals, Table definitions, and Table requirements reflect the Secretary's best efforts to identify those serious physical injuries causally related to the covered countermeasures. The causal linkages between the covered countermeasures and these associated Table injuries are based on compelling, reliable, valid, medical and scientific evidence. The Secretary will stay informed of updates in the scientific and medical field concerning new information about causal association between injuries and covered countermeasures.

Pandemic Influenza Countermeasures Injury Table

In response to the 2009 H1N1 pandemic, the 2009 H1N1 vaccine was licensed by the Food and Drug Administration (FDA) as a strain change from the seasonal influenza vaccine. The vaccine was developed using the same FDA-approved manufacturing processes used to produce the seasonal influenza vaccine.

The United States has a long record of safety regarding seasonal influenza vaccines. Because the 2009 H1N1 vaccine was produced using the same processes as the annual seasonal influenza vaccine, its safety profile was expected to be similar to that of any strain change of the seasonal influenza vaccine.

The Federal response to the 2009 H1N1 influenza pandemic centered on a mass vaccination program unprecedented in its size and scope in the United States. Because of this response, the Federal government significantly increased its vaccine safety monitoring efforts.[40] After the 2009 H1N1 vaccination program began in the fall of 2009, HHS and its Agencies worked in close partnership with the Department of Defense and others in the areas of research, surveillance, and programmatic activities to determine if vaccine safety signals or adverse events following immunization were related to the 2009 H1N1 vaccine by chance or were truly adverse reactions to the vaccine. In addition, the National Vaccine Advisory Committee (NVAC), which provides advice to the HHS Assistant Secretary for Health (ASH), established the H1N1 Vaccine Safety Risk Assessment Working Group (the Working Group), with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 vaccine. The Working Group met regularly to review available data from Federal vaccine safety monitoring systems. The NVAC deliberated on the Working Group's findings and shared information with the ASH. HHS also worked with other countries to share vaccine data and safety information on the 2009 H1N1 vaccine. At the local level, public health departments and public and private medical health entities collaborated in Federal vaccine safety monitoring efforts as well.

The Secretary is aware of minor adverse events associated with the 2009 H1N1 vaccine and other pandemic influenza vaccines. Specifically, for the 2009 H1N1 injectable vaccine, common minor adverse events included temporary tenderness, pain, redness, and swelling at the injection site, and acute systemic reactions such as headache, malaise, and muscle aches in people of all ages, and fever in children. For the 2009 H1N1 intranasal vaccine, common minor temporary adverse events include runny nose, cough, nasal congestion, and headache in all age groups; sore throat and tiredness or weakness in adults; and abdominal

[40] Daniel A. Salmon, ''Immunization-Safety Monitoring Systems for the 2009 H1N1 Monovalent Influenza Vaccination Program,'' Pediatrics: Supplement 1; May 2011, S79.

pain, vomiting, diarrhea, and fever in children. Cases involving unusually severe forms of minor adverse events that meet the serious physical injury standard may qualify as non-Table injuries and will be reviewed on a case-by-case basis by the Program. As described above, minor injuries are excluded from the Table.

The proposed Table not only includes the covered injuries listed, but also the necessary time intervals between the administration of the vaccine and the first symptom or manifestation of onset of the Table injury required for a Table presumption of causation. In addition, the Table lists Table definitions and Table requirements for each covered injury.

The proposed Table lists the injuries of anaphylaxis, syncope, and deltoid bursitis for pandemic influenza vaccines, including the 2009 H1N1 vaccine, and Guillain-Barre Syndrome (GBS) for only the 2009 H1N1 vaccine.

Anaphylaxis

Anaphylaxis is a single discrete event that presents as a severe and potentially life threatening multi-organ reaction, particularly affecting the skin, respiratory tract, cardiovascular system, and the gastrointestinal tract. In an anaphylactic reaction, an immediate reaction generally occurs within minutes after exposure, and in most cases, the individual develops signs and symptoms within four hours after exposure to the antigen. The immediate reaction leads to a combination of skin rash, mucus membrane swelling, leakage of fluid from the blood into surrounding tissues, tightening of the air passages in the lungs with tissue swelling, and gastrointestinal symptoms that can lead to shock, organ damage, and death if not promptly treated.

Symptoms may include swelling, itching, rash, trouble breathing, chest tightness, and/or dizziness. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema (throat swelling) or bronchospasm and may be associated with cardiovascular collapse.

Other significant clinical signs and symptoms may include the following: cyanosis (bluish coloration in the skin due to low blood oxygen levels), hypotension (low blood pressure), bradycardia (slow heart rate), tachycardia (fast heart rate), arrhythmia (irregular heart rhythm), edema (swelling) of the pharynx and/or larynx (throat or upper airway) with stridor (noisy breathing on inspiration), dyspnea (shortness of breath), diarrhea, vomiting, and abdominal pain. Autopsy findings may include acute emphysema (a type of lung abnormality), which results from lower respiratory tract obstruction, edema (swelling) of the upper airway, and minimal findings of eosinophilia (an excess of a type of white blood cell associated with allergy) in the liver. When death occurs within minutes of exposure without signs of respiratory distress, lack of significant pathologic findings would not exclude a diagnosis of anaphylaxis.

Anaphylaxis may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations. Most treated cases resolve without *sequelae.* Anaphylaxis can be due to an exaggerated acute systemic hypersensitivity reaction, especially involving immunoglobulin E antibodies, as in allergic anaphylaxis, or it could be a non-immunologically mediated reaction leading to similar clinical symptomatology as in non-immune anaphylaxis. Non-immune anaphylaxis cannot be detected by skin tests or *in vitro* allergy diagnostic procedures. As stated, anaphylaxis is a single discrete event. It is not an initial episode of a chronic condition such as chronic urticaria (hives).

Anaphylaxis following immunization is a rare occurrence with estimates in the range of 1–10 per 1 million doses distributed, depending on the vaccine studied.[41] The Institute of Medicine (IOM) has reported that the evidence favors acceptance of a causal relationship between certain vaccines and anaphylaxis based on case reports and case series. The IOM has reported that causality could be inferred with reasonable certainty based on one or more case reports because of the unique nature and timing of anaphylaxis following vaccine administration and provided there is an absence of likely alternative causes.[42] It also has found that the evidence convincingly supports a causal relationship between influenza vaccine and anaphylaxis.[43]

Because influenza vaccines are currently prepared from influenza viruses propagated in embryonated chicken eggs, the final vaccine product contains a limited quantity of egg protein that can induce immediate hypersensitivity reactions in some persons with severe egg allergies. The inactivated injectable vaccine (prepared from inactivated or killed influenza virus) may also contain gelatin proteins, which can be a source of allergic reactions in sensitized individuals. The live attenuated intranasal vaccine (containing living weakened virus) contains egg proteins, gentamicin, and gelatin, which may cause allergic reactions in sensitized individuals.

The 1994 IOM Report noted in support of a causal association that there exists an observation of a spectrum of host responses to the influenza vaccine that follow a logical biological gradient from true anaphylaxis to milder hypersensitivity reactions. Biological gradient refers to the observation of a spectrum of responses from mild to severe, and in the case of hypersensitivity reactions the reported spectrum after the vaccine runs from mild skin manifestations to chest and throat tightness and cardiovascular events to full blown anaphylaxis.[44] The CDC adopted the Advisory Committee on Immunization Practice's findings, concluding that ''[i]mmediate—presumably allergic—reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components.'' [45]

For its 2012 report, the IOM reviewed certain adverse events for their association with seasonal influenza vaccine. The 2009 H1N1 vaccine contains many of the same anaphylaxis-causing components as the seasonal influenza vaccine (e.g., egg protein). Although the IOM reported limited confidence in the epidemiologic evidence, they assessed the mechanistic evidence regarding an association between influenza vaccine and anaphylaxis as strong. This assessment was based on 22 cases in the medical literature that present a strong temporal relationship, the finding of antigelatin IgE in two cases, the finding of two cases with positive skin prick tests to gelatin, and one case with positive rechallenge (where the same acute adverse event occurs after more than one administration of the vaccine). The IOM concluded that ''the evidence convincingly supports a causal

[41] The Brighton Collaboration Anaphylaxis Working Group, ''Anaphylaxis: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data,'' Vaccine, Aug. 2007; 5676.

[42] Institute of Medicine (IOM), Immunization Safety Review Vaccination and Sudden Unexpected Death in Infancy, (Washington, DC: The National Academies Press, 2003) 55.

[43] IOM, Adverse Effects of Vaccines: Evidence and Causality (Washington, DC: The National Academies Press, 2012) 288.

[44] IOM, Adverse Events Associated With Childhood Vaccines Evidence Bearing on Causality, (Washington, DC: The National Academies Press, 1994) 60.

[45] Scott A. Harper, MD, et al., ''Prevention and Control of Influenza,'' Morbidity and Mortality Weekly; July 29, 2005; 16.

relationship between influenza vaccine and anaphylaxis.'' [46]

The IOM also stated that the onset of anaphylaxis generally occurs within a few hours of exposure.[47] Consistent with the time interval for the first manifestation of anaphylaxis after vaccines covered by the National Vaccine Injury Compensation Program (VICP), the Program proposes an onset interval of 0–4 hours for anaphylaxis to be covered under the proposed Table.

Based on the nature and timing of anaphylaxis and the medical literature (including the fact that it is a very rare event with significant symptomatology), compelling, reliable, valid, medical and scientific evidence shows a direct link between influenza vaccines, including pandemic influenza vaccines (e.g., the 2009 H1N1 vaccine) and anaphylaxis.[48] Anaphylaxis is proposed for inclusion on the Table because it is a serious physical injury that may be directly caused by the use of the pandemic influenza vaccine, as supported by compelling, reliable, valid, medical and scientific evidence.

In a very small minority of cases of acute anaphylaxis, initial symptoms of the immediate reaction may present up to 12 hours after exposure. A more slowly evolving late phase hypersensitivity reaction is also possible, with an onset that usually begins 4–8 hours after the immediate reaction ends. The medical literature contains reports of late phase onset up to 72 hours later.[49] The late phase reaction results from a different immunologic mechanism of action. The late phase reaction is part of a biphasic reaction. It is possible for the first immediate hypersensitivity reaction to be relatively mild, unrecognized, or not observed.

There may be unusual cases in which the immediate reaction is delayed and/or cases in which the immediate reaction is not recognized, with the first apparent manifestation occurring in the late phase. These unusual cases will be evaluated on a case-by-case basis, and the Secretary will determine causation based on the presence of compelling, reliable, valid, medical and scientific evidence.

[46] IOM, Adverse Effects of Vaccines, 345.

[47] IOM, Immunization Safety Review Vaccination, 5.

[48] Hector S. Izurieta, et al., ''Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine,'' Journal of the American Medical Association, Dec. 7, 2005; 2721 and Stanley A. Plotkin, et al., Vaccines, 5th Edition, (United Kingdom: Elsevier, 2008) 97, 982.

[49] The Brighton Collaboration, 5678.

Vasovagal Syncope

Vasovagal syncope is a temporary loss of consciousness (fainting) and postural tone that includes a reflex drop in blood pressure and may be triggered by an event associated with pain or anxiety. This reaction is known to occur as a result of any injection, including the injection of a vaccine. Some people may experience jerking movements after losing consciousness which generally are not seizures.

In its 2012 report, the IOM concluded, based on mechanistic evidence, that the evidence convincingly supports a causal relationship between the injection of a vaccine and syncope. Included in the evidence was one case of positive re-challenge involving influenza vaccine.[50] As a rule, syncope after vaccination is not associated with serious injuries; however, in approximately 10 percent of reported cases it can cause serious injury related to physical trauma from an associated fall or other related accidents. Only serious injuries are eligible for compensation.

Most cases of syncope occur within one hour of vaccination. The Program will therefore propose an onset interval of 0–1 hour for vasovagal syncope caused by injected pandemic influenza vaccine to be covered under the proposed Table. Vasovagal syncope is proposed for inclusion on the Table because it may result in serious physical injury that is directly caused by the use of the vaccine, as supported by compelling, reliable, valid, medical and scientific evidence.

Subdeltoid Bursitis

Subdeltoid bursitis (i.e., deltoid bursitis, subacromial bursitis) is an inflammation of the bursa located between the deltoid muscle and the capsule of the shoulder joint. A bursa is a closed fluid-containing sac. Bursae serve to reduce friction between bones and tendons, or bones and skin. The pain from subacromial or subdeltoid bursitis is usually located in the lateral aspect of the shoulder. There is frequently tenderness to direct palpation (the process of using your hands to examine the body, especially while perceiving/diagnosing a disease or illness) below the acromion process (part of the shoulder). A shoulder with isolated bursitis should have full passive range of motion with more tenderness on actively resisted abduction than on passive abduction. This bursa extends below the deltoid muscle, and it is possible for a deep injection given high in the shoulder to inadvertently enter the bursa causing an inflammatory bursitis. Subdeltoid bursitis can result in debilitating pain or immobility. Only serious injuries are eligible for compensation.

The IOM evaluated three cases of positive re-challenge associated with influenza vaccine from the Vaccine Adverse Event Reporting System (VAERS) in addition to a published report of 13 claims in the VICP. Most of the cases had onset of symptoms within 48 hours of vaccination. The IOM concluded that the evidence convincingly supports a causal relationship between the injection of a vaccine and deltoid bursitis.[51] The Program will therefore propose an onset interval of 0–48 hours for subdeltoid bursitis caused by injected pandemic influenza vaccine to be covered under the proposed Table.

Injury to other musculoskeletal structures in the shoulder or upper arm (e.g., tendons, ligaments, bone, muscle, nerves) due to direct injection of the vaccine into these structures, or injuries resulting from the localized inflammation caused by the vaccine in close proximity to these structures, will be reviewed on a case-by-case basis.

Subdeltoid bursitis is proposed for inclusion on the Table because it may be a serious physical injury that may be directly caused by the use of the pandemic influenza vaccine, as supported by compelling, reliable, valid, medical and scientific evidence.

Guillain-Barrè Syndrome (GBS)

Multiple studies performed to monitor the safety of 2009 H1N1 vaccine provide evidence that demonstrates a small, statistically significant increased risk of GBS in the six weeks following administration of the 2009 H1N1 vaccine, as outlined below.

GBS is an acute paralysis caused by dysfunction in the peripheral nervous system (i.e., the nervous system outside the brain and spinal cord). GBS may manifest with weakness, abnormal sensations, and/or abnormality in the autonomic (involuntary) nervous system. In the United States, each year approximately 3,000 to 4,000 cases of GBS are reported, and the incidence of GBS increases in older individuals. Senior citizens tend to have a poorer prognosis. Most people fully recover from GBS, but some people can either develop permanent disability or die due to respiratory difficulties. It is not fully understood why some people develop GBS, but it is believed that stimulation of the body's immune system, as occurs

[50] IOM, Adverse Effects of Vaccines, 343.

[51] IOM, Adverse Effects of Vaccines, 18.

with infections, can lead to the formation of autoimmune antibodies and cell-mediated immunity that play a role in its development.

GBS may present as one of several clinicopathological subtypes. The most common type in North America and Europe, comprising more than 90 percent of cases, is acute inflammatory demyelinating polyneuropathy (AIDP), which has the pathologic and electrodiagnostic features of focal demyelination of motor and sensory peripheral nerves and roots. Demyelinating refers to a loss or disruption of the myelin sheath, which wraps around the axons of some nerve cells and which is necessary for the normal conduction of nerve impulses in those nerves that contain myelin. Polyneuropathy refers to the involvement of multiple peripheral nerves. Motor nerves affect muscles or glands. Sensory nerves transmit sensations. Another subtype called acute motor axonal neuropathy (AMAN) is generally seen in other parts of the world and is predominated by axonal damage that primary affects motor nerves. AMAN lacks features of demyelination. The axon is a portion of the nerve cell that transmits nerve impulses away from the nerve cell body. Another less common subtype of GBS includes acute motor and sensory neuropathy (AMSAN), which is an axonal form of GBS that is similar to AMAN, but also affects the axons of sensory nerves and roots.

The diagnosis of the AIDP, AMAN, and AMSAN subtypes of GBS requires bilateral flaccid (relaxed with decreased muscle tone) limb weakness and decreased or absent deep tendon reflexes in weak limbs, and a monophasic illness pattern with the interval between onset and nadir of weakness between 12 hours and 28 days with a subsequent clinical plateau. (The clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse. Death may occur without clinical plateau. Treatment-related fluctuations in all subtypes of GBS can occur within nine weeks of GBS symptom onset and recurrence of symptoms after this time frame would not be consistent with GBS.). In addition, there must not be a more likely alternative diagnosis for the weakness.

Other factors in all subtypes of GBS that add to diagnostic certainty but are not required for diagnosis include electrophysiologic findings consistent with GBS or cytoalbuminologic dissociation (i.e., elevation of cerebral spinal fluid (CSF) protein and a total white cell count in the CSF less than 50 cells per microliter).

The weakness in the AIDP, AMAN, and AMSAN subtypes of GBS is usually, but not always symmetric, and usually has an ascending pattern of progression from legs to arms. However, other patterns of progression may occur. The cranial nerves can be involved. Respiratory failure can occur due to respiratory involvement. Fluctuations in the degree of weakness prior to reaching the point of greatest weakness or during the plateau or improvement phase may occur, especially in response to treatment. These fluctuations occur in the first nine weeks after onset and are generally followed by eventual improvement.

According to the Brighton Collaboration,[52] Fisher Syndrome (FS), also known as Miller Fisher Syndrome, is a subtype of GBS characterized by ataxia, areflexia, and ophthalmoplegia, and overlap between FS and GBS may be seen with limb weakness. The diagnosis of FS requires bilateral ophthalmoparesis; bilateral reduced or absent tendon reflexes; ataxia; the absence of limb weakness (the presence of limb weakness suggests a diagnosis of AIDP, AMAN, or AMSAN); a monophasic illness pattern; an interval between onset and nadir of weakness between 12 hours and 28 days; subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms or subsequent improvement without significant relapse); no alteration in consciousness; no corticospinal track signs; and the absence of an identified more likely alternative diagnosis. Death may occur without a clinical plateau.

Exclusionary criteria for the diagnosis of GBS include the ultimate diagnosis of any of the following conditions: Chronic inflammatory demyelinating polyneuropathy (CIDP), carcinomatous meningitis, brain stem encephalitis (other than Bickerstaff brainstem encephalitis), myelitis, spinal cord infarct, spinal cord compression, anterior horn cell diseases such as polio or West Nile virus infection, subacute inflammatory demyelinating polyradiculoneuropathy, multiple sclerosis, cauda equina compression, metabolic conditions such as hypermagnesemia or hypophosphatemia, tick paralysis, heavy metal toxicity (such as arsenic, gold, or thallium), drug-induced neuropathy (such as vincristine, platinum compounds, or nitrofurantoin), porphyria, critical illness neuropathy, vasculitis, diphtheria, myasthenia gravis, organophosphate poisoning, botulism, critical illness myopathy, polymyositis, dermatomyositis, hypokalemia, or hyperkalemia. The above list is not exhaustive.[53]

For all subtypes of GBS (AIDP, AMAN, AMSAN, and FS), the onset of symptoms less than three days (72 hours) after exposure essentially excludes that exposure as a cause because the immunologic steps necessary to create symptomatic disease require a minimum of three days.

CIDP is clinically and pathologically distinct from GBS. The onset phase of CIDP is generally greater than eight weeks and the weakness may remit and relapse. CIDP is also not monophasic.[54]

In the past, GBS has been causally associated with certain vaccines. For example, rabies vaccines produced in nervous system tissue such as goat, sheep, or suckling mouse brain have been tied to an increased risk of GBS in people vaccinated with this vaccine. However, this method of vaccine production is no longer used in the United States.

Another example is the 1976 influenza A (swine flu) vaccine, which was found by the IOM to be causally associated with GBS. The risk of developing GBS in the six-week period after receiving the 1976 swine flu vaccine was 9.2 times higher than the risk for those who were not vaccinated.[55] Since the 1976 influenza season, numerous studies have been conducted to evaluate whether other influenza vaccines were associated with GBS. In most published studies, no association was found, but one large study published in the *New England Journal of Medicine* evaluated the 1992–93 and 1993–94 influenza seasons and suggested approximately one additional case of GBS out of one million persons vaccinated, in the six weeks following vaccination, may be attributable to the vaccine formulation used in those years. The background incidence of GBS not associated with vaccine among adults was documented in the study to be 0.87 cases per million persons for any 6-week period.[56]

[52] Sejvar, 599–612.

[53] Sejvar, 599–612.

[54] Sejvar, 599–612.

[55] Lawrence B. Schonberger, et al., ''Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976–1977,'' American Journal of Epidemiology, 25 Apr. 1979; 118 and IOM, ''Immunization Safety Review: Influenza Vaccines and Neurological Complications,'' (Washington, DC: The National Academies Press, 2004) 25.

[56] Tamar Lasky, et al., ''The Guillain-Barrè Syndrome and the 1992–1993 and 1993–1994 Influenza Vaccines,'' The New England Journal of Medicine, Dec. 17, 1998; 1797.

The IOM published a thorough scientific review of the peer reviewed literature in 2004 [57] and concluded that people who received the 1976 swine influenza vaccine had an increased risk for developing GBS. Based on its review of the published literature, the IOM also decided that the evidence linking GBS and influenza vaccines in influenza seasons other than 1976 was not clear. This led to the IOM's conclusion that the evidence was inadequate to accept or reject a causal relationship between influenza immunization and GBS for years other than 1976.

In 2012, the IOM published another report that evaluated the association of seasonal influenza vaccine and GBS. Pandemic vaccines, such as the influenza vaccine used in 1976 and the 2009 H1N1 influenza vaccine, were specifically not evaluated. The IOM concluded that the evidence is inadequate to accept or reject a causal relationship between seasonal influenza vaccine and GBS.[58]

The Working Group, in its February 7, 2012, final report to the NVAC regarding 2009 H1N1 safety surveillance, reported that a meta-analysis combining the results from each study group participating in the 2009 H1N1 enhanced safety surveillance revealed a small, statistically significant increased risk of GBS in the six weeks after receiving the 2009 H1N1 vaccine. The meta-analysis was predominantly based on enhanced safety surveillance studies performed by different investigators with different populations in the Emerging Infections Program (EIP), the Vaccine Safety Datalink (VSD), and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System.

The VSD enhanced safety surveillance includes active surveillance and medical record review in a well-defined population of nine million people. The self-controlled risk interval study design showed a statistically significant relative risk of 4.4 of GBS after monovalent inactivated 2009 H1N1 influenza vaccine. The corresponding risk difference or attributable risk was 5.0 per million vaccine doses in the six weeks following vaccination. The authors concluded that there was a relatively small elevated risk (a quadrupling of the risk) of GBS following monovalent inactivated 2009 H1N1 vaccine, but that there was no increased risk following the trivalent seasonal vaccine (when administered without 2009 H1N1) in the 2009–2010 influenza season.[59]

The EIP implemented active population-based surveillance for GBS following H1N1 vaccine in 10 different areas of the country, capturing a population of approximately 45 million people. Analyses using self-controlled methods found a statistically significant increased relative risk of GBS after 2009 H1N1 influenza vaccine of between 2.1 and 3.0, depending on the exact methods used. The corresponding attributable risks per million doses administered in the six weeks after vaccination were 1.5 and 2.8. The authors concluded that the results suggest a low increased risk (a doubling or tripling of the risk) of GBS following the monovalent 2009 H1N1 influenza vaccine.[60]

Another analysis using EIP data found a statistically significant adjusted rate ratio of 1.57 with a corresponding attributable risk of 0.74 excess GBS cases per one million vaccine doses in the six weeks following monovalent 2009 H1N1 influenza vaccination. The findings for seasonal vaccine demonstrated a rate ratio similar to that for 2009 H1N1 vaccine, but the association was not statistically significant. Although the authors conclude that the relationship between monovalent 2009 H1N1 influenza vaccine and GBS during the 2009–2010 influenza season was likely weak (the study found a 57 percent increased risk of GBS in the six weeks after vaccination compared to controls) and that the excess risk of GBS was small, these data support a causal connection due to the results showing a statistically significant increased risk.[61] The consistent trend across studies of an increased risk provides support that the measured association of a 57 percent increase in risk after the vaccination is real and that it reflects a causal association even if this one analysis demonstrates a modest or small increase in relative risk.

The EIP combined the data obtained from doses of the monovalent live attenuated 2009 H1N1 vaccine and the monovalent inactivated 2009 H1N1 vaccine and therefore the conclusions provide compelling evidence related to the administration of both vaccines and GBS.

The PRISM system is a cohort-based active surveillance network that conducted a retrospective analysis to determine if the 2009 H1N1 vaccine was associated with an increased risk of any of 14 pre-specified outcomes. Five health insurance and associated companies with 38 million members, together with nine immunization registries, contributed records related to approximately 2.6 million doses of 2009 H1N1 vaccine. The self-controlled risk interval analysis of chart-confirmed GBS cases found an elevated but not statistically significant incident rate ratio for GBS after inactivated 2009 H1N1 vaccine. The incident rate ratio was 2.5 with a confidence interval of 0.42 to 15.[62] Although this study does not reach statistical significance, the results trend in the same direction of an increased risk of GBS after receiving the 2009 H1N1 vaccine as outlined in, and consistent with, the studies above. The wide confidence interval suggests this analysis did not have sufficient power to reach statistical significance.

A meta-analysis was performed of the VSD, EIP, and PRISM data mentioned above, together with additional data from safety surveillance studies performed by Medicare, the Department of Defense, and the Department of Veterans Affairs, which analyzed data from 23 million vaccinated people. The meta-analysis found that the 2009 H1N1 inactivated vaccine was associated with a small increased risk of GBS within six weeks of vaccination. This excess risk is equivalent to 1.6 excess cases in the six weeks after vaccination per million people vaccinated.

The meta-analysis provides the benefit of additional statistical power. Statistical power reflects the ability of a study to detect a true effect from the exposure being studied. Additional statistical power allows for the analyses of certain hypotheses, not possible to analyze individually in the six studies that made up the meta-analysis. This increased risk found in the meta-analysis was consistent: (1) Across studies looking at different groups of people; (2) using different definitions of

[57] IOM, Immunization Safety Review: Influenza Vaccines and Neurological Complications, 25.

[58] IOM, Adverse Effects of Vaccines, 334.

[59] Sharon K. Greene, et al., ''Risk of Confirmed Guillain-Barrè Syndrome Following Receipt of Monovalent Inactivated Influenza A (H1N1) and Seasonal Influenza Vaccines in the Vaccine Safety Datalink Project, 2009–2010,'' American Journal of Epidemiology, Jun. 1, 2012; 1100.

[60] Jerome I. Tokars, et al., ''The Risk of Guillain-Barrè Syndrome Associated with Influenza A (H1N1) 2009 Monovalent Vaccine and 2009–2010 Seasonal Influenza Vaccines: Results from a Self-Controlled Analysis,'' Pharmacoepidemiology and Drug Safety, May 2012; 546.

[61] Matthew E. Wise, et al., ''Guillain-Barre Syndrome During the 2009–2010 H1N1 Influenza Vaccination Campaign: Population-based Surveillance Among 45 Million Americans,'' American Journal of Epidemiology, Jun. 1, 2012; 1110.

[62] W. Katherine Yih, et al., ''Surveillance for Adverse Events Following Receipt of Pandemic 2009 H1N1 Vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010,'' American Journal of Epidemiology, Jun. 1, 2012; 1120.

illness; (3) in people who received or did not receive a concurrent seasonal influenza vaccine or had influenza like symptoms; (4) across various time windows; and (5) in different age categories. This suggests that these five factors did not affect the risk of developing GBS.[63]

Considering the totality of the evidence, and particularly the enhanced surveillance studies and meta-analysis performed to monitor the safety of the 2009 H1N1 vaccine, compelling evidence demonstrates a small increased risk of GBS in the six weeks following administration of the 2009 H1N1 vaccine. The Program will therefore propose an onset interval of 3–42 days for GBS caused by the 2009 H1N1 influenza vaccine to be covered under the proposed Table. Day 3 begins 72 hours after administration of the vaccination and takes into account the time interval needed to show first signs or symptoms after exposure.[64] GBS is proposed for inclusion on the Table because it is a serious physical injury, and the fact that it may be directly caused by the use of the 2009 H1N1 vaccine is supported by compelling, reliable, valid, medical and scientific evidence.

Pandemic Influenza Countermeasure Conditions of Special Interest

Although the conditions listed below are of special interest to the public and are being monitored by HHS, the Secretary does not propose including them on the Table at this time because compelling, reliable, valid, medical and scientific evidence of causation does not currently exist. The conditions include the following:

(1) Spontaneous Miscarriage

The Secretary has a special interest in spontaneous miscarriages with respect to the 2009 H1N1 vaccine because pregnant women were a priority group targeted for this vaccination. Spontaneous miscarriages commonly occur regardless of the use or administration of any vaccines. There are about six million clinically recognized pregnancies in the United States each year, and approximately 15 percent of those pregnancies will end in clinically recognized miscarriages with no known cause (spontaneous miscarriages). This calculates to approximately 900,000 miscarriages per year, or an average of 2,466 per day in the United States regardless of vaccination status. Given the large number of women who experience spontaneous miscarriages with no known cause and the large number of pregnant women who received the 2009 H1N1 vaccine, it is expected that a significant number of pregnant women would demonstrate a coincidental temporal association between the vaccine and miscarriages with no other evidence of a causative role.

The H1N1 Working Group, in its February 7, 2012, final report to the NVAC regarding 2009 H1N1 safety surveillance, reported on pregnancy outcomes. Some studies showed weak statistical signals for an increased risk of pre-eclampsia and miscarriage after 2009 H1N1 vaccine administration. These results were not consistent across different studies, and there were several important methodological limitations to these analyses, suggesting that it was not a real association with the vaccine. The H1N1 Working Group concluded that surveillance associated with the 2009 H1N1 vaccine was adequate to detect serious pregnancy complications that occurred with a high incidence. However, a high incidence of serious pregnancy complications was not seen. To discern smaller effects, the Working Group recommended the performance of methodological work to enhance surveillance of vaccine adverse events in pregnant women.

There is, therefore, no compelling evidence to date supporting a causal relationship between the 2009 H1N1 vaccine and spontaneous miscarriage. For this reason, the Secretary does not propose including spontaneous miscarriage as a Table injury. Should compelling, reliable, valid, medical and scientific evidence demonstrate such a link, the Secretary may add this injury to the Table. Unless such an amendment is made, the Program will consider any claims for spontaneous miscarriage on a case-by-case basis as non-Table claims.

(2) Febrile Seizures

Influenza vaccinations are known to occasionally cause fever in some children. Seizures secondary to fever (febrile seizures) from any cause have been observed in 2–5 percent of children between the ages of three months and five years, with the peak age being 14 to 18 months.

For its 2012 report, the IOM reviewed the medical evidence for non-pandemic influenza vaccine causing seizures. The IOM had a moderate degree of confidence in the epidemiologic evidence. The studies reviewed had sufficient validity and precision to assess an association between influenza vaccine and seizures. These studies consistently reported a null association. The IOM concluded that the evidence is inadequate to accept or reject a causal relationship between seasonal influenza vaccine and seizures.[65] In addition, enhanced surveillance to assess the safety of the 2009 H1N1 vaccine provided evidence that this vaccine did not cause seizures.[66]

In 2011, enhanced surveillance for febrile seizures in the United States was conducted through the VSD. More than 200,000 children between the ages of six months and four years were studied. The analyses showed that febrile seizures following trivalent seasonal influenza vaccine and pneumococcal vaccine (PCV 13) given at different visits rarely occurred. The seizures were most common in children age 12 to 23 months when the two vaccines were given in the same health care visit. The analyses demonstrated one additional febrile seizure among every 2,000 to 3,000 children vaccinated. However, these analyses do not apply to the 2009 H1N1 vaccine.

Compelling, reliable, valid, medical and scientific evidence does not currently exist causally linking seizures, including febrile seizures, with the 2009 monovalent H1N1 influenza vaccine. The Program will consider a claim for febrile seizure leading to serious injury or death on a case-by-case basis as a non-Table claim.

(3) Bronchospasm

Bronchospasm is a constriction of the muscles in the walls of the smaller breathing tubes (bronchioles) in the lungs. It is facilitated by cells in the immune system under the influence of various stimuli. The resulting constriction and inflammation causes a narrowing of the airways and an increase in mucus production, which reduces air exchange. This causes breathlessness, coughing, and wheezing. Some common causes of bronchospasm in a susceptible person are allergic reactions to certain foods and medications, chemical irritation, and infections.

Evidence indicates that the 2009 H1N1 intranasal vaccine may be associated with bronchospasm in children younger than two years of age; however, this has not been observed consistently in older individuals. For this reason, the intranasal vaccine is not recommended for children younger than two years of age. To date, no direct link

[63] Daniel A. Salmon et al., ''Association Between Guillain-Barre Syndrome and Influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a Meta-analysis,'' Lancet, electronically published March 13, 2013, *http://dx.doi.org/10.1016/S0140-6736(12)62189-8*.

[64] Peripheral Neuropathy (Philadelphia, PA: Elsevier Saunders, 2005), 626.

[65] IOM, Adverse Effects of Vaccines, 304.

[66] Yih, 1123.

has been shown between bronchospasm and the 2009 H1N1 vaccination through surveillance when given to recommended populations. Therefore, the Secretary does not propose including bronchospasm on the Table for the 2009 H1N1 vaccine at this time.

In its 2012 report, the IOM concluded that the evidence is inadequate to accept or reject a causal relationship between seasonal Live Attenuated Influenza Vaccine (LAIV) and asthma exacerbation or reactive airway disease episodes in both children younger than five years of age and persons who are five years of age or older. In addition, this same IOM committee concluded that the evidence favors rejection of a causal relationship between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults.[67]

Should compelling, reliable, valid, medical and scientific evidence arise to demonstrate a direct link between bronchospasm and the 2009 H1N1 vaccine with respect to populations for which the vaccine is indicated, the Secretary may add this injury to the Table. Unless such an amendment is made, the Program will consider any claims for bronchospasm leading to serious injury or death on a case-by-case basis as a non-Table claim.

Pandemic Influenza Antiviral Medications

Influenza antiviral medications including Tamiflu and Relenza have been reported in controlled trials to shorten the time to symptom improvement in acute uncomplicated influenza caused by circulating viral strains; based on retrospective observational studies and pooled analyses, many experts believe they can reduce the severity and duration of influenza and can reduce the risk of influenza-related complications, severe illness, and death. Tamiflu, Relenza, and peramivir have been used to combat influenza A and B viruses by inhibiting the viral neuraminidase enzyme involved in releasing viral particles from the infected cell. These antivirals were used to treat and protect against illness due to the 2009 H1N1 virus in the 2009–2010 pandemic influenza season. Tamiflu and Relenza are covered when used to treat or protect against a current or potential pandemic influenza. Peramivir is covered when used to treat 2009 H1N1 influenza during the 2009 pandemic season. The use of these drugs for the treatment or prevention of seasonal influenza is not covered.

[67] IOM, Adverse Effects of Vaccines, 356.

Tamiflu is a prescription medicine taken by mouth for the prevention and treatment of influenza. Similarly, Relenza is an inhaled prescription drug used for the prevention and treatment of influenza. Peramivir is an intravenous investigational antiviral drug currently limited in use in the United States. For example, it has been used in clinical trials and for a time was available under an emergency use authorization (EUA) in response to the 2009 H1N1 pandemic. However, this EUA is currently not in effect.

The proposed Table currently includes anaphylaxis for Tamiflu, Relenza and peramivir because compelling, reliable, valid, medical and scientific evidence establishes a causal relationship between these drugs and anaphylaxis. A discussion of anaphylaxis can be found in the pandemic influenza vaccines section of this preamble to this NPRM. Further support for causation is based on the well-established biological mechanism that anaphylaxis, according to the IOM reports of 1994 and 2003 on vaccine adverse events, can occur after exposure to a foreign antigen or drug and by the temporal sequence of observed events following exposure. In addition, the spectrum of host responses that follows a logical biologic gradient, as described by the IOM, from mild hypersensitivity reactions to true anaphylaxis have been observed and are known to occur in post marketing surveillance for Tamiflu and Relenza. During the pandemic there was only limited use of peramivir under IND or EUA in the United States, and postmarketing experience comparable to Tamiflu and Relenza is not available, but peramivir is included here on the basis of experience with similar drugs.

Compelling, reliable, valid, scientific and medical evidence supports that antiviral drugs can cause anaphylaxis if the onset of the condition occurs within four hours after the administration or use of the antiviral.[68] According to the American College of Allergy, Asthma, and Immunology, any person can develop an allergic drug reaction to any drug (*http://www.acaai.org/allergist/allergies/Types/drug-allergy/Pages/default.aspx*).

Tamiflu capsules contain gelatin, which is a protein known to cause allergic reactions and anaphylaxis in sensitized individuals. With Relenza, each dose inhaled contains lactose powder that also contains milk proteins, which may cause the spectrum of allergic reactions in sensitized individuals. Based on the unique nature of the presentation and timing of anaphylaxis together with consensus in the medical community regarding causation and the existing medical literature, the Secretary proposes including anaphylaxis on the Table for Tamiflu, Relenza, and peramivir. For the reasons discussed for anaphylaxis, the Secretary proposes including an onset interval of 0–4 hours on the Table after the administration or use of Tamiflu, Relenza, or peramivir. Anaphylaxis is proposed for inclusion on the Table because it is a serious physical injury that may be directly caused by the use of these antiviral medications, as supported by compelling, reliable, valid, medical and scientific evidence.

[68] Werner J. Pichler, et al., ''Drug Hypersensitivity Reactions: Pathomechanisms and Clinical Symptoms,'' Medical Clinics North America, July 2010; 651–654.

Since only serious physical injuries qualify as covered injuries, the Secretary does not propose including minor adverse events for Tamiflu, Relenza and peramivir on the Table. Minor side effects associated with Tamiflu include nausea and vomiting, which usually occur in the first two days of treatment. Minor side effects associated with Relenza include cough, nasal irritation, nausea, vomiting, headache, and ear, nose, and throat infections. The more commonly reported side effects of peramivir, which may or may not be related causally, are diarrhea, nausea, vomiting, and a decrease in white blood cell count. These side effects were reported from clinical trials. Possible side effects of receiving any medication (including peramivir) by vein are brief pain, bleeding, bruising of the skin where the needle entered, soreness and swelling, and inflammation or infection at the needle entry point. These reactions are usually minor and resolve without complication. However, in cases in which these symptoms worsen and lead to serious physical injury or death, the Program will consider these claims on a case-by-case basis as non-Table claims.

Pandemic Influenza Antivirals Conditions of Special Interest

The Secretary does not propose to include the following conditions associated with the antiviral drugs on the Table at this time, although they are of special interest to the public. These conditions may be added in the future if compelling, reliable, valid, medical and scientific evidence becomes available showing a direct link between the antiviral drug(s) and these conditions. Such conditions include:

(1) Bronchospasm

Bronchospasm is a constriction of the muscles in the walls of smaller breathing tubes (bronchioles) in the lungs. It is facilitated by cells in the immune system under the influence of various stimuli. The resulting constriction, inflammation, and increased mucus production causes a narrowing of the airways which reduces air exchange and may lead to breathlessness, coughing, and/or wheezing.

Serious cases of bronchospasm, including fatalities, have been reported to FDA and manufacturers during treatment with Relenza in patients with and without underlying airway disease.[69] Many of these cases were reported during post-marketing surveillance and causality was difficult to assess because, for example, some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble this adverse drug reaction.

Should compelling, reliable, valid, medical and scientific evidence become available and demonstrate a direct link between bronchospasm and Relenza the Program may add this injury to the Table. Unless such an amendment is made, the Program will consider any claims for bronchospasm leading to serious injury or death on a case-by-case basis as non-Table claims.

(2) Neuropsychiatric Events

Rarely, transient neuropsychiatric events such as self-injury or delirium have been reported in post-market monitoring among persons taking Tamiflu and Relenza. The majority of reports were among children and adolescents living in Japan. Because influenza infection itself may be associated with a variety of neurologic and behavioral symptoms (e.g., seizures, delirium and hallucinations), it is unclear whether the antiviral drugs are responsible for these neuropsychiatric effects. To date, retrospective analyses conducted by the manufacturers of Tamiflu and Relenza and the Vaccine Safety Datalink have not found evidence for an increased risk of neuropsychiatric events after Tamiflu or Relenza use.[70]

Should compelling, reliable, valid, medical and scientific evidence become available and demonstrate a direct link between neuropsychiatric effects and Tamiflu and/or Relenza, the Program may add these injuries to the Table. Unless such an amendment is made, the Program will consider any claims for neuropsychiatric effects leading to serious injury or death on a case-by-case basis as non-Table claims.

Pandemic Influenza Personal Respiratory Protection Devices

To reduce the risk of infection in certain populations and areas with confirmed cases of 2009 H1N1 influenza, the CDC has put forward recommendations for the use of personal respiratory protection devices. Personal respiratory protection devices are for use by individuals to reduce wearer exposure to pathogenic biological airborne particulates according to the Secretarial declaration of December 17, 2008.[71] Such devices also can be used to reduce transmission of infection from the person wearing the device to another. Examples of personal respiratory protection devices are ''facemasks'' and respirators. The term ''facemask'' refers to disposable facemasks approved by FDA for use as medical devices, including facemasks labeled as surgical, dental, medical procedure, isolation, or laser masks. These facemasks loosely fit the face. They have specific levels of protection from penetration of blood and body fluids and help stop droplets from being spread by the individuals wearing them. Furthermore, a facemask acts to prevent splashes or sprays from reaching the mouth and nose of the person wearing the facemask. A facemask generally does not protect against breathing in very small aerosolized particles that may contain viruses.

A respirator refers to an N95 or higher filtering face piece respirator. A respirator that fits properly on the face can filter out virus-containing small particles in the aerosol that can be generated by an infected person. Compared to a facemask, it is harder to breathe through a respirator for long periods of time. Although some respirators may cause latex or contact allergies, these reactions are generally self-limited and do not usually rise to the level of serious injury.

The Secretary considered potential injuries due to the use or administration of personal respiratory protection devices. The use of personal respiratory protection devices may cause injury in some wearers. However, the Secretary finds that use or administration of personal respiratory protection devices generally are not known to cause serious physical injuries. Therefore, the proposed Table indicates that there presently is ''[N]o condition covered'' for this countermeasure. Injuries may be added in the future if compelling, reliable, valid, medical and scientific evidence develops revealing a causal relationship between a personal respiratory protection device and a serious adverse event. The Program will consider a claim leading to serious injury or death from the use or administration of a personal respiratory protection device on a case-by-case basis as a non-Table claim.

Pandemic Influenza Respiratory Support Devices

Infection with the 2009 H1N1 virus and other pandemic strains of influenza can lead to serious respiratory tract disease, including pneumonia. Additionally, influenza infection can make people more susceptible to bacterial pneumonia and other serious complications. Individuals infected with covered influenza A viruses may require respiratory support with respiratory devices, such as mechanical ventilators, lung expansion devices, and extracorporeal membrane oxygenation (ECMO). Mechanical ventilators assist or control respiration continuously. Lung expansion devices include products such as intermittent positive-pressure breathing, nasal positive end-expiratory pressure, and continuous nasal positive airway pressure. ECMO mechanically provides for essential lung functions outside the body.

Generally, patients requiring respiratory support devices already have a significant degree of injury or compromise to their lungs. Notwithstanding any prior lung injuries, it is possible to sustain serious respiratory tract damage directly from these devices. Complications from the underlying influenza infection may have a great deal of overlap with effects or adverse events secondary to the use of respiratory support devices.

The proposed Table includes post-intubation tracheal stenosis, ventilator-induced lung injury (VILI), ventilator-associated pneumonia (VAP), and ventilator-associated tracheobronchitis (VAT) as injuries caused by mechanical ventilators. Bleeding events also are listed as Table injuries associated with receiving anticoagulation medication for ECMO. These are proposed for inclusion on the Table because they are serious

[69] Relenza (zanamivir) Inhalation Powder, for oral inhalation [package insert]. Research Triangle Park, NC: GlaxoSmithKine: December 2011. *http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021036s027lbl.pdf.* Accessed March 22, 2013.

[70] Toovey, Stephen, et al., ''Post-Marketing Assessment of Neuropsychiatric Adverse Events in Influenza Patients Treated with Oseltamivir: An Updated Review,'' Adv Ther, October 2012; 826–48; and Greene, Sharon, et al., ''Risk of adverse events following oseltamivir treatment in influenza outpatients, Vaccine Safety Datalink Project, 2007–2010,'' Pharmacoepidemiology and Drug Safety, October 2012; published online (no page numbers).

[71] 73 FR 78362.

physical injuries that may be directly caused by the use of respiratory support devices, as supported by compelling, reliable, valid, medical and scientific evidence.

Tracheal Stenosis

The proposed Table includes tracheal stenosis, which is an abnormal narrowing in the windpipe that can increase the work of breathing. Oral or nasal endotracheal tubes or tracheostomy tubes (tubes placed in the throat to assist with breathing) are most commonly used to deliver mechanical ventilatory support in respiratory failure. Despite technological improvements, tracheal stenoses still constitute an important group of complications after intubation and tracheostomy. Early endotracheal tubes were not designed to minimize pressure from the tube's cuff, leading to a much higher incidence of tracheal stenosis than is seen with more modern endotracheal tubes with more compliant cuffs. These newer cuffs have been shown to greatly reduce, but not eliminate, the incidence of tracheal stenosis. Endotracheal intubation is used to secure a patient's airway, to act as a means to deliver oxygen gas from the ventilator to the patient, to prevent aspiration, and/or to help to clear secretions. Pressure from the endotracheal tube itself or from the cuff of the endotracheal tube, which achieves a pneumatic seal between the tube and trachea, can lead to regions of tracheal ischemia (a restriction in blood supply) that may eventually cause tracheal stenosis.

The reported incidence of symptomatic or clinically significant tracheal stenosis following tracheostomy and laryngotracheal intubation currently is less than one percent. When stenosis occurs, the process leading to airway narrowing can begin at any time after intubation or placement of a tracheostomy tube. Tracheal stenosis due to endotracheal intubation mostly occurs at the cuff of the tube due to decreased blood flow to the trachea caused by the cuff. The most important reason for stenosis at the tracheal stoma site (the opening of a tracheostomy) is damaged cartilage and wound infection. In addition, previous cervical or tracheal trauma can negatively affect healing of the stoma leading to stenosis.

The usual presenting symptoms of tracheal stenosis may include shortness of breath, stridor (an abnormal, high-pitched, inspiratory sound produced by turbulent airflow through a partially obstructed airway), and/or wheezing. A slow resumption of physical activity after being on a ventilator can mask or delay the first symptom or manifestation of the onset of injury of tracheal stenosis. These obstructive symptoms appearing in a person who is at rest indicate the diameter of the trachea has decreased to 30 percent or less of its normal size at the point of narrowing. Less stenosis can become symptomatic with exertion, and shortness of breath on exertion is the most common presenting symptom. Symptoms usually develop within 2 to 42 days after removal of the tube in people who develop symptoms.

The length and severity of a tracheal stenosis lesion is ideally determined by bronchoscopic evaluation including laryngoscopy to assess vocal cord function and the presence and location of stenosis in the windpipe. Computerized axial tomography (CT) scans can serve as a rough guide to the location of the stenosis. Other causes of tracheal stenosis include malignant and benign tumors, infections of the trachea (such as tuberculosis and fungal diseases), radiotherapy, tracheal surgery, trauma, congenital abnormality, inflammatory diseases, and autoimmune diseases.

Compelling, reliable, valid, medical and scientific literature support a direct link between tracheal stenosis and ventilators due to the placement of an endotracheal or a tracheostomy tube.[72] Therefore, this injury is proposed for inclusion on the Table.

Ventilator-Associated Pneumonia (VAP) and Ventilator-Associated Tracheobronchitis (VAT)

VAP and VAT are other potential conditions that can be caused by ventilator use. VAP and VAT are defined as occurring in patients who manifest pneumonia or tracheobronchitis more than 48 hours after being intubated. There is no minimum period of time of ventilator use for the pneumonia or tracheobronchitis to be considered ventilator-associated. Bacteria growing in the mouth and on the breathing tube can easily enter the normally bacteria-free trachea and lungs, and this is generally the source of the bacteria for VAP and VAT. Most of the diagnostic criteria for VAP and VAT include clinical symptoms and signs of infection, including the signs of a lung infection, new onset of fever, purulent sputum (upper respiratory secretions containing pus), leukocytosis (increased white blood cell count), leukopenia (decreased white blood cell count), wheezing, cough, bradycardia (diminished heart rate), chest pain, coughing blood, abnormal breath sounds, altered mental status, laboratory evidence of infection, and a decline in the ability to oxygenate and remove carbon dioxide from the blood.[73] An individual with these symptoms and signs and no abnormalities on chest x-ray may have VAT because the infection in the trachea may not be seen on a chest x-ray. Patients with chest x-ray findings consistent with pneumonia may have VAP. VAT can be related to VAP with regard to cause, but is different because the location of the infection is in the trachea instead of the lungs.

VAP is the most common infection acquired in intensive care units. Recent publications report that the rate of VAP ranges from 0.0 to 5.8 cases per 1,000 ventilator days.[74] Patients with VAP require more days of mechanical ventilation and hospitalization, and more medications. The mortality rate may exceed 10 percent.

There is compelling reliable, valid, medical and scientific evidence indicating that VAP and VAT are injuries that may be caused by mechanical ventilator use.[75] Thus, VAP and VAT are proposed Table injuries for respiratory support devices that are used to mechanically ventilate covered patients.

There may be cases where an individual has VAP or VAT but does not meet the proposed definition of VAP or VAT. Such cases will be evaluated on a case-by-case basis, and the Secretary will determine medical eligibility based on the presence of compelling, reliable, valid, medical and scientific evidence.

Ventilator-Induced Lung Injury (VILI)

The medical literature demonstrates that mechanical ventilation can harm the lung and result in VILI.[76] VILI occurs as a result of mechanical trauma to lung structures induced by the positive pressure delivered to the lungs

[72] John C. Wain, Jr., ''Postintubation Tracheal Stenosis,'' Seminars in Thoracic and Cardiovascular Surgery, Fall 2009; 284–286; and Mitlu M. Gokhan and Phillip Factor, ''Complications of Mechanical Ventilation,'' Respiratory Care Clinics of North America; Jun. 2, 2000; 230.

[73] Centers for Disease Control and Prevention (CDC), Ventilator-Associated Event; January 2013; *http://www.cdc.gov/nhsn/PDFs/pscManual/10-VAE_FINAL.pdf.*

[74] CDC, 6–1.

[75] Dennis L. Kasper, MD, Harrison's ''Principles of Internal Medicine, 16th edition''; (United States of America: McGraw-Hill, 2005); 777; and Susan E Coffin, et al., ''Strategies to Prevent Ventilator Associated Pneumonia in Acute Care Hospitals,'' Infection Control and Hospital Epidemiology, Oct. 2008; S31–S40.

[76] Lee Goldman, MD and J. Claude Bennett, MD, ''Cecil's Textbook of Medicine, 21st edition''; (United States of America: W.B. Saunders, 2000); 493.

by the ventilator. The positive pressure produces alveolar (air sac) stretching leading to non-physiologic (abnormal) stretching which leads to lung damage (volutrauma). Trauma caused by the positive pressure from the ventilator is called barotrauma. The non-physiologic stress and strain produced by barotraumas and volutrauma can promote the release of inflammatory chemicals (cytokines) resulting in lung inflammation. This biological reaction to mechanical forces is known as biotrauma. Serious abnormal conditions included under VILI, that are known to be caused by the barotrauma and volutrauma forces generated by mechanical ventilators, include pneumothorax (a type of lung collapse), pneumomediastinum (abnormal air in the middle portion of the chest), lung cysts, systemic air embolism, and acute respiratory distress syndrome (ARDS).[77]

Compelling, reliable, valid, medical and scientific evidence indicates that VILI is an injury directly caused by mechanical ventilator use. Thus, VILI is proposed to be added to the Table as a covered injury for respiratory support devices that are used to mechanically ventilate patients who have developed an infection caused by a pandemic influenza.

As mentioned above, diffuse alveolar damage that is identical to ARDS may occur as a result of alveolar trauma resulting from mechanical ventilation. In addition, ARDS may also be caused by an underlying airway disease that leads to the requirement of mechanical ventilation. The mechanical ventilation may or may not aggravate a case of ARDS caused by something other than a respiratory support device. It may be difficult to differentiate the cause for ARDS because it can be caused by: (1) An underlying lung disease; (2) a 2009 H1N1 influenza pneumonia; or (3) the ventilator treatment needed to support a patient with 2009 H1N1 influenza pneumonia. ARDS is a frequent complication of severe influenza pneumonia.[78]

Because of the difficulties in determining the cause of ARDS, for purposes of the Table, ARDS will not be considered part of the VILI disease spectrum and will not be added to the Table. However, the Program will consider a claim for ARDS leading to serious injury or death on a case-by-case basis as a non-Table claim.

Positive pressure mechanical ventilation may also compromise the cardiovascular system because the positive airway pressure during inspiration reduces blood return to the heart and may decrease cardiac output with decreased profusion.[79] A decreased cardiac output can adversely affect multiple organ systems. Because of the complexity of the potential effects of this diminished cardiac output on multiple organ systems, these cases will be reviewed on a case-by-case basis.

Extracorporeal Membrane Oxygenation

As mentioned under the previous section, the 2009 H1N1 influenza virus was a worldwide cause of acute respiratory distress syndrome (ARDS). Most people with fatal 2009 H1N1 influenza infections died as a result of unrelenting hypoxemia (low oxygen levels in the blood) and respiratory failure. Conventional treatment of this condition with a ventilator can lead to additional lung injury due to factors such as barotrauma, volutrauma, and biotrauma. Select patients with severe ARDS who do not respond to advanced modes of mechanical ventilation may have extracorporeal membrane oxygenation (ECMO) as a treatment option. ECMO uses cardiac bypass technology to provide gas exchange (the function of the lungs) mechanically outside the body in a bedside machine. This temporary takeover of the lung function by ECMO allows ventilator settings to be reduced, thereby causing less lung damage and providing the opportunity for the lungs to heal and improve.

With ECMO, catheters are inserted through the skin into large veins for drainage and infusion of blood. People on ECMO must have their blood thinned (anti-coagulated). ECMO involves the removal of large volumes of venous blood from the person receiving treatment, and then circulating the blood with a pump outside the body through an oxygenator (artificial lung) that inserts oxygen into the blood and a carbon dioxide scrubber that removes carbon dioxide. The oxygenated blood is then re-infused back into the treated person as arterial blood.

An international registry compiled by the Extracorporeal Life Support Organization, referred to as the ''ECMO registry,'' indicates that ECMO has been used frequently to treat H1N1 influenza associated with respiratory failure. This is likely because critically ill H1N1 patients are mostly young, otherwise healthy people without other significant illnesses who are therefore prime candidates for ECMO. The most recent statistics from the H1N1 ECMO registry reflect that as of April 13, 2011, there were 323 patients from 76 centers on the registry.[80]

An observational study that examined 68 patients with 2009 H1N1 influenza-associated ARDS treated with ECMO found that 54 percent of patients had bleeding complications (due to the necessary anti-coagulation), with the most common sources being the catheter insertion site (22 percent), the gastrointestinal tract (10 percent), the respiratory tract (10 percent), vaginal bleeding (9 percent), and intracranial hemorrhage (9 percent).[81]

The above-referenced bleeding complications are related to the use of ECMO and may be a consequence of the use of this countermeasure. These events constitute serious physical injuries that may be caused by the use of ECMO, as supported by compelling, reliable, valid, medical and scientific evidence, and therefore are proposed to be added to the Table. The time interval for the first manifestation of the covered injury is the time period during which the injured person is under the effects of the anti-coagulant therapy, including the time needed to clear any clinically significant effect after the medication is stopped, as measured by relevant coagulation testing.

Pandemic Influenza Diagnostic Testing Devices

Pandemic influenza diagnostics are tests to identify or otherwise aid in the diagnosis of avian or other animal influenza A viruses that pose a pandemic threat.[82] A number of diagnostic tests are available to detect the presence of influenza infection in respiratory specimens. The tests differ in many ways, including their sensitivity and specificity for detecting influenza viruses, their commercial availability, processing time, approved clinical setting, and ability to distinguish among different influenza virus types and among influenza A subtypes (e.g., 2009 H1N1 versus seasonal H1N1 versus seasonal H3N2 viruses).

The tests most commonly used to diagnose infection with the 2009 H1N1 virus are the real-time reverse transcriptase polymerase chain reaction

[77] Goldman, 493 and Luciano Gattinoni, et al., ''Ventilator-induced lung injury: The anatomical and physiological framework,'' Critical Care Medicine, Oct 2010; S539–S540.

[78] Goldman, 1799.

[79] Goldman, 493.

[80] Extracorporeal Life Support Organization, H1N1 ECMO Registry, Apr. 13, 2011, *http://www.elso.med.umich.edu/h1n1registry.html.* At this time Extracorporeal Life Support Organization has stopped collecting additional information on H1N1 cases.

[81] Andrew Davies, et al., ''Extracorporeal Membrane Oxygenation for 2009 Influenza A (H1N1) Acute Respiratory Distress Syndrome,'' Journal of the American Medical Association, Nov. 4, 2009; 1892.

[82] 73 FR 78362.

tests (rRT–PCR tests). The rRT–PCR tests identify the 2009 H1N1 virus by amplifying the viral genetic material from a sample. A positive result indicates that the patient is presumptively infected with the 2009 H1N1 virus, but it does not identify the stage of infection. A negative result does not, by itself, exclude the possibility of the 2009 H1N1 virus infection.

Tests, such as a CT scan or magnetic resonance imaging (MRI), performed to determine the extent or seriousness or *sequelae* of influenza infection in a patient are not considered diagnostic tests for the purpose of diagnosing the presence of pandemic infection in the individual or for the purposes of this Program. Only influenza diagnostic tests performed for the purpose of identifying the presence in the body of the pandemic influenza virus are covered.

The Secretary considered potential serious injuries due to the use or administration of pandemic influenza diagnostics testing devices. Adverse events associated with the use or administration of these testing devices include potential consequences of an inaccurate result and potential discomfort during sample collection. However, these diagnostic testing devices are generally not known to cause serious physical injury. Therefore, the proposed Table does not list any injuries related to pandemic influenza diagnostic testing devices and indicates that there presently is ''[N]o condition covered'' for this countermeasure. However, injuries may be added to the Table if compelling, reliable, valid, medical and scientific evidence develops showing causation between a serious physical injury and a diagnostic test. The Program will consider a claim from the administration or use of diagnostic testing devices leading to serious injury or death on a case-by-case basis as a non-Table claim.

Compensation will not be available merely because a diagnostic test provides inaccurate results, such as failure to diagnose a pandemic influenza infection that is present or yielding a positive result for a pandemic influenza infection that is not present. The Program cannot compensate for injuries that are the direct result of the covered condition or disease for which the countermeasure was administered or used, and that are not the direct result of the administration or use of the covered countermeasure (for example, if the covered countermeasure is ineffective). See 42 CFR 110.20(d).

Regulatory Impact Analysis

HRSA has examined the impact of this rulemaking as required by Executive Order 12866 on Regulatory Planning and Review (September 30, 1993), Executive Order 13563 on Improving Regulation and Regulatory Review (January 18, 2011), the Congressional Review Act (5 U.S.C. 804(2)), the Regulatory Flexibility Act (RFA) (September 19, 1980, Pub. L. 96–354), section 202 of the Unfunded Mandates Reform Act of 1995 (March 2, 1995; Pub. L. 104–4), section 654(c) of the Treasury and General Government Appropriations Act of 1999, and Executive Order 13132 on Federalism (August 4, 1999).

Executive Order 12866 requires that all regulations reflect consideration of alternatives, costs, benefits, incentives, equity, and available information. Regulations must meet certain standards, such as avoiding an unnecessary burden. Regulations that are ''significant'' because of cost, adverse effects on the economy, inconsistency with other agency actions, effects on the budget, or novel legal or policy issues, require special analysis. In 2011, President Obama supplemented and reaffirmed Executive Order 12866. This rulemaking is not being treated as a significant regulatory action under section 3(f) of Executive Order 12866. Accordingly, the proposed rule has not been reviewed by the Office of Management and Budget.

Executive Order 13563 provides that, to the extent feasible and permitted by law, the public must be given a meaningful opportunity to comment through the Internet on any proposed regulations, with at least a 60-day comment period. In addition, to the extent feasible and permitted by law, agencies must provide timely on-line access to both proposed and final rules of the rulemaking docket on Regulations.gov, including relevant scientific and technical findings, in an open format that can be searched and downloaded. Federal agencies must consider approaches to maintain the freedom of choice and flexibility, including disclosure of relevant information to the public. Regulations must be guided by objective scientific evidence, easy to understand, consistent, and written in plain language. Furthermore, Federal agencies must attempt to coordinate, simplify, and harmonize regulations to reduce costs and promote certainty for the public.

In this NPRM, the Secretary proposes a Table identifying serious physical injuries that shall be presumed to result from the administration or use of the covered countermeasures, and the time interval in which the onset of the first symptom or manifestation of each such serious physical injury must manifest in order for such presumption to apply. The Secretary is also proposing Table definitions and requirements. This proposed rule would have the effect of affording certain persons a presumption that particular serious physical injuries were sustained as the result of the administration or use of covered countermeasures. The Table, if implemented, will establish a presumption of causation and relieve requesters of the burden of demonstrating causation for covered injuries listed on the Table. However, this presumption is rebuttable based on the Secretary's review of the evidence. This Table may afford some requesters a new filing deadline.

Other than showing that a serious physical injury or death directly resulted from an injury included on the Table for compensation purposes, individuals may, in the alternative, receive compensation if they are eligible and can show a causation-in-fact relationship between an injury or death and a covered countermeasure. This NPRM is based upon legal authority.

Because any resources required to implement the regulatory requirements imposed by the Program are not required by virtue of the establishment of a Table, and because the Secretary conducted an independent analysis concerning any burdens associated with the implementation of the Program when the Secretary published the companion regulation [83] setting forth the Program's administrative implementation, the Secretary has determined that no resources are required to implement the provisions included in this NPRM. Therefore, in accordance with the Regulatory Flexibility Act of 1980 (RFA) and the Small Business Regulatory Enforcement Fairness Act of 1996, which amended the RFA, the Secretary certifies that this NPRM will not have a significant impact on a substantial number of small entities.

The Secretary has also determined that this NPRM does not meet the criteria for a major rule as defined by Executive Order 12866 and would have no major effect on the economy or Federal expenditures. The Secretary has determined that this NPRM is not a ''major rule'' within the meaning of the statute providing for Congressional Review of Agency Rulemaking, 5 U.S.C. 801. Similarly, it will not have effects on State, local, and tribal governments and on the private sector such as to require consultation under the Unfunded Mandates Reform Act of

[83] 75 FR 64955.

1995. This NPRM comports with the 2011 supplemental requirements.

Unfunded Mandates Reform Act of 1995

The Secretary has determined that this NPRM will not have effects on State, local, and tribal governments and on the private sector such as to require consultation under the Unfunded Mandates Reform Act of 1995.

Federalism Impact Statement

The Secretary has also reviewed this NPRM in accordance with Executive Order 13132 regarding federalism, and has determined that it does not have ''federalism implications.'' This NPRM, if implemented, would not ''have substantial direct effects on the States, or on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.''

Impact on Family Well-Being

This NPRM will not adversely affect the following elements of family well-being: Family safety, family stability, marital commitment; parental rights in the education, nurture, and supervision of their children; family functioning, disposable income, or poverty; or the behavior and personal responsibility of youth, as determined under section 654(c) of the Treasury and General Government Appropriations Act of 1999. In fact, this NPRM may have a positive impact on the disposable income and poverty elements of family well-being to the extent that injured persons or their families may receive medical, lost employment income, and/or death benefits paid under this part without imposing a corresponding burden on them.

Paperwork Reduction Act of 1995, as Amended

This NPRM has no information collection requirements.

List of Subjects in 42 CFR Part 110

Anaphylaxis, Anticoagulation, Antiviral, Avian, Benefits, Biologics, Bleeding, Bursitis, Compensation, Countermeasure, Declaration, Deltoid, Diagnostics, Device, Eligibility, Extra-Corporeal Membrane Oxygenation (ECMO), Fisher Syndrome, Guillain-Barre Syndrome, 2009 H1N1, Influenza, Injury Table, Immunization, Oseltamivir, Pandemic, Peramivir, Public Readiness and Emergency Preparedness Act (PREP Act), Radiation Syndrome, Respiratory Protection, Relenza, Respirator, Respirator Support, Tamiflu, Tracheal Stenosis, Vaccine, Vasovagal Syncope, Ventilator, Ventilator-Associated Pneumonia and Tracheobronchitis, Ventilator-Induced Lung Injury, Zanamivir.

Dated: February 28, 2014.

Mary Wakefield,

Administrator, Health Resources and Services Administration.

Approved: March 13, 2014.

Kathleen Sebelius,

Secretary.

Therefore, for the reasons stated in the preamble, the Department of Health and Human Services proposes to amend 42 CFR part 110 as follows:

PART 110—COUNTERMEASURES INJURY COMPENSATION PROGRAM

■ 1. The authority citation for part 110 continues to read as follows:

Authority: 42 U.S.C. 247d–6e.

■ 2. Add § 110.100 to subpart K to read as follows:

§ 110.100 Injury tables.

(a) *Pandemic Influenza Countermeasures Injury Table.*

Covered countermeasures under secretarial declarations	Serious physical injury (illness, disability, injury, or condition) [1]	Time interval (for first symptom or manifestation of onset of injury after administration or use of covered countermeasure, unless otherwise specified)
I. Pandemic influenza vaccines administered by needle into or through the skin.	A. Anaphylaxis	A. 0–4 hours.
	B. Deltoid Bursitis	B. 0–48 hours.
	C. Vasovagal Syncope	C. 0–1 hour.
II. Pandemic influenza intranasal vaccines	A. Anaphylaxis	A. 0–4 hours.
III. Pandemic influenza 2009 H1N1 vaccine	A. Guillain-Barrè Syndrome	A. 3–42 days (not less than 72 hours and not more than 42 days).
IV. Oseltamivir Phosphate (Tamiflu) when administered or used for pandemic influenza.	A. Anaphylaxis	A. 0–4 hours.
V. Zanamivir (Relenza) when administered or used for pandemic influenza.	A. Anaphylaxis	A. 0–4 hours.
VI. Peramivir when administered or used for 2009 H1N1 influenza.	A. Anaphylaxis	A. 0–4 hours.
VII. Pandemic influenza personal respiratory protection devices.	A. No condition covered [2]	A. Not applicable.
VIII. Pandemic influenza respiratory support devices.	A. Postintubation Tracheal Stenosis	A. 2–42 days (not less than 48 hours and not more than 42 days) after extubation (removal of a tracheostomy or endotracheal tube).
	B. Ventilator-Associated Pneumonia and Ventilator-Associated Tracheobronchitis.	B. More than 48 hours after intubation (placement of an endotracheal or tracheostomy tube) and up to 48 hours after extubation (removal of the tube).
	C. Ventilator-Induced Lung Injury	C. Throughout the time of intubation (breathing through an endotracheal or tracheostomy tube) and up to 48 hours after extubation (removal of the tube).
IX. Pandemic influenza respiratory support device: extra-corporeal membrane oxygenation (ECMO).	A. Bleeding Events	A. Throughout the time of anticoagulation treatment for ECMO therapy, including the time needed to clear the effect of the anticoagulant treatment from the body.

Covered countermeasures under secretarial declarations	Serious physical injury (illness, disability, injury, or condition) [1]	Time interval (for first symptom or manifestation of onset of injury after administration or use of covered countermeasure, unless otherwise specified)
X. Pandemic influenza diagnostic testing devices.	A. No condition covered	A. Not applicable.

[1] Serious physical injury as defined in 42 CFR 110.3(z). Only injuries that warranted hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability will be considered serious physical injuries.

[2] The use of ''No condition covered'' in the Table reflects that the Secretary at this time does not find compelling, reliable, valid, medical and scientific evidence to support that any serious injury is presumed to be caused by the associated covered countermeasure. For injuries alleged to be due to covered countermeasures for which there is no associated Table injury, requesters must demonstrate that the injury occurred as the direct result of the administration or use of the covered countermeasure. *See* 42 CFR 110.20(b), (c).

(b) *Qualifications and aids to interpretation (table definitions and requirements).* The following definitions and requirements shall apply to the Table set forth in this subpart and only apply for purposes of this subpart.

(1) *Anaphylaxis* Anaphylaxis is an acute, severe, and potentially lethal systemic reaction that occurs as a single discrete event with simultaneous involvement of two or more organ systems. Most cases resolve without *sequelae.* Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse. Other significant clinical signs and symptoms may include the following: Cyanosis, hypotension, bradycardia, tachycardia, arrhythmia, edema of the pharynx and/or trachea and/or larynx with stridor and dyspnea. There are no specific pathological findings to confirm a diagnosis of anaphylaxis.

(2) *Deltoid Bursitis.* Deltoid bursitis is an inflammation of the bursa that lies beneath the deltoid muscle and between the acromion process and the rotator cuff. Subdeltoid bursitis manifests with pain in the lateral aspect of the shoulder similar to rotator cuff tendonitis. The presence of tenderness on direct palpation beneath the acromion process distinguishes this bursitis from rotator cuff tendonitis. Similar to tendonitis, isolated bursitis will have full passive range of motion. Other causes of bursitis such as trauma (other than from vaccination), metabolic disorders, and systemic diseases such as rheumatoid arthritis, dialysis, and infection will not be considered Table injuries. This list is not exhaustive. The deltoid bursitis must occur in the same shoulder that received the pandemic influenza vaccine.

(3) *Vasovagal Syncope.* Vasovagal syncope (also sometimes called neurocardiogenic syncope) means loss of consciousness (fainting) and loss of postural tone caused by a transient decrease in blood flow to the brain occurring after the administration of an injected countermeasure. Vasovagal syncope is usually a benign condition but may result in falling and injury with significant *sequelae.* Vasovagal syncope may be preceded by symptoms such as nausea, lightheadedness, diaphoresis, and/or pallor. Vasovagal syncope may be associated with transient seizure-like activity, but recovery of orientation and consciousness generally occurs simultaneously. Loss of consciousness resulting from the following conditions will not be considered vasovagal syncope: Organic heart disease; cardiac arrhythmias; transient ischemic attacks; hyperventilation; metabolic conditions; neurological conditions; psychiatric conditions; seizures; trauma; and situational as can occur with urination, defecation, or cough. This list is not complete. Episodes of recurrent syncope occurring after the applicable time period are not considered to be *sequelae* of an episode of syncope meeting the Table requirements.

(4) *Guillain-Barre Syndrome (GBS).* (i) GBS is an acute monophasic peripheral neuropathy that encompasses a spectrum of four clinicopathological subtypes described below. For each subtype of GBS, the interval between the first appearance of symptoms and the nadir of weakness is between 12 hours and 28 days. This is followed in all subtypes by a clinical plateau with stabilization at the nadir of symptoms, or subsequent improvement without significant relapse. Death may occur without a clinical plateau. Treatment related fluctuations in all subtypes of GBS can occur within nine weeks of GBS symptom onset and recurrence of symptoms after this time frame would not be consistent with GBS.

(ii) The most common subtype in North America and Europe, comprising more than 90 percent of cases, is acute inflammatory demyelinating polyneuropathy (AIDP) which has the pathologic and electrodiagnostic features of focal demyelination of motor and sensory peripheral nerves and nerve roots. Another subtype called acute motor axonal neuropathy (AMAN) is generally seen in other parts of the world and is predominated by axonal damage that primarily affects motor nerves. AMAN lacks features of demyelination. Another less common subtype of GBS includes acute motor and sensory neuropathy (AMSAN), which is an axonal form of GBS that is similar to AMAN, but also affects the sensory nerves and roots. AIDP, AMAN, and AMSAN are typically characterized by symmetric motor flaccid weakness, sensory abnormalities, and/or autonomic dysfunction caused by autoimmune damage to peripheral nerves and nerve roots. The diagnosis of AIDP, AMAN, and AMSAN requires bilateral flaccid limb weakness and decreased or absent deep tendon reflexes in weak limbs; a monophasic illness pattern; an interval between onset and nadir of weakness between 12 hours and 28 days; subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse); and, the absence of an identified more likely alternative diagnosis. Death may occur without a clinical plateau.

(iii) Fisher syndrome (FS), also known as Miller Fisher Syndrome, is a subtype of GBS characterized by ataxia, areflexia, and ophthalmoplegia, and overlap between FS and AIDP may be seen with limb weakness. The diagnosis of FS requires bilateral ophthalmoparesis; bilateral reduced or absent tendon reflexes; ataxia; the absence of limb weakness (the presence of limb weakness suggests a diagnosis of AIDP); a monophasic illness pattern; an interval between onset and nadir of weakness between 12 hours and 28 days; subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse); no alteration in consciousness; no corticospinal track signs; and, the absence of an identified more likely alternative diagnosis. Death may occur without a clinical plateau.

(iv) Evidence that is supportive, but not required, of a diagnosis of all subtypes of GBS includes

electrophysiologic findings consistent with GBS or an elevation of cerebral spinal fluid (CSF) protein with a total CSF white blood cell count below 50 cells per microliter. Both CSF and electrophysiologic studies are frequently normal in the first week of illness in otherwise typical cases of GBS.

(v) For all types of GBS, the onset of symptoms less than three days (72 hours) after exposure to the influenza vaccine excludes vaccine exposure as a cause.

(vi) To qualify as GBS, there must not be a more likely alternative diagnosis for the weakness. Exclusionary criteria for the diagnosis of all subtypes of GBS include the ultimate diagnosis of any of the following conditions: Chronic immune demyelinating polyradiculopathy (''CIDP''), carcinomatous meningitis, brain stem encephalitis (other than Bickerstaff brainstem encephalitis), myelitis, spinal cord infarct, spinal cord compression, anterior horn cell diseases such as polio or West Nile virus infection, subacute inflammatory demyelinating polyradiculoneuropathy, multiple sclerosis, cauda equina compression, metabolic conditions such as hypermagnesemia or hypophosphatemia, tick paralysis, heavy metal toxicity (such as arsenic, gold, or thallium), drug-induced neuropathy (such as vincristine, platinum compounds, or nitrofurantoin), porphyria, critical illness neuropathy, vasculitis, diphtheria, myasthenia gravis, organophosphate poisoning, botulism, critical illness myopathy, polymyositis, dermatomyositis, hypokalemia, or hyperkalemia. The above list is not exhaustive.

(5) *Tracheal Stenosis.* (i) Postintubation tracheal stenosis means an iatrogenic (caused by medical treatment) and symptomatic stricture of the airway (narrowing of the windpipe) resulting from:

(A) Trauma or necrosis from an endotracheal tube;

(B) Stomal injury from a tracheostomy; or

(C) A combination of the two.

(ii) Tracheal stenosis or narrowing due to tumors (malignant or benign), infections of the trachea (such as tuberculosis, fungal diseases), radiotherapy, tracheal surgery, trauma, congenital, and inflammatory or autoimmune diseases will not be considered postintubation tracheal stenosis. Postintubation tracheal stenosis requires either tracheostomy with placement of a tracheostomy tube or endotracheal intubation. Diagnosis requires symptoms of upper airway obstruction such as stridor (inspiratory wheeze) or exertional dyspnea (increased shortness of breath with exertion), and positive radiologic studies showing abnormal narrowing of the trachea or bronchoscopic evaluation that demonstrates abnormal narrowing.

(6) *Ventilator-Associated Pneumonia (VAP)* and *Ventilator-Associated Tracheobronchitis (VAT).* (i) Definition-VAP is defined as an iatrogenic pneumonia caused by the medical treatment of mechanical ventilation. Similarly, VAT is an iatrogenic infection of the trachea and/or bronchi caused by mechanical ventilation. The initial manifestation of VAP and VAT must occur more than 48 hours after intubation (placement of the breathing tube) and up to 48 hours after extubation (removal of the breathing tube). VAP will be considered to be present when the patient demonstrates a new or progressive radiographic infiltrate in the lungs that is consistent with pneumonia, fever, leukocytosis (increased white blood cell count) or leucopenia (decreased white blood cell count), purulent (containing pus) tracheal secretions from a tracheal aspirate, and a positive lower respiratory tract culture. The positive lower respiratory tract culture is a diagnostic requirement only if there has not been a change in antibiotics in the 72 hours prior to collection of the culture. In addition, a tracheal aspirate that does not demonstrate bacteria or inflammatory cells in a patient without a change in antibiotics in the previous 72 hours is unlikely to be VAP and shall not be considered a condition set forth in the Table.

(ii) VAT will be considered to be present when the patient demonstrates fever, leukocytosis or leukopenia, purulent tracheal secretions, and a positive tracheal aspirate culture in the absence of a change of antibiotics within the 72 hours prior to culture. Tracheal colonization with microorganisms is common in intubated patients, but in the absence of clinical findings is not a sign of VAT.

(7) *Ventilator-Induced Lung Injury (VILI).* VILI results from mechanical trauma such as volutrauma leading to rupture of alveoli (air sacs in the lungs where oxygen and carbon dioxide are exchanged with the blood) with subsequent abnormal leakage of air. VILI manifests as iatrogenic pneumothorax (abnormal air from alveolar rupture in the pleural space), pneumomediastinum (abnormal air from alveolar rupture in the mediastinum (middle part of the chest between the lungs)), pulmonary interstitial emphysema (abnormal air in the lung interstitial space between the alveoli), subpleural air cysts (an extreme form of pulmonary emphysema where the abnormal air in the interstitial space has pooled into larger pockets), subcutaneous emphysema (abnormal air from alveolar rupture that has dissected into the skin), pneumopericardium (abnormal air from alveolar rupture that has traveled to the pericardium (covering of the heart)), pneumoperitoneum (abnormal air from alveolar rupture that has moved into the abdominal space), or systemic air embolism (abnormal air from alveolar rupture that has moved into the blood). These manifestations must occur in patients who are being mechanically ventilated at the time of initial manifestation of the VILI.

(8) *Bleeding events.* Bleeding events are defined as excessive or abnormal bleeding in patients under the pharmacologic effects of anticoagulant therapy provided for extracorporeal membrane oxygenation (ECMO) treatment.

(c) *Covered countermeasures.* (1) *Pandemic influenza vaccines.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2010-03-05/pdf/2010-4644.pdf.* Any amendments will be automatically incorporated into this declaration and be published in the **Federal Register**.

(2) *Tamiflu.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2009-06-19/pdf/E9-14412.pdf.* Any amendments will be automatically incorporated into this declaration and be published in the **Federal Register**.

(3) *Relenza.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2009-06-19/pdf/E9-14412.pdf.* Any amendments will be automatically incorporated into this declaration and be published in the **Federal Register**.

(4) *Peramivir.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2009-10-02/pdf/E9-23761.pdf.* Any amendments will be automatically incorporated into this declaration and be published in the **Federal Register**.

(5) *Personal respiratory protection devices.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2008-12-22/pdf/E8-30510.pdf.* Any amendments will be automatically incorporated into this declaration and published in the **Federal Register**.

(6) *Respiratory support devices.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2008-12-22/pdf/E8-30510.pdf.* Any amendments will be automatically

incorporated into this declaration and published in the **Federal Register**.

(7) *Diagnostic testing devices.* See the most recent Secretarial declaration at *http://www.gpo.gov/fdsys/pkg/FR-2008-12-22/pdf/E8-30510.pdf.* Any amendments will be automatically incorporated into this declaration and published in the **Federal Register**.

[FR Doc. 2014–06102 Filed 3–28–14; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF THE INTERIOR

Fish and Wildlife Service

50 CFR Part 17

[Docket No. FWS–R7–ES–2012–0093; 4500030113]

Endangered and Threatened Wildlife and Plants; 90-Day Finding on a Petition To List the Alexander Archipelago Wolf as Threatened or Endangered

AGENCY: Fish and Wildlife Service, Interior.

ACTION: Notice of petition finding and initiation of status review.

SUMMARY: We, the U.S. Fish and Wildlife Service (Service), announce a 90-day finding on a petition to list the Alexander Archipelago wolf (*Canis lupus ligoni*) as a threatened or endangered species and to designate critical habitat under the Endangered Species Act of 1973, as amended (Act). Based on our review, we find that the petition presents substantial scientific or commercial information indicating that listing the Alexander Archipelago wolf may be warranted. Therefore, with publication of this notice, we are notifying the public that when resources become available, we will be conducting a review of the status of the species to determine if listing the Alexander Archipelago wolf is warranted. To ensure that this status review is comprehensive, we are requesting scientific and commercial data and other information regarding wolves of Southeast Alaska and adjacent coastal British Columbia. Based on the status review, we will issue a 12-month finding on the petition, which will address whether the petitioned action is warranted, as provided in section 4(b)(3)(B) of the Act.

DATES: We request that we receive information to consider for the status review on or before May 30, 2014. The deadline for submitting information using the Federal eRulemaking Portal (see **ADDRESSES** section, below) is 11:59 p.m. Eastern Time on this date. After May 30, 2014, you must submit information directly to the Division of Policy and Directives Management (see **ADDRESSES** section below). Please note that we might not be able to address or incorporate information that we receive after the above requested date.

ADDRESSES: You may submit information by one of the following methods:

(1) *Electronically:* Go to the Federal eRulemaking Portal: *http://www.regulations.gov.* In the Search box, enter FWS–R7–ES–2012–0093, which is the docket number for this action. Then click on the Search button. You may submit information for the status review by clicking on ''Comment Now!.''

(2) *By hard copy:* Submit by U.S. mail or hand-delivery to: Public Comments Processing, Attn: FWS–R7–ES–2012–0093; Division of Policy and Directives Management; U.S. Fish and Wildlife Service; 4401 N. Fairfax Drive, MS 2042–PDM; Arlington, VA 22203.

We will not accept email or faxes. We will post all information we receive on *http://www.regulations.gov.* This generally means that we will post any personal information you provide us (see the Request for Information section below for more details).

FOR FURTHER INFORMATION CONTACT: Steve Brockmann, Juneau Fish and Wildlife Field Office, 3000 Vintage Blvd., Suite 201, Juneau, AK 99821; by telephone at 907–780–1160; or by facsimile at 907–586–7099. If you use a telecommunications device for the deaf (TDD), please call the Federal Information Relay Service (FIRS) at 800–877–8339.

SUPPLEMENTARY INFORMATION:

Request for Information

When we make a finding that a petition presents substantial information indicating that listing a species may be warranted, we are required to review the status of the species (status review). For the status review to be complete and based on the best available scientific and commercial information, we request information on the Alexander Archipelago wolf from governmental agencies, Native American tribes, the scientific community, industry, and any other interested parties. We seek information on:

(1) The species' biology, range, and population trends, including:

(a) Habitat requirements for feeding, breeding, and sheltering;

(b) Genetics and taxonomy;

(c) Historical and current range including distribution patterns;

(d) Historical and current population levels, and current and projected trends; and

(e) Past and ongoing conservation measures for the species, its habitat, or both.

(2) The factors that are the basis for making a listing determination for a species under section 4(a) of the Act (16 U.S.C. 1531 *et seq.*), which are:

(a) The present or threatened destruction, modification, or curtailment of its habitat or range;

(b) Overutilization for commercial, recreational, scientific, or educational purposes;

(c) Disease or predation;

(d) The inadequacy of existing regulatory mechanisms; or

(e) Other natural or manmade factors affecting its continued existence.

If, after the status review, we determine that listing the Alexander Archipelago wolf is warranted, we will propose critical habitat (see definition in section 3(5)(A) of the Act) under section 4 of the Act, to the maximum extent prudent and determinable at the time we propose to list the species. Therefore, we also request data and information on:

(1) What may constitute ''physical or biological features essential to the conservation of the species,'' within the geographical range currently occupied by the species;

(2) Where these features are currently found;

(3) Whether any of these features may require special management considerations or protection;

(4) Specific areas outside the geographical area occupied by the species that are ''essential for the conservation of the species;'' and

(5) What, if any, critical habitat you think we should propose for designation if the species is proposed for listing, and why such habitat meets the requirements of section 4 of the Act.

Please include sufficient information with your submission (such as scientific journal articles or other publications) to allow us to verify any scientific or commercial information you include.

Submissions merely stating support for or opposition to the action under consideration without providing supporting information, although noted, will not be considered in making a determination. Section 4(b)(1)(A) of the Act directs that determinations as to whether any species is an endangered or threatened species must be made ''solely on the basis of the best scientific and commercial data available.''

You may submit your information concerning this status review by one of the methods listed in the **ADDRESSES**