

and Welfare and Advance Notice of Proposed Rulemaking in the **Federal Register** on July 1, 2015. This action provides notice of three updates regarding the public hearing.

DATES: The EPA will hold a public hearing on August 11, 2015 in Washington, DC starting at 10 a.m. local time.

ADDRESSES: The hearing will be held at the Headquarters office of the US EPA, the William Jefferson Clinton East Building, Room 1153, 1201 Constitution Avenue NW., Washington, DC 20004.

FOR FURTHER INFORMATION CONTACT: Ms. JoNell Iffland, Office of Transportation and Air Quality, Assessment and Standards Division (ASD), Environmental Protection Agency, 2000 Traverwood Drive, Ann Arbor, Michigan 48105, telephone number: (734) 214-4454, fax number: (734) 214-4816, email address: Iffland.jonell@epa.gov.

SUPPLEMENTARY INFORMATION: EPA published a proposed finding that greenhouse gas emissions from aircraft cause or contribute to air pollution that may reasonably be anticipated to endanger public health and welfare and an advance notice of proposed rulemaking regarding aircraft engine greenhouse gas emissions on July 1, 2015 (80 FR 37758). This action corrects a typographical error in the street address for the public hearing and provides notice of availability of a conference call-in number for the public to listen to the hearing. Additionally, this action provides notice that video recording will be allowed in the hearing room provided that it does not interfere with or interrupt the public hearing.

Updates

The **DATES** section of the proposed finding and advance notice of proposed rulemaking published in the **Federal Register** on July 1, 2015 (78 FR 37758), provided information on the public hearing. This action updates that information.

The EPA will hold a public hearing on August 11, 2015 in Washington, DC, at the William Jefferson Clinton East Building, Room 1153, 1201 Constitution Avenue NW., Washington, DC 20004. The EPA will provide the opportunity for the public to listen to the hearing through the following conference call-in line: 1-866-299-3188, conference code 1433527160. Please note that this conference line will allow the public to listen only; persons listening will not be able to give an oral presentation via the conference line.

Additionally, the proposed finding and advance notice of proposed

rulemaking stated that no large signs will be allowed in the building, cameras may only be used outside of the building and demonstrations will not be allowed on federal property for security reasons. This update confirms that video recording will be allowed in the hearing room provided that it does not interfere with or interrupt the public hearing.

Dated: July 21, 2015.

Christopher Grundler,

Director, Office of Transportation and Air Quality, Office of Air and Radiation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 100

RIN 0906-AB01

National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table

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

ACTION: Notice of proposed rulemaking (NPRM).

SUMMARY: The Secretary proposes to amend the Vaccine Injury Table (Table) by regulation. These proposed regulations will have effect only for petitions for compensation under the National Vaccine Injury Compensation Program (VICP) filed after the final regulations become effective. The Secretary is seeking public comment on the proposed revisions to the Table.

DATES: Written comments must be submitted on or before January 25, 2016.

ADDRESSES: You may submit comments, identified by the Regulatory Information Number (RIN) 0906-AB01 in one of three ways, as listed below. The first is the preferred method. Please submit your comments in only *one* of these ways to minimize the receipt of duplicate submissions.

1. *Federal eRulemaking Portal.* You may submit comments electronically to <http://www.regulations.gov>. Click on the link "Submit electronic comments on HRSA regulations with an open comment period." Submit your comments as an attachment to your message or cover letter. (Attachments should be in Microsoft Word or WordPerfect; however, Microsoft Word is preferred).

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, Program cannot accept comments by facsimile (FAX) transmission. In commenting, by any of the above methods, please refer to file code (#HRSA-0906-AB01). All comments received on a timely basis will be available for public inspection without change, including any personal information provided, in 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 5:00 p.m. (excluding Federal holidays). Phone: (301) 443-1785. This is not a toll-free number.

FOR FURTHER INFORMATION CONTACT: Please visit the National Vaccine Injury Compensation Program's Web site, <http://www.hrsa.gov/vaccinecompensation/>, or contact Dr. Avril Melissa Houston, Director, Division of Injury Compensation Programs, Healthcare Systems Bureau, Health Resources and Services Administration, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, MD 20857. Phone calls can be directed to (301) 443-6593.

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 (HHS) 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 name and contact information of the subject-matter expert 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 contact HRSA's Regulations Officer at Parklawn Building, Room 14-101, 5600 Fishers Lane, Rockville, MD 20857; or by telephone at 301-443-1785, to obtain this information in an accessible format. This is not a toll free telephone number. Please visit <http://www.HHS.gov/regulations> for more information on HHS rulemaking and opportunities to comment on proposed and existing rules.

A public hearing on this proposed rule will be held before the end of the public comment period. A separate notice will be published in the **Federal Register** providing details of this hearing. Subject to consideration of the comments received, the Secretary intends to publish a final regulation.

Background

The National Childhood Vaccine Injury Act of 1986, title III of Public Law 99-660 (42 U.S.C. 300aa-10 *et seq.*), established a Federal compensation program for persons thought to be injured by vaccines. The statute governing the program has been amended several times since 1986 and is hereinafter referred to as "the Act." Petitions for compensation under this Program are filed in the United States Court of Federal Claims, with a copy served on the Secretary, who is denominated the "Respondent." The Court, acting through judicial officers called Special Masters, makes findings as to eligibility for, and amount of, compensation.

In order to receive an award under this Program, a petitioner must establish a vaccine-related injury or death, either by proving that a vaccine actually caused or significantly aggravated an injury (causation-in-fact) or by demonstrating the occurrence of what has been referred to as a "Table Injury." That is, a petitioner may show that the vaccine recipient suffered an injury of the type enumerated in the regulations at 42 CFR 100.3—the "Vaccine Injury Table"—corresponding to the vaccination in question, and that the onset of such injury took place within a time period also specified in the Table. If so, the injury is presumed to have been caused by the vaccination, and the petitioner is entitled to compensation (assuming that other requirements are satisfied), unless the respondent affirmatively shows that the injury was caused by some factor other than the vaccination (see sections

300aa-11(c)(1)(C)(i), 300aa-13(a)(1)(B)), and 300aa-14(a) of the Act). Currently, cases are often resolved by settlements reached by both parties and approved by the Court.

When Congress first enacted the Act, it mandated reviews by the Institute of Medicine (IOM) of the National Academy of Sciences with the express purpose of providing a better scientific rationale for any presumptions of vaccine causation. Under sections 312 and 313 of Public Law 99-660, Congress mandated that the IOM review the scientific literature and other information on specific adverse consequences of vaccines covered by the Program. Congress enacted a mechanism for modification of the statutory Table, through the promulgation of regulatory changes by the Secretary, after consultation with the Advisory Commission on Childhood Vaccines (ACCV). By statutory directive, the membership of the ACCV reflects a variety of stakeholders with different perspectives (42 U.S.C. 300aa-19).

Efforts by the Secretary to modify the initial statutory Table, and its definitional counterpart, the Qualifications and Aids to Interpretation (QAI) began with publication of the two congressionally mandated IOM reviews in 1991 and 1994, respectively. With a few exceptions, the approach by the Secretary was straightforward: If the IOM concluded that there was evidence that a condition was "causally related," it was added to or left on the Table. However, if there was no proven scientific evidence of an association, it was not added to the Table or it was removed. The entire process, from publication of the IOM reports, to promulgation of final rules in 1995 and 1997 took approximately 3 to 4 years.

The IOM has analyzed numerous possible vaccine injury connections over the years and after conducting a third comprehensive review of the scientific literature on vaccines and adverse events, released a report entitled, *Adverse Effects of Vaccines: Evidence and Causality* (2012). This third IOM report was conducted under the Department's initiative and was not statutorily mandated. The committee charged with undertaking this review consisted of 16 members with expertise in the following fields: Pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law (<http://www.iom.edu/reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx>). The members of the review committee are subject to the

stringent conflict of interest criteria imposed by the IOM. The committee met eight times over the course of 35 months, surveying more than 11,000 abstracts and reviewing in-depth 1,487 scientific and medical studies. The committee did not perform any original research.

The IOM Committee undertook the task of judging whether, based on available scientific evidence, a causal relationship exists between each adverse event examined and exposure to the following eight vaccines: Measles-mumps-rubella vaccine, varicella virus vaccine, seasonal influenza vaccines (which did not include the H1N1 influenza vaccine distributed in 2009), hepatitis A vaccine, hepatitis B vaccine, human papillomavirus vaccine, diphtheria tetanus toxoid and acellular pertussis-containing vaccines, and meningococcal vaccine. The charge to the Committee involved these eight vaccines because they are the vaccines with the vast majority of alleged adverse events in the claims for compensation filed under the Program. In addition, some of these vaccines had not been reviewed previously by the IOM.

Two types of evidence were utilized by the IOM in determining the strength of a causal association: Epidemiologic evidence from studies of populations and mechanistic evidence derived primarily from biological and clinical studies in animals and humans such as case reports. To determine the weight of the evidence, the IOM used a summary classification scheme that incorporated both the quality and quantity of the individual articles and the consistency of the group of articles in terms of direction of effect. Four weight-of-evidence categories were utilized, with epidemiologic evidence assessed to be high, moderate, limited or insufficient, and mechanistic evidence assessments of strong, intermediate, weak or lacking.

The IOM started each adverse event assessment from a position of neutrality, moving in either direction (*i.e.*, evidence favoring or rejecting causation) only when the epidemiologic and/or mechanistic evidence suggested a more definitive assessment. As with the previous IOM studies, a classification system was used to categorize the IOM's conclusions about the strength of a causal association. These categories are as follows:

1. Evidence convincingly supports a causal relationship;
2. Evidence favors acceptance of a causal relationship;
3. Evidence favors rejection of a causal relationship; or
4. Evidence is inadequate to accept or reject a causal relationship.

The IOM Committee concluded in certain circumstances that the evidence convincingly supports, or favors acceptance of, a causal relationship based only on a mechanistic assessment, even when the epidemiological evidence was inconclusive or absent. The 2012 IOM Report, on pages 17–18 explains that strong mechanistic evidence “always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. . . . This conclusion [attributing the disease to the vaccine and not to other etiologies] can be reached even if the epidemiologic evidence is rated high in the direction of no increased risk or even decreased risk.”

The IOM concluded the evidence convincingly supports 14 specific vaccine-adverse event relationships, with all but one based on strong mechanistic evidence, and the epidemiologic evidence rated as either having limited confidence or being insufficient. Four vaccine adverse events judged to have either epidemiologic evidence of moderate certainty or mechanistic evidence of intermediate weight were placed in the “evidence favors acceptance of a causal relationship” category, while five other vaccine adverse events were placed in the “evidence favors rejection” category. A finding against a causal relationship required high or moderate epidemiologic evidence in the direction of no effect or decreased risk along with the absence of strong or intermediate mechanistic evidence supporting a causal relationship. The vast majority (135 vaccine-adverse event combinations) were placed in the “evidence is inadequate to accept or reject a causal relationship” category.

After release of the report, nine HHS workgroups including HRSA and the Centers for Disease Control and Prevention (CDC) medical staff reviewed the IOM conclusions on 158 vaccine-adverse events, as well as any newly published scientific literature not contained in the IOM report, and developed a set of proposed changes to the Table and QAI. The work of the HHS workgroups ended and HRSA continued to monitor the literature.

In 2006, the ACCV established “Guiding Principles for Recommending Changes to the Vaccine Injury Table” (Guiding Principles) to assist the ACCV in evaluating proposed Table revisions and determining whether to recommend changes to the Table to the Secretary. The Guiding Principles consist of two overarching principles: (1) The Table should be scientifically and medically credible; and (2) where there is credible

scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners. The Guiding Principles also state, among other factors, that “[t]o the extent that the [IOM] has studied the possible association between a vaccine and an adverse effect, the conclusions of the IOM should be considered by the ACCV and deemed credible but those conclusions should not limit the deliberations of the ACCV.” Although not binding on the Secretary, the ACCV Guiding Principles were utilized by the nine HHS workgroups in the development of the proposed changes to the Table. In particular, recommendations regarding appropriate time intervals for the onset of a Table injury, or diagnostic criteria in the QAI were influenced by the Guiding Principles. As part of its mandate under the Act, the ACCV considered the proposed changes set forth in this NPRM in its quarterly meetings on March 8, 2012, September 5, 2013, December 5, 2013, June 5, 2014, and September 4, 2014. The ACCV deliberations included scientific and public policy considerations, and were also influenced by the 2006 Guiding Principles. For each proposed change by the Secretary, the ACCV voted for one of three options:

1. ACCV concurs with the proposed change(s) to the Table (and QAI) and would like the Secretary to move forward (with or without comments);

2. ACCV does not concur with the proposed change(s) to the Table (and QAI) and would not like the Secretary to move forward; or

3. ACCV would like to defer a recommendation on the proposed change(s) to the Table (and QAI) pending further review at a future ACCV meeting.

Findings

In prior Table revisions, the Secretary determined that the appropriate framework for making changes to the Table is to make specific findings as to the illnesses or conditions that can reasonably be determined in some circumstances to be caused or significantly aggravated by the vaccines under review and the circumstances under which such causation or aggravation can reasonably be determined to occur. The Secretary continues this approach based on the 2012 IOM report, the work of the nine workgroups that reviewed the IOM findings, and after giving due consideration to the ACCV’s recommendations.

For the vast majority of the vaccine adverse event pairs that were reviewed by the IOM (135), the IOM determined that the evidence is inadequate to accept or reject a causal relationship. With the exception of seasonal influenza vaccine and Guillain-Barré Syndrome (GBS), unless the IOM findings addressed a condition that was already on the Table, the Secretary makes no additional findings and proposes no change to the Table with regard to the vaccine adverse event pairs in this category. For seasonal influenza vaccines, the Secretary proposes to add the injury of GBS to the Table for the policy reasons discussed in this NPRM. For any vaccine adverse event pairs for which future scientific evidence develops to support a finding of a causal relationship, the Secretary will consider future rulemaking to revise the Table accordingly.

Applying the remaining IOM conclusions, with the Guiding Principles, the Secretary intends to make certain changes to the Table, and also intends to leave certain items already on the Table unchanged. In so doing, the Secretary makes the following findings:

Findings That Result in Additions or Changes to the Table

1. The scientific evidence convincingly supports a causal relationship between measles-mumps-rubella (MMR) vaccine and measles inclusion body encephalitis.

2. The scientific evidence convincingly supports a causal relationship between varicella vaccine and vaccine disseminated varicella infection (widespread chickenpox rash shortly after vaccination).

3. The scientific evidence convincingly supports a causal relationship between varicella vaccine and disseminated varicella infection with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies.

4. The scientific evidence convincingly supports a causal relationship between varicella vaccine and vaccine strain viral reactivation.

5. The scientific evidence convincingly supports a causal relationship between varicella vaccine and vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.

6. The scientific evidence convincingly supports a causal relationship between varicella vaccine and anaphylaxis.

7. The scientific evidence convincingly supports a causal

relationship between influenza vaccines and anaphylaxis.

8. The scientific evidence convincingly supports a causal relationship between meningococcal vaccines and anaphylaxis.

9. The scientific evidence favors acceptance of a causal relationship between human papillomavirus vaccines and anaphylaxis.

10. The scientific evidence convincingly supports a causal relationship between an injection-related event and deltoid bursitis. For reasons detailed below, the Secretary proposed adding a more expansive injury of Shoulder Injury Related to Vaccine Administration (SIRVA) to the Table.

11. The scientific evidence convincingly supports a causal relationship between an injection-related event and syncope.

12. The scientific evidence is inadequate to accept or reject a causal relationship between seasonal influenza vaccines and GBS. However, the Secretary proposes a Table change for the reasons discussed in this NPRM.

Findings That Do Not Result in Changes to the Table Because the Injury Is Already on the Table

1. The scientific evidence convincingly supports a causal relationship between MMR vaccine and anaphylaxis.

2. The scientific evidence convincingly supports a causal relationship between Hepatitis B vaccine and anaphylaxis.

3. The scientific evidence convincingly supports a causal relationship between tetanus toxoid vaccine and anaphylaxis.

4. The scientific evidence is inadequate to accept or reject a causal relationship between tetanus toxoid-containing vaccines (including those containing the acellular pertussis component but not the whole cell pertussis component) and encephalopathy and encephalitis.

5. The scientific evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthritis in women.

6. The scientific evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthritis in children.

7. The scientific evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalopathy or encephalitis.

Findings That Do Not Result in Changes to the Table Because the Injury Is Transient in Nature

1. The scientific evidence convincingly supports a causal relationship between MMR vaccine and febrile seizures.

2. The scientific evidence favors acceptance of a causal relationship between MMR vaccine and transient arthralgia in women.

3. The scientific evidence favors acceptance of a causal relationship between MMR vaccine and transient arthralgia in children.

Findings That Do Not Result in Changes to the Table Because the Evidence Favors Rejection of a Causal Relationship

1. The scientific evidence favors a rejection of a causal relationship between MMR vaccine and autism.

2. The scientific evidence favors a rejection of a causal relationship between MMR vaccine and type 1 diabetes.

3. The scientific evidence favors a rejection of a causal relationship between DTaP (tetanus) vaccine and type 1 diabetes.

4. The scientific evidence favors a rejection of a causal relationship between inactivated (as opposed to the live intranasal) influenza vaccine and Bell's palsy.

5. The scientific evidence favors a rejection of a causal relationship between inactivated influenza vaccine and exacerbation of asthma or reactive airway disease episodes in children and adults.

Discussion of Proposed Table Changes

The Secretary has examined the recommendations of the ACCV and proposes that the Table set forth at 42 CFR 100.3 be revised as described below. Following each vaccine and adverse event there is a discussion of the IOM conclusion and, where applicable, other relevant conclusions, as well as the Department's proposal. It should be noted that the ACCV concurred with all of the proposals regarding the Table and QAI. Each of the changes proposed by the Department and the rationale for the proposal is described in detail. An important consideration in proposing changes to the Table is the need to make the Table as easy to understand and as clear as possible. With this goal in mind, the Secretary has proposed new language and clarified certain sections of the QAI which must be used by the Special Masters and the parties in understanding when a particular set of

symptoms is consistent with a particular Table injury.

As provided in 42 U.S.C. 300aa-14(c)(4), the modified Table will apply only to petitions filed under the Program after the effective date of the final regulation. Petitions must also be filed within the applicable statute of limitations. The general statute of limitations applicable to petitions filed with the VICP, set forth in 42 U.S.C. 300aa-16(a), continues to apply. In addition, the statute identifies a specific exception to this statute of limitations that applies when the effect of a revision to the Table makes a previously ineligible person eligible to receive compensation or when an eligible person's likelihood of obtaining compensation significantly increases. Under this section, an individual who may be eligible to file a petition based on the revised Table may file the petition for compensation not later than 2 years after the effective date of the revision if the injury or death occurred not more than 8 years before the effective date of the revision of the Table (42 U.S.C. 300aa-16(b)). This is true even if such individual previously filed a petition for compensation, and is thus an exception to the "one petition per injury" limitation of 42 U.S.C. 300aa-11(b)(2).

Based on the requirements of the Administrative Procedure Act, the Department publishes a Notice of Proposed Rulemaking in the **Federal Register** before a regulation is promulgated. The public is invited to submit comments on the proposed rule. In addition, a public hearing will be held for this proposed rule. After the public comment period has expired, the comments received and the Department's responses to the comments will be addressed in the preamble to the final regulation. The Department will publish the final rule in the **Federal Register**.

In the following sections, background information on different categories of vaccines as well as the Secretary's rationale for any proposed Table change is provided. It should also be noted that the proposed QAIs are designed to define the conditions covered on the Table and to rule out other conditions that are not covered on the Table (and for which there has been no finding of a causal relation to the vaccines). In addition, the QAIs make clear that if certain other circumstances exist that do not, in the Secretary's view, warrant a presumption of causation, the Table presumption will not be apply.

I. Vaccines Containing Tetanus Toxoid

Currently there are four tetanus-diphtheria (Td) vaccines licensed in the United States, two of which also contain acellular pertussis vaccines (Tdap and DTap); a diphtheria-tetanus (DT) vaccine for children younger than age 7 years; and one tetanus toxoid vaccine (TT). In addition, there are three combination vaccines approved for use in children, including (DTaP–IPV–HepB), (DTaP–IPV–Hib), and (DTaP–IPV). Immunity to tetanus wanes over time, so booster doses are needed. According to the CDC recommended schedule of immunizations for children, an infant and child should receive four doses of DTaP in the first 18 months of life and a booster dose between 4 to 6 years. Tdap is recommended at age 11 to 12 years.

Since 2005, the Advisory Committee on Immunization Practices (ACIP) and the CDC have recommended a Tdap vaccine booster dose for all adolescents aged 11 through 18 years of age and for adults aged 19 through 64 years who have not received a dose. A Td booster is recommended every 10 years thereafter. As part of wound management care to prevent tetanus, a tetanus toxoid-containing vaccine is recommended for wound management in anyone who has not received a tetanus-containing vaccine for 5 years or more. The CDC recommends that one dose of Tdap be administered to pregnant women during each pregnancy regardless of the interval since the prior Td or Tdap vaccination.

A. Shoulder Injury Related to Vaccination

Shoulder Injury Related to Vaccine Administration (SIRVA) is an adverse event following vaccination thought to be related to the technique of intramuscular percutaneous injection (the procedure where access to a muscle is obtained by using a needle to puncture the skin) into an arm resulting in trauma from the needle and/or the unintentional injection of a vaccine into tissues and structures lying underneath the deltoid muscle of the shoulder. As the proposed definition indicates, SIRVA is an injury related to the intramuscular injection of a vaccine. Consequently, by definition, a Table injury of SIRVA will not result for those vaccines that are not administered by intramuscular injection, including oral polio and rotavirus; subcutaneous MMR, MMRV, varicella, and meningococcal-polysaccharide; intranasal influenza; and intradermal influenza. In addition, a Table injury of SIRVA will not result for those vaccines

that are administered via a needleless jet device. Jet injectors are needleless systems for vaccine or medication administration that utilize a high-pressure jet of liquid to penetrate the skin. During administration, the needleless syringe is placed against the injection site and as the medication or vaccine passes through the injector under high pressure it forms a jet of fluid that penetrates the skin. These devices do not penetrate the skin to a degree that would result in SIRVA. Current information regarding routes of administration for various vaccine formulations is available on the Centers for Disease Control and Prevention's Web site: http://www.cdc.gov/vaccines/recs/vac-admin/default.htm?s_cid=.

Clinical signs of shoulder pain and restricted motion in the affected shoulder appear shortly after vaccination. Medical review of VICP claims shows more than 30 cases of severe, persistent shoulder pain beginning shortly after vaccination and resulting in prolonged restriction of function. Often these cases were diagnosed as deltoid bursitis. [Atanasoff S, Ryan T, Lightfoot R, and Johann-Liang R, 2010, Shoulder injury related to vaccine administration (SIRVA), *Vaccine* 28(51):8049–8052.]

The IOM reviewed the scientific and medical literature finding evidence that convincingly supports a causal relationship between vaccine injection (with a needle) into an arm and deltoid bursitis. The report noted that the published VICP case series (Atanasoff et al.), as described, were clinically consistent with deltoid bursitis. The VICP case series found that 93 percent of patients had the onset of shoulder pain within 24 hours of vaccine administration and 54 percent had immediate pain following vaccine injection. The VICP case series found several diagnoses, beyond deltoid bursitis, that resulted in shoulder pain following vaccination, including tendonitis, impingement syndrome, frozen shoulder syndrome, and adhesive capsulitis. Another case series reported two cases of shoulder pain, weakness and reduced range of motion following vaccination with onset of symptoms within 48 hours of vaccination. [Bodor M, Montalvo E, Vaccination related shoulder dysfunction, *Vaccine* 25(2007) 585–587.]

In order to capture the broader array of potential injuries, the Secretary proposes to add SIRVA for all tetanus toxoid-containing vaccines that are administered intramuscularly through percutaneous injection into the upper arm. The interval of onset will be less than or equal to 48 hours.

While the Secretary proposes adding SIRVA to the Table for the MMR and Varicella vaccines, to meet the proposed QAI for SIRVA, the vaccine must be one intended for intramuscular administration in the upper arm. The Secretary acknowledges that currently there are no MMR or Varicella vaccines that are administered by intramuscular injection. However, the Secretary proposes that the Table include SIRVA as an injury for those vaccines, recognizing that, presently, the absence of an intramuscular formulation of the vaccines will prevent petitioners from meeting the Table QAI for SIRVA with respect to those vaccines. The advantage of such proposal is that the Table would not require modification should an intramuscular formulation of those vaccines develop. The disadvantage of this proposal could be confusion about whether a Table injury for SIRVA may be satisfied for those vaccines, despite the QAI's requirement that the associated vaccine be intended for intramuscular administration. Accordingly, the Secretary specifically seeks the public's views on her proposal to include SIRVA as a Table injury for the MMR and varicella vaccines notwithstanding the fact that there currently is not an intramuscular formulation. Consequently, by definition, a Table injury of SIRVA will not result for those vaccines that are not administered by intramuscular injection, including oral polio and rotavirus; subcutaneous MMR, MMRV, varicella, and meningococcal-polysaccharide; intranasal influenza; and intradermal influenza.

B. Vasovagal Syncope

Vasovagal syncope is the loss of consciousness (fainting) caused by a transient decrease in blood flow to the brain. Vasovagal syncope is usually a benign condition but may result in falling and injury. Vaccination is known to be one cause of vasovagal syncope. Both serious and non-serious injuries can occur as a result of syncope. The types of serious injuries that may occur following a syncopal episode include, but are not limited to, skin lacerations, bone fractures, dental injuries, traumatic brain injuries, and death. Other injuries include traumatic injuries sustained from automobile accidents that occurred due to a vaccinee experiencing syncope while driving within a short time period after vaccine receipt.

The IOM reviewed the literature concerning a possible link between the injection of a vaccine and syncope. Although the Committee found the epidemiologic evidence was insufficient or absent to assess an association

between the injection of a vaccine (with a needle) and syncope, the Committee concluded the mechanistic evidence was strong based on 35 cases presenting definitive clinical evidence. In addition, the HHS's Division of Injury Compensation Programs (DICP) has identified eight cases from its database alleging syncope as a vaccine injury (unpublished data). All had six months of residual symptoms as a result of syncope. In all eight cases, DICP found that syncope was directly related to vaccine administration.

The IOM concluded that the evidence convincingly supports a causal relationship between the injection of a vaccine (with a needle) and syncope. It did not limit this conclusion to a particular vaccine and explained that the evidence from one case report it examined as part of the mechanistic evidence it reviewed suggested "that the injection, and not the contents of the vaccine, contributed to the development of syncope."

In order to be eligible for compensation, the Act requires that the residual effects of the alleged vaccine injury must have continued for a period of at least 6 months (unless the injury results in in-patient hospitalization and surgery, or death). The Secretary recognizes that in many instances cases involving syncope will not meet the statutory severity criteria, as the reaction can be short-lived and treated effectively. However, there is a known risk of serious residual injury or of death from syncope.

Although syncope typically has no long term consequences, the Program has found that not infrequently, syncope is associated with residual effects lasting more than 6 months. Therefore, the Secretary proposes to add vasovagal syncope to the Table for all tetanus toxoid containing vaccines that are administered through percutaneous injection to permit an award of compensation in serious cases meeting the severity criteria. The proposed time interval of onset is less than or equal to 1 hour following vaccination. Syncope is an injury related to the injection of a vaccine. Consequently, the Secretary does not propose adding syncope as a Table injury for those vaccines that are not administered by injection, including oral polio and rotavirus vaccine. With respect to other vaccines, such as the intranasal influenza vaccine, while syncope is proposed as an injury for the general category of vaccines (*i.e.*, seasonal influenza vaccines), the specific formulation will not result in a Table injury of syncope by definition because it is not administered by injection. The Secretary is not aware of

any reliable and persuasive evidence demonstrating that syncope occurs following administration of a vaccine via a needleless jet device; however, it may be plausible for syncope to occur with this route of administration. Therefore, the Secretary seeks the public's views as to whether the Secretary should include syncope as a Table injury for those vaccines that are administered via a needleless jet device. The Secretary also seeks the public's views as to whether syncope should be a Table injury for other categories of vaccines (*e.g.*, rotavirus) notwithstanding the fact that there currently is not a formulation that is administered by injection in order to encompass future formulations that may be administered by injection.

II. Vaccines Containing Extracted or Partial Cell Pertussis Bacteria, or Specific Pertussis Antigen(s)

Diphtheria, tetanus, and whole cell pertussis (DTwP) vaccines were used for much of the 20th century to control pertussis (whooping cough) disease. Concerns about the safety of DTWP (also referred to as DTP) vaccine prompted development of vaccines with an acellular pertussis component. With data showing fewer local, systemic, and more serious adverse events after acellular (DTaP) vaccine when compared to whole cell DTWP vaccine, the FDA licensed diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines in 1991 for use in children aged 15 months to 6 years, and in 1996 for use in infants and children aged 6 weeks to 6 years. By 2000, DTaP had replaced DTWP and, like the whole cell pertussis vaccine, was subsequently licensed in combination with other vaccines for routine use in children. Further, in 2005, FDA licensed tetanus and diphtheria toxoid (Td) and, acellular pertussis (Tdap) vaccine, for use in persons 10 years of age and older, as this vaccine is thought to decrease the number of pertussis carriers in the population, which would lead to a decrease in the number of pertussis outbreaks.

The Secretary notes that there are significant differences between whole cell and acellular pertussis vaccines. Although both vaccine types were developed for the same purpose (*i.e.*, immunization against pertussis), they have significantly different compositions, and different effects on biological systems (*e.g.*, the immune and nervous systems). DTWP is distinct from DTaP because the former contains many bacterial proteins, including endotoxins (some of which are known neurotoxins) and the latter does not. These

neurotoxins are thought to possibly act synergistically to cause adverse neurologic events in susceptible DTWP vaccine recipients. To date, no adequate study has been published that demonstrates a causal relationship between acellular pertussis vaccines and encephalopathy/encephalitis. Furthermore, studies have demonstrated a significant reduction in the number of common adverse events with acellular pertussis, such as crying and fevers, and less common ones, such as febrile seizures. [Pertussis vaccination: use of acellular pertussis vaccines among infants and young children recommendations of the advisory committee on immunization practices (ACIP), MMWR, 1997; 46(RR-7):1-25.] [Le Saux N, et al. Health Canada Immunization Monitoring Program-Active (IMPACT)] [Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: A report from IMPACT. Pediatrics. 2003; 112(5):e348.] Pertussis antigen-containing vaccines were included in the original statutory Table.

A. Encephalopathy/Encephalitis

The initial Table and QAI set forth in the 1986 statute reflected Congress' initial legislative determinations on vaccine-related injuries for DTWP vaccine. Further, modifications to the Table and QAI promulgated by the Secretary in 1995 were based on the scientific findings related to DTWP vaccine, the key study being the British National Childhood Encephalopathy Study (NCES), which found some evidence of acute neurologic illness (encephalopathy) 1 to 7 days after vaccination with the whole cell pertussis vaccine. Similarly, a 10 year NCES follow-up found evidence of chronic nervous system effects. However, the evidence from this follow-up study remained insufficient to indicate the presence or absence of a causal relation between DTP and chronic nervous system dysfunction. On the other hand, a more recent epidemiologic study of whole cell pertussis-containing vaccines did not show a relationship with encephalopathy or encephalitis (Ray et al). The IOM conclusions in 1991 and 1994 were mixed regarding the statistically significant findings of encephalopathy in both the original NCES and its 10 year follow-up. [IOM, Adverse Effects of Pertussis and Rubella Vaccines, 1991. IOM, Adverse Events Associated with Childhood Vaccines, 1994.] In the end, the Secretary, with

unanimous support of the ACCV, retained encephalopathy on the Table, but clarified the definition of encephalopathy in the QAI to make it more clinically precise. [Miller D, Wadsworth J, Ross E, Severe neurological illness: Further analysis of the British National Childhood Encephalopathy Study. *Tokai J Exp Clin Med*. 1988; 13(suppl):145–155; Miller D, Madge N, Diamond J, Wadsworth J, and Ross E, Pertussis Immunization and Serious Acute Neurological Illnesses in Children, *BMJ*, 1993;307:1171–6; Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, Shinefield H, Marcy M, Huff K, Ward J, Mullooly J, Chen R, Davis R, and the Vaccine Safety Datalink Group, Encephalopathy After Whole-Cell Pertussis or Measles Vaccination: Lack of Evidence for a Causal Association in a Retrospective Case-Control Study. *Ped Infec Dis J*. 2006; 25(9):768–773.]

Acellular pertussis-containing vaccines were developed because of concerns about events due to whole cell pertussis. Toxicologists argue that components in these two types of pertussis vaccines differ greatly and should be treated as separate entities. Animal models have demonstrated that whole cell pertussis constituents have different effects than those with acellular pertussis. In one study, only whole cell pertussis vaccines caused seizure activity in mice. Levels of inflammatory markers were elevated in the whole cell pertussis group but not the acellular pertussis group. In another study, mice that received whole cell pertussis intravenously succumbed while those that received acellular pertussis did not. [Sato Y, Sato H, Comparison of Toxicities of Acellular Pertussis Vaccine with Whole Cell Pertussis Vaccine in Experimental Animals, *Dev Biol Stand*, 1991; 73:251–62; Donnelly S, Loscher CE, Lynch MA, Mills KH, Whole-cell but not Acellular Pertussis Vaccines Induce Convulsive Activity in Mice: evidence of a role for toxin-induced interleukin-1beta in a new murine model for analysis of neuronal side effects of vaccination. *Infect Immun*. 2001 July; 69(7):4217–4223.]

The 2012 IOM report on adverse events found that the evidence was inadequate to accept or reject a causal association between acellular pertussis-containing vaccines and encephalopathy and encephalitis. As previously stated, there is no credible evidence of a causal relationship between acellular pertussis vaccines and encephalopathy/encephalitis. Clinical studies have demonstrated a significant reduction in the number of

common adverse events with acellular pertussis vaccine, as compared to whole cell pertussis vaccine, such as crying and fevers, and less common ones, such as febrile seizures. Although there have been large-scale surveillance studies conducted on the effects of acellular pertussis vaccines in infants and young children, such as those done in Canada and Australia, the study design used passive surveillance and therefore, the evidence is not as definitive as a controlled, well-designed epidemiologic study using a case control or cohort design [Le Saux N, et al. e348] [Lawrence G., Menzies R., Burgess M., McIntyre P., Wood N., Boyd I., Purcell P., Isaacs D. Surveillance of adverse events following immunization: Australia, 2000–2002. *Commun Dis Intell*. 2003; 27(3):307–23]. With regard to adolescents and adults, the Committee included a study by Yih (2009) which found that the number of encephalitis, encephalopathy or meningitis cases within 42 days of Tdap vaccination were less than a historical Td cohort with a relative risk of 0.84. [Yih W. K., Nordin J.D., Kulldorff M., Lewis E., Lieu T.A., Shi P., and Weintraub E. S., 2009, An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the vaccine safety datalink, *Vaccine* 27(32):4257–4262]

In view of the limited epidemiological data, and as influenced by the Guiding Principles, the Secretary does not propose to make any changes to the Table, leaving intact the Table injury of encephalopathy/encephalitis for vaccines containing pertussis antigens, with an onset less than 72 hours from vaccination. However, the Secretary proposes to re-organize, clarify, and update the QAI for acute and chronic encephalopathy, and to include a new definition for acute encephalitis based on the Brighton Collaboration criteria and several other references. The Brighton Collaboration is an international voluntary collaboration that develops globally accepted and standardized case definitions of adverse events following immunizations. More information can be found at: <https://brightoncollaboration.org/public>.

B. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA for pertussis antigen-containing vaccines. [See I.A.] The interval of onset will be less than or equal to 48 hours.

C. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for pertussis antigen-containing vaccines. [See I.B.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

III. Vaccines Containing Measles, Mumps, and Rubella Vaccine or Any of Its Components

Since the 1960s, measles, mumps, and rubella (MMR), a live, attenuated virus vaccine, has been routinely administered to children in the U.S. In 2005, the tetravalent measles, mumps, rubella, and varicella (MMRV) vaccine was added to the immunization schedule. MMR vaccine was included in the original statutory Table.

A. Vaccine Strain Measles Viral Disease Including Measles Inclusion Body Encephalitis (MIBE)

Severe complications associated with the measles virus or a mutated form of the virus, such as measles inclusion body encephalitis (MIBE), can be broadly categorized as measles viral diseases. The Table currently lists “vaccine-strain measles viral infection in an immunodeficient recipient” as a Table injury for vaccines containing measles virus, with an onset of 6 months. This condition is defined in the QAI as “a disease caused by the vaccine-strain that should be determined by vaccine-specific monoclonal antibody or polymerase chain reaction tests.”

MIBE is a rare, slow encephalitis caused by chronic with the measles virus, and is thus a subset of the condition already listed on the Table. MIBE is confined to immunodeficient individuals and is frequently fatal. MIBE occurs primarily in children and young adults, and typically occurs within 1 year of the initial infection or vaccination. A gradual decline in intellectual abilities and behavioral alterations are followed by progressive myoclonus; muscle spasticity; seizures; dementia; autonomic dysfunction; and ataxia. Death usually occurs 1 to 3 years after disease onset. Pathologic features include perivascular cuffing, eosinophilic cytoplasmic inclusions, neurophagia, and fibrous gliosis.

The IOM concluded that the evidence convincingly supports a causal relationship between MMR vaccine and MIBE in individuals with demonstrated immunodeficiencies. Out of the five case reports the IOM found, two had wild-type measles infection and these did not contribute to the weight of evidence. Only one out of the three

contributing case reports had vaccine-strain measles virus isolated. Because of limitations due to testing and viral properties, in most cases it is difficult to characterize wild-type versus vaccine-strain measles. [Bitnun A., Shannon P., Durward A., Rota P.A., Bellini W.J., Graham C., Wang E., Ford-Jones E.L., Cox P., Becker L., Fearon M., Petric M., and Teller R., 1999. Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. *Clinical Infectious Diseases* 29(4):855–861.] The current Table lists “Vaccine-strain measles viral infection in an immunodeficient recipient” for measles virus-containing vaccines with a time interval of onset of 6 months. Case reports of MIBE cited by the IOM showed a time interval of onset that varied from 8 days to 11 months.

For the reasons discussed above and in keeping with the spirit of the Guiding Principles, the Secretary proposes to change the injury of “vaccine-strain measles viral infection in an immunodeficient recipient” to “vaccine-strain measles viral disease in an immunodeficient recipient.” Because MIBE is a type of measles virus-associated disease occurring in immunodeficient individuals, the Secretary proposes a new time interval of onset of up to 12 months from the date of vaccination for those cases in which the typing of vaccine strain was not performed, because most cases of vaccine-strain disease occur within 1 year of vaccination. There is no time interval for onset proposed if the vaccine strain of the virus is identified, as it can be concluded that the vaccine is a contributing cause of the injury. Cases in which wild-type measles strain is isolated will be excluded. Revisions to the Table will distinguish between cases in which the measles vaccine strain is identified versus those cases in which laboratory testing was not done or the results were inconclusive. In addition, the Secretary proposes adding diagnostic criteria to the QAI.

B. Encephalopathy and Encephalitis

The IOM concluded that the evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalopathy or encephalitis. Not only is there limited epidemiologic evidence on a possible causal association, the mechanistic evidence is weak, based on current knowledge about natural infection and few case reports. Natural (wild-type) infection (measles, mumps, and/or rubella virus) is thought to cause neurologic illness through damage to the neurons by direct viral invasion. This is thought to be either from direct viral infection and/or

viral reactivation (particularly in immunocompromised patients). These same mechanisms may be responsible for vaccine-associated encephalopathy/encephalitis, but evidence linking these mechanisms directly to MMR vaccine strains (detection of viral antigens or antibodies) has not been shown. [Makela A., J. P. Nuorti, and H. Peltola. 2002. Neurologic disorders after measles-mumps-rubella vaccination. *Pediatrics* 110(5):957–963.] [Ray, P., J. Hayward, D. Michelson, E. Lewis, J. Schwalbe, S. Black, H. Shinefield, M. Marcy, K. Huff, J. Ward, J. Mullooly, R. Chen, and R. Davis. 2006. Encephalopathy after whole-cell pertussis or measles vaccination: Lack of evidence for a causal association in a retrospective case-control study. *Pediatric Infectious Disease Journal* 25(9):768–773.]

In view of the limited mechanistic data, and as influenced by the Guiding Principles, the Secretary does not propose to make any changes to the Table, leaving intact the Table injury of encephalopathy/encephalitis for MMR vaccines, with an onset not less than 5 days and no more than 15 days from vaccination. However, the Secretary proposes to re-organize, clarify, and update the QAI for acute and chronic encephalopathy and include a new definition for acute encephalitis based on the Brighton Collaboration criteria and several other references. [Ford-Jones L., MacGregor D., Richardson S., et al. Acute childhood encephalitis and meningoencephalitis: Diagnosis and management. *Paediatr Child Health* (1988). Jan–Feb;3(1):33–40] [Ball R., Halsey N., Braun M., et al. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the Vaccine Adverse Event Reporting System. *Journal of Clinical Epidemiology* (2002). 55:819–824.]

C. Febrile Seizures

Febrile seizures are a common cause of convulsions in young children. Generally viewed as benign and not indicative of brain disease, they occur in two to four percent of children up to age 5 years. Febrile seizures are often seen as the body temperature increases rapidly; but, may develop as the fever is declining. Most events last a minute or two, although some can be as brief as a few seconds. A family history of febrile seizures increases the child’s risk of occurrence. Anything that causes fever, such as viral or bacterial infections, can bring on a febrile seizure.

The IOM Committee concluded that the evidence convincingly supports a causal relationship between MMR

vaccine and febrile seizures. Based on seven epidemiologic studies, the Committee had a high degree of confidence that there is an increased risk of febrile seizures after receipt of MMR vaccine. The Committee assessed the mechanistic evidence regarding an association between MMR vaccine and febrile seizures as intermediate based on 12 cases presenting clinical evidence. [Farrington, P., S. Pugh, A. Colville, A. Flower, J. Nash, P. Morgan-Capner, M. Rush, and E. Miller. 1995. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 345(8949):567–569.] [Miller, E., N. Andrews, J. Stowe, A. Grant, P. Waight, and B. Taylor. 2007. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *American Journal of Epidemiology* 165(6):704–709.] [Barlow, W. E., R. L. Davis, J. W. Glasser, P. H. Rhodes, R. S. Thompson, J. P. Mullooly, S. B. Black, H. R. Shinefield, J. I. Ward, S. M. Marcy, F. DeStefano, and R. T. Chen. 2001. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *New England Journal of Medicine* 345(9):656–661.]

Patients who had post-MMR vaccination febrile seizures had no higher risk of subsequent seizure or neurodevelopmental disability than other children with febrile seizures in the absence of vaccine administration. The long-term rate of epilepsy was not increased in children who had febrile seizures following MMR vaccination compared with children who had febrile seizures of a different etiology [Vestergaard, M., A. Hviid, K. M. Madsen, J. Wohlfahrt, P. Thorsen, D. Schendel, M. Melbye, and J. Olsen. 2004. MMR vaccination and febrile seizures: Evaluation of susceptible subgroups and long-term prognosis. *Journal of the American Medical Association* 292(3):351–357.] [Barlow, W. E., R. L. Davis, J. W. Glasser, P. H. Rhodes, R. S. Thompson, J. P. Mullooly, S. B. Black, H. R. Shinefield, J. I. Ward, S. M. Marcy, F. DeStefano, and R. T. Chen. 2001. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *New England Journal of Medicine* 345(9):656–661.]

Although febrile seizures can be alarming to parents and other family members, the overwhelming majority of children who have febrile seizures recover quickly and have no lasting effects. Only very rarely can febrile seizures lead to serious injury or disability.

The National Childhood Vaccine Injury Act of 1986 requires the effects of the alleged vaccine injury must have continued for at least 6 months (unless the injury results in in-patient hospitalization *and* surgery, or death). Because the current medical literature supports febrile seizures only very rarely have long term consequences this condition is not being proposed for inclusion on the Table. However, the Program will consider causation-in-fact claims for febrile seizures leading to serious injury or death on a case-by-case basis.

D. Transient Arthralgia in Women and Children

Arthralgia means joint pain without signs of inflammation (*e.g.* erythema, warmth, pallor, edema, or decreased range of movement). Arthritis is arthralgia with signs of inflammation. Arthropathy encompasses arthralgia or arthritis and refers to any joint disease. Unlike arthritis, arthralgia is a symptom and there may be no objective measures for confirmation. The IOM concluded that the evidence favors acceptance of a causal relationship between MMR vaccine (attributable to the rubella component) and transient arthralgia in women and children. The IOM had a moderate degree of confidence in the epidemiologic evidence for women (based on four studies) that consistently reported an increased risk of transient arthralgia after MMR vaccination. Similarly, the mechanistic evidence regarding an association between rubella vaccine and transient arthralgia in women was intermediate based on 13 case reports. Two-thirds of the studies involved post-partum women. [Slater, P. E., T. Ben-Zvi, A. Fogel, M. Ehrenfeld, and S. Ever-Hadani. 1995. Absence of an association between rubella vaccination and arthritis in underimmunized postpartum women. *Vaccine* 13(16):1529–1532.] [Ray, P., S. Black, H. Shinefield, A. Dillon, J. Schwalbe, S. Holmes, S. Hadler, R. Chen, S. Cochi, and S. Wassilak. 1997. Risk of chronic arthropathy among women after rubella vaccination. *Journal of the American Medical Association* 278(7):551–556] [Tingle, A. J., L. A. Mitchell, M. Grace, P. Middleton, R. Mathias, L. MacWilliam, and A. Chalmers. 1997. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 349(9061):1277–1281.] [Mitchell, L. A., A. J. Tingle, L. MacWilliam, C. Home, P. Keown, L. K. Gaur, and G. T. Nepom. 1998. HLA–DR class II associations with rubella vaccine-induced joint manifestations.

Journal of Infectious Diseases 177(1):5–12.]

There were seven epidemiologic studies of children that consistently reported an increased risk of arthralgia after MMR vaccination. The IOM had a moderate degree of confidence in the epidemiologic evidence based on the seven studies with sufficient validity and precision to assess an association between MMR vaccine and transient arthralgia in children. The mechanistic evidence was weak based on knowledge about natural rubella infection. [Peltola, H., and O. P. Heinonen. 1986. Frequency of true adverse reactions to measles-mumps-rubella vaccine. *Lancet* 327(8487):939–942.] [Virtanen, M., H. Peltola, M. Paunio, and O. P. Heinonen. 2000. Day-to-day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination. *Pediatrics* 106(5):E62.] [Benjamin, C. M., G. C. Chew, and A. J. Silman. 1992. Joint and limb symptoms in children after immunization with measles, mumps, and rubella vaccine. *BMJ* 304(6834):1075–1078.] [Davis, R. L., E. Marcuse, S. Black, H. Shinefield, et al. 1997. MMR2 immunization at 4 to 5 years and 10 to 12 years of age: A comparison of adverse clinical events after immunization in the vaccine safety datalink project. *Pediatrics* 100(5):767–771] [dos Santos, B. A., T. S. Ranieri, M. Bercini, M. T. Schermann, S. Famer, R. Mohrdieck, T. Maraskin, and M. B. Wagner. 2002. An evaluation of the adverse reaction potential of three measles-mumps-rubella combination vaccines. *Revista Panamericana de Salud Publica/Pan American Journal of Public Health* 12(4):240–246.] [LeBaron, C. W., D. Bi, B. J. Sullivan, C. Beck, and P. Gargiullo. 2006. Evaluation of potentially common adverse events associated with the first and second doses of measles-mumps-rubella vaccine. *Pediatrics* 118(4):1422–143] [Heijstek, M. W., G. C. S. Pileggi, E. Zonneveld-Huijssoon, et al. 2007. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases* 66(10):1384–1387.]

Because transient arthralgia is a subjective symptom that frequently lacks objective evidence for confirmation and has no long-term effects or consequences, this condition is not being proposed for inclusion on the Table.

E. Chronic Arthropathy in Women and Children and Arthropathy in Men

The IOM concluded that the evidence was inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthropathy in

women and children, as well as arthropathy in men. The committee had limited confidence in the epidemiologic evidence for rubella vaccine and chronic arthralgia or arthritis. The epidemiologic evidence was insufficient or absent to assess an association between measles or mumps vaccine and chronic arthralgia or chronic arthritis in women. The IOM assessed the mechanistic evidence regarding rubella vaccine and chronic arthralgia or chronic arthritis in women as low-intermediate; and as lacking between measles or mumps vaccine and chronic arthralgia or chronic arthritis in women. In children, the IOM found the epidemiologic evidence to be insufficient or absent for the association between MMR and chronic arthropathy. The IOM found the mechanistic evidence between rubella vaccine and chronic arthropathy to be weak and they found the evidence to be lacking for measles and mumps vaccines. The IOM had limited confidence in the epidemiologic evidence for an association between MMR vaccine and arthropathy in men. The IOM found the mechanistic evidence regarding the association between rubella vaccine and arthropathy in men to be weak. The IOM found the mechanistic evidence between measles or mumps vaccine and arthropathy in men as lacking. [Ray, P., S. Black, H. Shinefield, A. Dillon, J. Schwalbe, S. Holmes, S. Hadler, R. Chen, S. Cochi, and S. Wassilak. 1997. Risk of chronic arthropathy among women after rubella vaccination. *Journal of the American Medical Association* 278(7):551–556.] [Tingle, A. J., L. A. Mitchell, M. Grace, P. Middleton, R. Mathias, L. MacWilliam, and A. Chalmers. 1997. Randomised double-blind placebo-controlled study on adverse effects of rubella immunization in seronegative women. *Lancet* 349(9061):1277–1281.] Peters, M. E., and S. Horowitz. 1984. Bone changes after rubella vaccination. *American Journal of Roentgenology* 143(1):27–28. Geiger, R., F. M. Fink, B. Solder, M. Sailer, and G. Enders. 1995. Persistent rubella infection after erroneous vaccination in an immunocompromised patient with acute lymphoblastic-leukemia in remission. *Journal of Medical Virology* 47(4):442–444.]

In spite of the limited epidemiological and mechanistic data, based on the Guiding Principles, the Secretary does not propose to make any changes to the Table, leaving intact the Table injury of chronic arthritis for MMR vaccines, with an onset not less than 7 days and no more than 42 days from vaccination. However, the Secretary proposes to

provide a definition for chronic arthritis in the QAI, based on the Brighton Collaboration criteria and several other references.

F. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA to the Table for vaccines containing measles, mumps and/or rubella virus. [See section I.A above.] The interval of onset will be less than or equal to 48 hours. However, the Secretary recognizes that there currently is no intramuscular formulation of this vaccine available and therefore, petitioners alleging an injury of SIRVA associated with this vaccine presently cannot meet the QAI for SIRVA. Please see section I.A., above, for additional discussion on this point.

G. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for vaccines containing measles, mumps and/or rubella virus. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

IV. Vaccines Containing Polio Inactivated Virus

Since 2000, inactivated polio vaccine (IPV) has been the only polio vaccine used in the United States, although live virus oral polio vaccine (OPV) is still used in many parts of the world. The Secretary proposes changes to the Table related only to IPV, as an injected vaccine. OPV was included in the original statutory Table and remains on the regulatory Table.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for vaccines containing polio inactivated virus. [See Section I.A above.] The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for vaccines containing polio inactivated virus. [See Section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

V. Hepatitis B Vaccines

The recombinant hepatitis B vaccine was first licensed by the FDA in 1986. Produced from cultured and purified yeast cells, it is the current form of vaccine used in the United States. Prior to 1991, the vaccine was recommended only for high risk individuals. However,

the recommendation was extended to include all infants, since infected infants and children are at higher risk for developing chronic liver disease with subsequent liver cancer, and approximately one-third of those who acquire hepatitis B infection do not have any identified risk factors, and, therefore, were frequently not immunized. The effective date of coverage for hepatitis B vaccine is August 6, 1997.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for hepatitis B vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for hepatitis B vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

VI. *Haemophilus Influenzae* Type B Vaccines

Haemophilus influenzae type b (Hib) conjugate vaccines were first licensed by the FDA in 1987 and have been recommended by the CDC for routine use since 1991. The vaccine is given to infants and children up to the age of school entry. The effective date of coverage for Hib vaccines is August 6, 1997, with no injuries or conditions specified.

In order for a category of vaccines to be covered under the VICP, the category of vaccine must be recommended for routine administration to children by the Centers for Disease Control and Prevention (for example, vaccines that protect against seasonal influenza), subject to an excise tax by Federal law, and added to the Program by the Secretary of Health and Human Services. The Internal Revenue Code defines a "taxable vaccine" as including "[a]ny HIB vaccine". See 26 U.S.C. 4132(a)(1)(H). Thus, the Secretary proposes to modify category IX on the Table from "*Haemophilus influenzae* type b polysaccharide conjugate vaccines" to "*Haemophilus influenzae* type b vaccines," as a technical change in order to be most inclusive.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for Hib vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for Hib vaccines. [See I.B.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

VII. *Varicella* Vaccines

The varicella (chickenpox) virus vaccine, which was first licensed by the Food and Drug Administration in 1995, contains a live, attenuated strain of the varicella virus. Chickenpox is a highly contagious disease and although usually mild, infants, adolescents, adults, pregnant women, and immunocompromised individuals are at higher risk for serious complications. Since the introduction of the vaccine there has been a significant decrease in the number of cases of the disease with the greatest effect in states with the highest vaccination coverage. *Varicella* vaccine is listed on the Table, effective August 6, 1997, with no injuries or conditions specified.

A. Disseminated Vaccine-Strain Viral Disease

Disseminated varicella vaccine-strain viral disease is a condition in which the affected individual develops the varicella rash caused by the vaccine strain that spreads beyond the dermatome (an area of skin supplied by the nerve fibers of a single spinal root) involved in the vaccination and/or there is involvement of other organs such as the brain, lungs, and liver. For organs other than the skin, disease, not just mildly abnormal laboratory values, must be demonstrated in the involved organ. In this section, the word "disseminated" is defined by the IOM as the spreading of the rash (or the virus) beyond the dermatome involved in the vaccination.

The IOM reviewed the evidence for vaccine causation of disseminated varicella disease with and without involvement of organs beyond the skin. They found three case reports in which vaccinated individuals developed lesions confined to the skin after immunization, and in whose lesions the vaccine strain of the varicella virus was identified. In addition, the IOM identified 550 cases reported to passive surveillance systems in which an attempt was made to identify the virus from skin lesions in individuals who developed disseminated varicella disease after vaccination without involvement of another organ. The wild-type virus was identified in 210 cases; the vaccine-strain virus was identified in 125 cases; and in the remaining cases either the sample was inadequate, the virus could not be identified, or there

was no virus present. The committee also identified nine cases in which the vaccine strain of the virus was identified in individuals who had meningitis, pneumonia or hepatitis in addition to skin lesions. Cases of disseminated disease, which were reviewed by the IOM in individuals who were thought to be immunocompetent, all occurred within 42 days of immunization. The time of onset was not further specified. In many cases the timeframe from vaccination to onset of disseminated illness, without other organ involvement, was not provided for immunocompromised individuals, but in the cases for which there was data, there was a broad range of onset, spanning from 1 week in one case to “up to 87 days” in another. For four cases, in which onset was reported, the interval following vaccination was 18 days to 6 weeks. For disseminated disease with other organ involvement, onset was 13 days after vaccination in the only immunocompetent patient for whom data was available, and onset was between 10 and 35 days in eight immunocompromised individuals. [Wise, R. P., M. E. Salive, M. M. Braun, G. T. Mootrey, J. F. Seward, L. G. Rider, and P. R. Krause. 2000. Postlicensure safety surveillance for varicella vaccine. *Journal of the American Medical Association* 284(10):1271–1279.] [Goulleret, N., E. Mauvisseau, M. Essevez-Roulet, M. Quinlivan, and J. Breuer. 2010. Safety profile of live varicella virus vaccine (Oka/Merck): Five-year results of the European varicella zoster virus identification program (EU VZVIP). *Vaccine* 28(36):5878–5882.]

The IOM found the evidence convincingly supports a causal relationship between varicella vaccine and disseminated varicella disease, both for cases confined to the skin and for cases where the spread involves other organs. However, the IOM limited their finding of causation in cases in which organs beyond the skin were involved to those with demonstrated immunodeficiencies. The Secretary notes that there is a significant overlap in the time-frames involved in the onset of disseminated disease in both immunocompetent and immunocompromised individuals. The Secretary further notes that although the IOM found convincing support for disseminated disease with other organ involvement only in immunocompromised individuals, the Secretary proposes, in accordance with the ACCV Guiding Principles, that the Table injury apply to all individuals, regardless of the status of their immune

system, because it is possible that an individual so affected may not have been completely evaluated for an existing immunodeficiency, or suffered from an immunodeficiency that is subtle and beyond our current ability to test.

The Secretary proposes to add disseminated vaccine-strain infection, both with and without other organ involvement, as a Table injury for varicella-containing vaccines. There is no time interval for onset if the vaccine strain of the virus is identified. However, if testing is not done or does not identify the virus, it is proposed that the injury qualify as a Table injury if the onset is 7 to 42 days following vaccination. If the wild-type virus or another non-vaccine-strain virus is identified, there will be no presumption of causation and it will not meet the Table criteria. If there is involvement of an organ beyond the skin, and no virus was identified in that organ, the involvement of all organs must occur as part of the same discrete illness.

B. Varicella Vaccine-Strain Viral Reactivation

Varicella vaccine-strain viral reactivation disease is defined as the presence of the rash of herpes zoster (shingles) with or without concurrent disease in another organ. Shingles is a painful, blistering skin rash due to the reactivation of varicella (chickenpox) virus that involves one or more sensory dermatomes. After natural varicella infection, the virus lies dormant in the spinal dorsal root ganglia. Shingles occurs after the virus becomes active again.

There is a significant body of literature showing that the vaccine-strain of the virus can cause shingles without other organ involvement. However, the wild-type chickenpox virus has been identified in many of the cases occurring after vaccination. The Committee reviewed 111 cases in which individuals who received a varicella-containing vaccine developed reactivated varicella disease without other organ involvement and in whom the vaccine-strain of the virus was identified. The IOM found six cases in which individuals who had received varicella vaccine developed reactivated disease in another organ, and in all the cases, the vaccine-strain of the virus was identified in the other organ. In four of those cases, the vaccine-strain of the virus was also identified in the skin. The findings for other organ involvement in these case reports were limited to the meninges and brain. The IOM concluded that the evidence convincingly supports a causal relationship between varicella vaccine

and vaccine-strain viral reactivation, with or without involvement of an organ other than the skin. [Chaves, S. S., P. Haber, K. Walton, R. P. Wise, H. S. Izurieta, D. S. Schmid, and J. F. Seward. 2008. Safety of varicella vaccine after licensure in the United States: Experience from reports to the vaccine adverse event reporting system, 1995–2005. *Journal of Infectious Diseases* 197(SUPPL. 2):S170–S177.] [Iyer, S., M. K. Mittal, and R. L. Hodinka. 2009. Herpes zoster and meningitis resulting from reactivation of varicella vaccine virus in an immunocompetent child. *Annals of Emergency Medicine* 53(6):792–795.] [Levin, M. J., R. L. DeBiasi, V. Bostik, and D. S. Schmid. 2008. Herpes zoster with skin lesions and meningitis caused by two different genotypes of the Oka varicella-zoster virus vaccine. *Journal of Infectious Diseases* 198(10):1444–1447.]

The Secretary proposes to add vaccine-strain viral reactivation, both with and without other organ involvement, as a Table injury for varicella-containing vaccines. Although the IOM specified whether they considered immunocompetent or immunocompromised individuals, their causality conclusions for vaccine-strain reactivation, with and without other organ involvement, did not differentiate between these two groups. Because disease caused by varicella virus reactivation can occur many years, or even decades, after the initial disease or vaccination, the Secretary proposes that the QAI require laboratory confirmation of the presence of the vaccine-strain of the virus. With such confirmation, the status of the affected individual’s immune system is not relevant. In addition, there is no proposed time interval for this injury, as laboratory confirmation of vaccine-strain virus obviates the need for such a proposal. Since petitioners must demonstrate the presence of vaccine-strain varicella infection, the presumption includes the involvement of skin and other organs.

C. 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. The diagnosis of anaphylaxis requires the simultaneous involvement of two or more organ systems. In an anaphylactic reaction, an immediate reaction generally occurs within minutes after exposure, and in most cases, the individual develops signs and symptoms within 4 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 sequela. 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. [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.] The 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. [Institute of Medicine (IOM), Immunization Safety Review Vaccination and Sudden Unexpected Death in Infancy, Washington, DC: The National Academies Press, 2003] 55.] The IOM concluded that the scientific evidence convincingly supports a causal relationship between varicella vaccine and anaphylaxis. There are multiple, well-documented reports in the literature that anaphylaxis occurs after receipt of the varicella vaccine. One case series reported 16 cases of anaphylaxis after vaccination against varicella, with nearly all demonstrating anti-gelatin immunoglobulin E (IgE) antibodies. [Sakaguchi, M., T. Nakayama, H. Fujita, M. Toda, and S. Inouye. 2000b. Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin. *Vaccine* 19(4–5):431–436.]

There is a long history of including anaphylaxis as a known adverse effect of vaccines, including in the initial Table contained in the Act. The time-frame for the first symptom or manifestation of onset contained in the original statutory Table was shortened from 24 hours to 4 hours in the Table changes promulgated in 1995. Since that time, anaphylaxis has been added as an injury for the Hepatitis B vaccine.

The statute requires that injuries eligible for compensation under the Program be of sufficient seriousness to cause continued effects for more than 6 months, result in death, or result in inpatient hospitalization and surgical intervention. The Secretary continues to recognize that in many instances, cases involving anaphylaxis will not meet the statutory severity criteria, as the reaction can be short-lived and treated effectively. However, because there is a known risk of serious residual injury or death from anaphylaxis, the Secretary continues to recommend that anaphylaxis be included on the Table for other vaccines, and be added for varicella virus vaccines.

The Secretary proposes to add anaphylaxis as a Table injury for varicella virus-containing vaccines, with an onset less than or equal to 4 hours

from the administration of the vaccine. In addition, the Secretary proposes to update the definition of anaphylaxis in the QAI. (see proposed regulation text at proposed paragraph (c)(1)).

D. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for varicella virus-containing vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours. However, the Secretary recognizes that there currently is no intramuscular formulation of this vaccine available, and therefore petitioners alleging an injury of SIRVA associated with this vaccine presently cannot meet the QAI for SIRVA. Please see section I.A., above, for additional discussion on this point.

E. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for varicella virus-containing vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

VIII. Pneumococcal Conjugate Vaccines

Pneumococcal conjugate vaccines were first licensed by FDA in 2000. Over the next decade, the heptavalent (seven serotypes) vaccine dramatically reduced the rate of invasive pneumococcal disease in young infants and nasal carriage of the vaccine serotypes among all age groups, including the immunocompromised and older individuals. A 13-valent pneumococcal conjugate vaccine licensed in 2010 has replaced the 7-valent product in the infant schedule. Pneumococcal conjugate vaccines are included on the Table, with an effective date of coverage of December 19, 1999, with no injuries or conditions specified.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for pneumococcal conjugate vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for pneumococcal conjugate vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

IX. Hepatitis A Vaccines

Hepatitis A vaccine was first licensed by FDA in 1996 and introduced incrementally, first for children living in

communities with the highest rates of disease and then in 1999 for children living in States/communities with consistently elevated rates of infection. The impact of immunization with hepatitis A vaccine has been a dramatic decline in the rates of disease and a sharp reduction in the groups with the highest risk of infection: Native Americans and Alaskan natives. Rates of hepatitis A infection are now similar in most areas of the United States. As a consequence, hepatitis A vaccine has now been recommended for all children in the United States who are 12–23 months of age. Hepatitis A vaccine is included on the Table, with an effective date of December 1, 2004.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for hepatitis A vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for hepatitis A vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

X. Seasonal Influenza Vaccines

All seasonal trivalent influenza vaccines have been covered under the VICP since July 1, 2005. At that time, all seasonal influenza vaccines were trivalent. Quadrivalent vaccines for seasonal influenza became available for general use for the 2013–14 influenza season. On June 25, 2013, Public Law 113–15 was enacted, extending the applicable excise tax on trivalent influenza vaccines to also include any other vaccines against seasonal influenza. See Public Law 113–15 (amending 26 U.S.C. 4132(a)(1)(N)). The amendment included in Public Law 113–15 ensured that seasonal influenza vaccines are covered under the Program. Seasonal influenza vaccines (other than trivalent influenza vaccines) were added to the Table under the final catch-all category (42 CFR 100.3(c)(8)) with an effective date of November 12, 2013. The Secretary proposes to modify category XIV on the Table from “Trivalent influenza vaccines” to “Seasonal influenza vaccines.”

There are currently six types of seasonal influenza vaccines distributed during flu season. The standard dose trivalent inactivated influenza vaccine (IIV3) contains three killed virus strains and is injected. IIV3 is indicated in individuals 6 months of age or older,

including healthy people and those with chronic medical conditions (such as asthma, diabetes, or heart disease). High dose trivalent inactivated influenza vaccine (IIV3 High dose) is indicated in individuals who are 65 years of age or older. Trivalent recombinant influenza vaccine (RIV3) is indicated for individuals between the ages of 18 and 49 years. The standard dose quadrivalent inactivated influenza vaccine (IIV4) has the same indications as IIV3. The quadrivalent live attenuated influenza vaccine (LAIV4) is indicated for healthy, non-pregnant persons aged 2–49 years. The cell-culture based inactivated influenza vaccine (ccIIV3) is indicated for individuals who are 18 years of age and older.

The covered injuries proposed for seasonal influenza vaccines are the same as those proposed for trivalent influenza vaccines. The trivalent influenza vaccine and the quadrivalent influenza vaccine, distributed each year during flu season, are types of seasonal influenza vaccines.

A. Anaphylaxis

The Secretary proposes to add anaphylaxis as a Table injury for seasonal influenza vaccines. [See section VII.C above.] The IOM concluded that the scientific evidence convincingly supports a causal relationship between trivalent influenza vaccines and anaphylaxis. Sensitivity to eggs has long been known to cause allergic reactions to influenza vaccination in some individuals. The IOM assessed the mechanistic evidence as strong, including the following: 21 case reports of potential anaphylaxis following influenza vaccine; a strong temporal relationship between vaccine administration and anaphylactic reaction; isolation of anti-gelatin IgE in two cases; positive skin testing as a positive re-challenge in two cases; and repeated symptoms to vaccination against influenza on two occasions. Their conclusion made no distinction between the intranasal live attenuated vaccine and the injected vaccine. [Coop, C.A., S.K. Balanon, K.M. White, B. A. Whisman, and M.M. Rathkopf. 2008. Anaphylaxis from the influenza virus vaccine. *International Archives of Allergy and Immunology* 146(1):85–88.] [Chung, E.Y., L. Huang, and L. Schneider. 2010. Safety of influenza vaccine administration in egg-allergic patients. *Pediatrics* 125(5):e1024–e1030.] [Lasley, M.V. 2007. Anaphylaxis after booster influenza vaccine due to gelatin allergy. *Pediatric Asthma, Allergy and Immunology* 20(3):201–205.]

The Secretary proposes to add anaphylaxis as a Table injury for seasonal influenza vaccines, with an onset of less than or equal to 4 hours from the administration of the vaccine. In addition, the Secretary proposes to update the definition of anaphylaxis in the QAI.

B. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA only for seasonal influenza vaccines that are injected intramuscularly (as detailed in the proposed QAI). As proposed, this injury would not apply to formulations of the live attenuated influenza vaccine (LAIV), as LAIV is not administered intramuscularly with a needle. [See section I.A above.] In addition, this injury would not apply to the formulations of influenza vaccine where the route of administration is intradermal, such as the formulation that delivers 0.1 milliliters of vaccine through a prefilled microinjection system that contains a needle that is only 1.5 millimeters long. This needle is not long enough to enter the deltoid bursa or any other structure in the shoulder related to the development of SIRVA. SIRVA would apply only to formulations of the seasonal influenza vaccine that are administered through intramuscular injection. The interval of onset will be less than or equal to 48 hours.

C. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for injected vaccines only (as detailed in the proposed QAI). As proposed, this injury would apply to the seasonal inactivated influenza vaccine that is injected intramuscularly but not to the LAIV, as LAIV is not administered with a needle, and the syncopal reaction appears to be related to the act of injection. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

D. Guillain-Barré Syndrome (GBS)

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 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. Demyelination 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. The axon is a portion of the nerve cell that transmits nerve impulses away from the nerve cell body. Another subtype of GBS, 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 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 9 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 9 weeks after onset and are generally followed by eventual improvement.

According to the Brighton Collaboration, 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. [James J. Sejvar et al. Guillain-Barre Syndrome and Fisher Syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data *Vaccine* 29(3):599–612]. 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. [Sejvar 599–612].

For all subtypes of GBS (AIDP, AMAN, AMSAN, and FS), the onset of symptoms less than 3 days (72 hours) after exposure excludes that exposure as a cause because the immunologic steps necessary to create symptomatic disease require a minimum of 3 days.

CIDP is clinically and pathologically distinct from GBS. The onset phase of CIDP is generally greater than 8 weeks and the weakness may remit and relapse. CIDP is also not monophasic. [Sejvar 599–612.]

In the past, GBS has been causally associated with certain vaccines. For example, the 1976 influenza A (swine flu) vaccine was found by the IOM to be causally associated with GBS. The risk of developing GBS in the 6 week period after receiving the 1976 swine flu vaccine was 9.2 times higher than the risk for those who were not vaccinated. [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]. 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 1 million persons vaccinated, in the 6 weeks following vaccination, may be attributable to the vaccine formulation used in those years. The background incidence of GBS not associated with a vaccine among adults was documented in the study to be 0.87 cases per million persons for any 6 week period. [Tamar Lasky, *et al.*, "The Guillain-Barré 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 and concluded that people who received the 1976 swine influenza vaccine had an increased risk for developing GBS [IOM, *Immunization Safety Review: Influenza Vaccines and Neurological Complications*, 25]. 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 monovalent 2009 H1N1 influenza vaccine, were specifically excluded and not evaluated. The IOM concluded that the evidence is inadequate to accept or reject a causal relationship between seasonal influenza vaccine and GBS. (IOM, *Adverse Effects of Vaccines* 334). It is important to note that monovalent vaccines are usually only given in response to an actual or potential pandemic, while seasonal influenza vaccines are offered annually. The monovalent 2009 H1N1 vaccine, a type of pandemic vaccine, is covered under the Countermeasures Injury Compensation Program. The VICP does not cover pandemic influenza vaccines, such as the 2009 H1N1 Influenza vaccine.

A meta-analysis of the VSD, EIP (Emerging Infections Program—an active population-based surveillance program), and PRISM (Post-Licensure-Rapid Immunization Safety Monitoring—a cohort-based active surveillance network) data was performed and published, together with additional data from safety surveillance studies performed by Medicare, the Department of Defense, and the Department of Veterans Affairs, which, in total, analyzed data from 23 million people who were vaccinated with the influenza A (H1N1) 2009 monovalent vaccine. [Daniel A. Salmon et al., “Association between Guillain-Barré 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](http://dx.doi.org/10.1016/S0140-6736(12)62189-8).] The meta-analysis provides the benefit of additional statistical power. Additional power allows for the analyses of certain hypotheses which were not possible to

analyze individually in the six studies that made up the meta-analysis. The meta-analysis found that the 2009 H1N1 inactivated vaccine was associated with a small increased risk of GBS within 6 weeks of vaccination. This excess risk is equivalent to 1.6 excess cases in the 6 weeks after vaccination per million people vaccinated. This increased risk found in the meta-analysis was consistent: (1) Across studies looking at different groups of people; (2) using different definitions of 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.

Considering the totality of the evidence with the enhanced surveillance studies and meta-analysis performed to monitor the safety of the monovalent 2009 H1N1 vaccine, scientific evidence demonstrates a small increased risk of GBS in the 6 weeks following administration of the monovalent 2009 H1N1 vaccines.

Presently, there is no scientific evidence demonstrating that current formulations of the seasonal influenza vaccine, which contain the H1N1 virus, can cause GBS. However, the degree of surveillance needed to detect an increased risk of one case per million vaccinations, as was seen with the monovalent 2009 H1N1 vaccine, is unlikely to be routinely performed as the strains in the flu vaccines change from year to year. Nonetheless, numerous studies have been conducted in order to determine whether a possible association between seasonal influenza vaccines and GBS exists, and almost all have not shown any causal relationship. The IOM reviewed literature concerning such studies and concluded that the evidence was inadequate to accept or reject a causal association for all versions of seasonal influenza vaccines since 1976.

Using studies demonstrating a causal association between the 2009 H1N1 and 1976 swine flu vaccines and GBS as background, the Secretary proposes to add the injury of GBS to the Table for seasonal influenza vaccines. Although the scientific evidence does not show a causal association for current formulations of seasonal flu vaccines and GBS, the Secretary proposes including the injury of GBS for seasonal influenza vaccines on the Table in accordance with the ACCV Guiding Principles, acknowledging the fact that seasonal influenza vaccine formulations, unlike other vaccines, change from year-to-year and that

enhanced surveillance activities may not occur with each virus strain change. This is done even though it appears that any instances of GBS caused by seasonal influenza vaccines, if they exist at all, are very rare. The Secretary proposes adding GBS to the Table for seasonal influenza vaccines and recognizes that this will create a presumption of causation that will result in compensation for numerous instances of GBS that are not vaccine-related.

While there is no evidence demonstrating that current formulations of the seasonal influenza vaccine can cause GBS, the totality of the evidence, particularly the enhanced surveillance studies and meta-analysis performed to monitor the safety of the 2009 H1N1 vaccine, provides compelling evidence of a small increased risk of GBS in the 6 weeks following the administration of the 2009 H1N1 vaccine. Utilizing this scientific data as background, the Secretary proposes an onset interval of 3–42 days for GBS presumed to be caused by the seasonal 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. [Peripheral Neuropathy (Philadelphia, PA: Elsevier Saunders, 2005, 626)].

XI. Meningococcal Vaccines

There are two types of meningococcal vaccines administered in the United States. The polysaccharide vaccine was licensed by the FDA in 1978, and is indicated for persons 2 years of age and older; the meningococcal conjugate vaccines were licensed starting in 2005. The conjugate vaccines were developed with the expectation that they would provide more long-lasting immunity, a more rapid immune response upon exposure to *Neisseria meningitidis*, and the development of “herd immunity” through reduction of the asymptomatic carrier state. The meningococcal polysaccharide and conjugate vaccines were added to the Table with an effective date of February 1, 2007.

A. Anaphylaxis

The Secretary proposes to add anaphylaxis as a Table injury for meningococcal vaccines. [See section VII.C above.] The IOM Committee, following an extensive review of the scientific and medical literature, concluded that the evidence convincingly supported a causal relationship between meningococcal vaccines and anaphylaxis. The Institute of Medicine based their conclusion on a case report of anaphylaxis with onset

30 minutes following vaccination. [Yergeau, A., L. Alain, R. Pless, and Y. Robert. 1996. Adverse events temporally associated with meningococcal vaccines. *Canadian Medical Association Journal* 154(4):503–507.]

The Secretary proposes to add anaphylaxis as a Table injury for meningococcal vaccines, with an onset less than or equal to 4 hours from the administration of the vaccine. In addition, the Secretary proposes to update the definition of anaphylaxis in the QAI.

B. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for meningococcal vaccines. [See section I.A above.] The interval of onset will be less than or equal to 48 hours.

C. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for meningococcal vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

XII. Human Papillomavirus Vaccines

The first human papillomavirus (HPV) vaccine was licensed by the FDA in June 2006 for females between the ages of 9–26 years. In 2011, one of the two licensed HPV vaccines was given a permissive use recommendation in males by the CDC and other recommending bodies (*i.e.*, the American Academy of Pediatrics and the American Academy of Family Physicians). HPV vaccine was added to the Table with an effective date of February 1, 2007.

A. Anaphylaxis

The Secretary proposes to add anaphylaxis as a Table injury for HPV vaccines. [See VII.C] The IOM Committee concluded that the evidence favors acceptance of a causal relationship between human papillomavirus vaccines and anaphylaxis. They based their conclusion on temporality and clinical symptoms consistent with anaphylaxis in 9 reports from VAERS over 31 months of surveillance. [Slade, B.A., L. Leidel, C. Vellozzi E.J. et al. Post licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *Journal of the American Medical Association* 2009. 302(7):750–757.]

The Secretary notes that there are limitations to the VAERS passive reporting system. First, there is underreporting; not all adverse events

following vaccines are reported to the system. The rates of underreporting have been examined for different disorders and are greatest for adverse events of mild severity. Second, many reports are filed before a complete clinical evaluation has been conducted. Therefore, the presumptive diagnosis that has been provided at the time of the report may not be the correct diagnosis. Third, investigations conducted after the initial report sometimes reveal alternative causes for the adverse event. In many instances, incomplete information is provided in the initial report. Follow-up of the reports by the CDC and FDA may be conducted to collect additional information from the healthcare providers. The primary purpose of VAERS is to look for signals for evidence of unexpected adverse events that would require other investigations to try to determine causal relationships. Although conclusions about causation are not possible for most adverse events reported to VAERS, the IOM found likely causality based on the distinctive nature of anaphylactic reactions and the temporal relationship between the HPV vaccine administration and the event. The Secretary proposes to add anaphylaxis as a Table injury for HPV vaccines, with an onset of less than or equal to 4 hours from the administration of the vaccine. In addition, the Secretary proposes to update the definition of anaphylaxis in the QAI.

B. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA as a Table injury for HPV vaccines. [See section I.A above.] The proposed time interval of onset is less than or equal to 48 hours.

C. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for HPV vaccines. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

XIII. Category for Any New Vaccine Recommended by the Centers for Disease Control and Prevention for Routine Administration to Children After Publication by the Secretary of a Notice of Coverage

Category XVII of the current Table pertains to any new vaccine recommended by the CDC for routine administration to children, after publication by the Secretary of a notice of coverage. This category pertains to vaccines that are covered under the Program, but with respect to which the

Secretary has not yet finalized actions adding the vaccines as separate categories to the Table. Through this rule, the Secretary proposes retaining this category and adding two associated injuries for vaccines covered by this category.

A. Shoulder Injury Related to Vaccination

The Secretary proposes to add SIRVA for the category of vaccines captured under Category XVII of the Table. [See section I.A above.] As detailed in the proposed QAI, this injury would only apply to intramuscular vaccines injected into the upper arm. The interval of onset will be less than or equal to 48 hours.

B. Vasovagal Syncope

The Secretary proposes to add vasovagal syncope to the Table for this category of vaccines. As detailed in the proposed QAI, this injury would apply only to injected vaccines as the syncopal reaction appears to be related to the act of injection. [See section I.B above.] The proposed time interval of onset is less than or equal to 1 hour following vaccination.

XIV. Additional Table Changes

The Secretary is proposing a number of organizational and structural changes to the Table and QAI designed to increase clarity and scientific accuracy, including the addition of a glossary of terms used within the Table and the QAI.

Organizational Changes

- To streamline the Table, the Secretary proposes a new paragraph (b), *Provision that applies to all vaccines listed*. This section includes any acute complication or sequela, including death, of the illness, disability, injury, or condition listed, rather than adding this provision to every line of the Table.
- To further streamline the Table, the Secretary proposes the deletion of redundant wording in the various definitions, particularly with regard to any references to the presumption of causation, and the importance of the entire medical record. These elements have been included in paragraph (b). In addition, complicated language previously included in the definition of encephalopathy, which indicated that idiopathic injuries do not rebut the Table presumption, has been simplified and made generally applicable to all injuries. This has also been included in paragraph (b).
- The QAI (proposed paragraph (c)) contain definitions for those terms that are used in the Table (paragraphs (a) and (b)).

- The newly added glossary (proposed paragraphs (d)) defines terms used in multiple places in the QAI (proposed paragraph (c)). Most of these terms were formerly contained in the QAI, and have been moved to the glossary so that each reference is consistent. These definitions include: chronic encephalopathy, significantly decreased level of consciousness, injected, and seizure.

- The proposed Table and QAI include some changes made by the Final Rule adding Intussusception as an Injury for Rotavirus Vaccines to the Vaccine Injury Table (80 FR 35848, June 23, 2015).

Expansion

- The Secretary proposes to add definitions for new Table injuries, including SIRVA, disseminated varicella-strain virus disease, varicella vaccine-strain viral reactivation disease, GBS, and vasovagal syncope.

- The Secretary proposes to add definitions of terms that had been on the Table or in the QAI, but that previously were undefined, including encephalitis, injected, and immunodeficient recipient.

Harmonization

- The Secretary proposes additional changes to the QAI to address certain changes in scientific nomenclature. Definitions, such as acute encephalopathy and acute encephalitis, both of which lead to chronic encephalopathy, have been harmonized. Definitions for brachial neuritis and SIRVA have also been harmonized.

- The Secretary proposes modification of category XIV on the Table from “Trivalent influenza vaccines” to “Seasonal influenza vaccines”.

- The Secretary proposes modification of category IX on the Table from “Haemophilus influenzae type b polysaccharide conjugate vaccines” to “Haemophilus influenzae type b vaccines”.

- Minor technical changes resulting from updated medical information have been included in the definitions of anaphylaxis, encephalopathy, chronic arthritis, brachial neuritis, thrombocytopenic purpura, and seizure.

All of the proposed changes were discussed and approved by the ACCV, although the ACCV expressed some reservations regarding the definition of “immunodeficient recipient”. The discussion was reviewed, and the Secretary has modified the definition to address the concerns raised by the ACCV.

Economic and Regulatory Impact

Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when rulemaking is necessary, to select regulatory approaches that provide the greatest net benefits (including potential economic, environmental, public health, safety, distributive, and equity effects). In addition, under the Regulatory Flexibility Act, if a rule has a significant economic effect on a substantial number of small entities the Secretary must specifically consider the economic effect of a rule on small entities and analyze regulatory options that could lessen the impact of the rule.

Executive Order 12866 requires that all regulations reflect consideration of alternatives, of costs, of benefits, of incentives, of equity, and of 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.

The Secretary has determined that no resources are required to implement the requirements in this rule. Compensation will be made in the same manner. This proposed rule only lessens the burden of proof for potential petitioners. Therefore, in accordance with the Regulatory Flexibility Act of 1980 (RFA), and the Small Business Regulatory Enforcement Act of 1996, which amended the RFA, the Secretary certifies that this rule will not have a significant impact on a substantial number of small entities.

The Secretary has also determined that this proposed rule 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. We have determined that the proposed rule 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 1995.

Nor on the basis of family well-being will the provisions of this rule affect the following family elements: 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.

This rule is not being treated as a “significant regulatory action” under section 3(f) of Executive Order 12866. Accordingly, the rule has not been reviewed by the Office of Management and Budget.

As stated above, this proposed rule would modify the Vaccine Injury Table based on legal authority.

Impact of the New Rule

This proposed rule will have the effect of making it easier for future petitioners alleging injuries that meet the criteria in the Vaccine Injury Table to receive the Table’s presumption of causation (which relieves them of having to prove that the vaccine actually caused or significantly aggravated the injury).

Paperwork Reduction Act of 1995

This proposed rule has no information collection requirements.

List of Subjects in 42 CFR Part 100

Biologics, Health insurance, Immunization.

Dated: June 24, 2015.

James Macrae,

Acting Administrator, Health Resources and Services Administration.

Approved: July 10, 2015.

Sylvia M. Burwell,
Secretary.

Accordingly, 42 CFR part 100 is proposed to be amended as set forth below:

PART 100—VACCINE INJURY COMPENSATION

■ 1. The authority citation for 42 CFR part 100 continues to read as follows:

Authority: Secs. 312 and 313 of Public Law 99–660 (42 U.S.C. 300aa–1 note); 42 U.S.C. 300aa–10 to 300aa–34; 26 U.S.C. 4132(a); and sec. 13632(a)(3) of Public Law 103–66.

■ 2. Revise § 100.3 to read as follows:

§ 100.3 Vaccine injury table.

(a) In accordance with section 312(b) of the National Childhood Vaccine Injury Act of 1986, title III of Public Law 99–660, 100 Stat. 3779 (42 U.S.C. 300aa–1 note) and section 2114(c) of the Public Health Service Act, as amended (PHS Act) (42 U.S.C. 300aa–14(c)), the following is a table of vaccines, the injuries, disabilities, illnesses, conditions, and deaths resulting from the administration of such vaccines, and the time period in which the first

symptom or manifestation of onset or of the significant aggravation of such injuries, disabilities, illnesses, conditions, and deaths is to occur after vaccine administration for purposes of receiving compensation under the Program. Paragraph (b) of this section

sets forth additional provisions that are not separately listed in this Table but that constitute part of it. Paragraph (c) of this section sets forth the Qualifications and Aids to Interpretation for the terms used in the Table. Conditions and injuries that do

not meet the terms of the Qualifications and Aids to Interpretation are not within the Table. Paragraph (d) of this section sets forth a glossary of terms used in paragraph (c).

VACCINE INJURY TABLE

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
I. Vaccines containing tetanus toxoid (e.g., DTaP, DTP, DT, Td, or TT)	A. Anaphylaxis	≤4 hours.
	B. Brachial Neuritis	2–28 days (not less than 2 days and not more than 28 days)
	C. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
II. Vaccines containing whole cell pertussis bacteria, extracted or partial cell pertussis bacteria, or specific pertussis antigen(s) (e.g., DTP, DTaP, P, DTP-Hib).	A. Anaphylaxis	≤4 hours.
	B. Encephalopathy or encephalitis	≤72 hours
	C. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
III. Vaccines containing measles, mumps, and rubella virus or any of its components (e.g., MMR, MM, MMRV).	A. Anaphylaxis	≤4 hours.
	B. Encephalopathy or encephalitis	5–15 days (not less than 5 days and not more than 15 days)
	C. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	D. Vasovagal syncope	≤1 hour.
IV. Vaccines containing rubella virus (e.g., MMR, MMRV)	A. Chronic arthritis	7–42 days (not less than 7 days and not more than 42 days).
V. Vaccines containing measles virus (e.g., MMR, MM, MMRV)	A. Thrombocytopenic purpura	7–30 days (not less than 7 days and not more than 30 days).
	B. Vaccine-Strain Measles Viral Disease in an immunodeficient recipient.	Not applicable.
	—Vaccine-strain virus identified	≤12 months.
	—If strain determination is not done or if laboratory testing is inconclusive.	
VI. Vaccines containing polio live virus (OPV)	A. Paralytic Polio	≤30 days.
	—in a non-immunodeficient recipient.	≤6 months.
	—in an immunodeficient recipient	Not applicable.
	—in a vaccine associated community case.	
	B. Vaccine-Strain Polio Viral Infection.	≤30 days.
	—in a non-immunodeficient recipient.	≤6 months.
	—in an immunodeficient recipient	Not applicable.
	—in a vaccine associated community case.	
VII. Vaccines containing polio inactivated virus (e.g., IPV)	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
VIII. Hepatitis B vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	C. Vasovagal syncope	≤1 hour.
IX. Haemophilus influenzae type b (Hib) vaccines	A. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	B. Vasovagal syncope	≤1 hour.
X. Varicella vaccines	A. Anaphylaxis	≤4 hours.
	B. Disseminated varicella vaccine-strain viral disease.	Not applicable.
	—Vaccine-strain virus identified	7–42 days (not less than 7 days and not more than 42 days).
	—If strain determination is not done or if laboratory testing is inconclusive.	
	C. Varicella vaccine-strain viral reactivation.	Not applicable.
	D. Shoulder Injury Related to Vaccine Administration.	≤48 hours.
	E. Vasovagal syncope	≤1 hour.

VACCINE INJURY TABLE—Continued

Vaccine	Illness, disability, injury or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
XI. Rotavirus vaccines	A. Intussusception	1–21 days (not less than 1 day and not more than 21 days).
XII. Pneumococcal conjugate vaccines	A. Shoulder Injury Related to Vaccine Administration. B. Vasovagal syncope	≤48 hours. ≤1 hour.
XIII. Hepatitis A vaccines	A. Shoulder Injury Related to Vaccine Administration. B. Vasovagal syncope	≤48 hours. ≤1 hour.
XIV. Seasonal influenza vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration. C. Vasovagal syncope	≤48 hours. ≤1 hour.
XV. Meningococcal vaccines	D. Guillain-Barré Syndrome	3–42 days (not less than 3 days and not more than 42 days).
	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration. C. Vasovagal syncope	≤48 hours. ≤1 hour.
XVI. Human papillomavirus (HPV) vaccines	A. Anaphylaxis	≤4 hours.
	B. Shoulder Injury Related to Vaccine Administration. C. Vasovagal syncope	≤48 hours. ≤1 hour.
XVII. Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by the Secretary of a notice of coverage.	A. Shoulder Injury Related to Vaccine Administration. B. Vasovagal syncope	≤48 hours. ≤1 hour.

(b) *Provisions that apply to all conditions listed.* (1) Any acute complication or sequela, including death, of the illness, disability, injury, or condition listed in paragraph (a) of this section (and defined in paragraphs (c) and (d) of this section) qualifies as a Table injury under paragraph (a) except when the definition in paragraph (c) requires exclusion.

(2) In determining whether or not an injury is a condition set forth in paragraph (a) of this section, the Court shall consider the entire medical record.

(3) An idiopathic condition that meets the definition of an illness, disability, injury, or condition set forth in paragraph (c) of this section shall be considered to be a condition set forth in paragraph (a) of this section.

(c) *Qualifications and aids to interpretation.* The following qualifications and aids to interpretation shall apply to, define and describe the scope of, and be read in conjunction with paragraphs (a), (b), and (d) of this section:

(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 sequela. 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) *Encephalopathy.* A vaccine recipient shall be considered to have suffered an encephalopathy if an injury meeting the description below of an acute encephalopathy occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.

(i) *Acute encephalopathy.* (A) For children less than 18 months of age who present:

(1) Without a seizure, an acute encephalopathy is indicated by a significantly decreased level of consciousness that lasts at least 24 hours,

(2) Following a seizure, an acute encephalopathy is demonstrated by a significantly decreased level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state—from a seizure or a medication.

(B) For adults and children 18 months of age or older, an acute encephalopathy is one that persists at least 24 hours and

is characterized by at least two of the following:

(1) A significant change in mental status that is not medication related (such as a confusional state, delirium, or psychosis);

(2) A significantly decreased level of consciousness which is independent of a seizure and cannot be attributed to the effects of medication; and

(3) A seizure associated with loss of consciousness.

(C) The following clinical features in themselves do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness: sleepiness, irritability (fussiness), high-pitched and unusual screaming, poor feeding, persistent inconsolable crying, bulging fontanelle, or symptoms of dementia.

(D) Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy and in the absence of other evidence of an acute encephalopathy seizures shall not be viewed as the first symptom or manifestation of an acute encephalopathy.

(ii) Regardless of whether or not the specific cause of the underlying condition, systemic disease, or acute event (including an infectious organism) is known, an encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by:

(A) An underlying condition or systemic disease shown to be unrelated to the vaccine (such as malignancy, structural lesion, psychiatric illness, dementia, genetic disorder, prenatal or perinatal central nervous system (CNS) injury); or

(B) An acute event shown to be unrelated to the vaccine such as a head trauma, stroke, transient ischemic attack, complicated migraine, drug use (illicit or prescribed) or an infectious disease.

(3) *Encephalitis*. A vaccine recipient shall be considered to have suffered encephalitis if an injury meeting the description below of an acute encephalitis occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.

(i) *Acute encephalitis*. Encephalitis is indicated by evidence of neurologic dysfunction, as described in paragraph (c)(3)(i)(A) of this section, plus evidence of an inflammatory process in the brain, as described in paragraph (c)(3)(i)(B) of this section.

(A) Evidence of neurologic dysfunction consists of either:

(1) One of the following neurologic findings referable to the CNS: Focal cortical signs (such as aphasia, alexia, agraphia, cortical blindness); cranial nerve abnormalities; visual field defects; abnormal presence of primitive reflexes (such as Babinski's sign or sucking reflex); or cerebellar dysfunction (such as ataxia, dysmetria, or nystagmus); or

(2) An acute encephalopathy as set forth in paragraph (c)(2)(i) of this section.

(B) Evidence of an inflammatory process in the brain (central nervous system or CNS inflammation) must include cerebrospinal fluid (CSF) pleocytosis (≤ 5 white blood cells (WBC)/mm³ in children >2 months of age and adults; >15 WBC/mm³ in children <2 months of age); or at least two of the following:

(1) Fever (temperature ≥ 100.4 degrees Fahrenheit);

(2) Electroencephalogram findings consistent with encephalitis, such as diffuse or multifocal nonspecific background slowing and periodic discharges; or

(3) Neuroimaging findings consistent with encephalitis, which include, but are not limited to brain/spine magnetic resonance imaging (MRI) displaying diffuse or multifocal areas of hyperintense signal on T2-weighted, diffusion-weighted image, or fluid-attenuation inversion recovery sequences.

(ii) Regardless of whether or not the specific cause of the underlying

condition, systemic disease, or acute event (including an infectious organism) is known, encephalitis shall not be considered to be a condition set forth in the Table if it is shown that the encephalitis was caused by:

(A) An underlying malignancy that led to a paraneoplastic encephalitis;

(B) An infectious disease associated with encephalitis, including a bacterial, parasitic, fungal or viral illness (such as herpes viruses, adenovirus, enterovirus, West Nile Virus, or human immunodeficiency virus), which may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing; or

(C) *Acute disseminated encephalomyelitis (ADEM)*. Although early ADEM may have laboratory and clinical characteristics similar to acute encephalitis, findings on MRI are distinct with ADEM displaying evidence of acute demyelination (scattered, focal, or multifocal areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; gray matter involvement may also be seen but is a minor component); or other conditions or abnormalities that would explain the vaccine recipient's symptoms.

(4) *Intussusception*. (i) For purposes of paragraph (a) of this section, intussusception means the invagination of a segment of intestine into the next segment of intestine, resulting in bowel obstruction, diminished arterial blood supply, and blockage of the venous blood flow. This is characterized by a sudden onset of abdominal pain that may be manifested by anguished crying, irritability, vomiting, abdominal swelling, and/or passing of stools mixed with blood and mucus.

(ii) For purposes of paragraph (a) of this section, the following shall not be considered to be a Table intussusception:

(A) Onset that occurs with or after the third dose of a vaccine containing rotavirus;

(B) Onset within 14 days after an infectious disease associated with intussusception, including viral disease (such as those secondary to non-enteric or enteric adenovirus, or other enteric viruses such as Enterovirus), enteric bacteria (such as *Campylobacter jejuni*), or enteric parasites (such as *Ascaris lumbricoides*), which may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing;

(C) Onset in a person with a preexisting condition identified as the lead point for intussusception such as intestinal masses and cystic structures (such as polyps, tumors, Meckel's

diverticulum, lymphoma, or duplication cysts);

(D) Onset in a person with abnormalities of the bowel, including congenital anatomic abnormalities, anatomic changes after abdominal surgery, and other anatomic bowel abnormalities caused by mucosal hemorrhage, trauma, or abnormal intestinal blood vessels (such as Henoch Schlein purpura, hematoma, or hemangioma); or

(E) Onset in a person with underlying conditions or systemic diseases associated with intussusception (such as cystic fibrosis, celiac disease, or Kawasaki disease).

(5) *Chronic arthritis*. Chronic arthritis is defined as persistent joint swelling with at least two additional manifestations of warmth, tenderness, pain with movement, or limited range of motion, lasting for at least 6 months.

(i) Chronic arthritis may be found in a person with no history in the 3 years prior to vaccination of arthropathy (joint disease) on the basis of:

(A) Medical documentation recorded within 30 days after the onset of objective signs of acute arthritis (joint swelling) that occurred between 7 and 42 days after a rubella vaccination; and

(B) Medical documentation (recorded within 3 years after the onset of acute arthritis) of the persistence of objective signs of intermittent or continuous arthritis for more than 6 months following vaccination; and

(C) Medical documentation of an antibody response to the rubella virus.

(ii) The following shall not be considered as chronic arthritis: Musculoskeletal disorders such as diffuse connective tissue diseases (including but not limited to rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, polymyositis/dermatomyositis, fibromyalgia, necrotizing vasculitis and vasculopathies and Sjogren's Syndrome), degenerative joint disease, infectious agents other than rubella (whether by direct invasion or as an immune reaction), metabolic and endocrine diseases, trauma, neoplasms, neuropathic disorders, bone and cartilage disorders, and arthritis associated with ankylosing spondylitis, psoriasis, inflammatory bowel disease, Reiter's Syndrome, blood disorders, or arthralgia (joint pain), or joint stiffness without swelling.

(6) *Brachial neuritis*. This term is defined as dysfunction limited to the upper extremity nerve plexus (*i.e.*, its trunks, divisions, or cords). A deep, steady, often severe aching pain in the

shoulder and upper arm usually heralds onset of the condition. The pain is typically followed in days or weeks by weakness in the affected upper extremity muscle groups. Sensory loss may accompany the motor deficits, but is generally a less notable clinical feature. Atrophy of the affected muscles may occur. The neuritis, or plexopathy, may be present on the same side or on the side opposite the injection. It is sometimes bilateral, affecting both upper extremities. A vaccine recipient shall be considered to have suffered brachial neuritis as a Table injury if such recipient manifests all of the following:

(i) Pain in the affected arm and shoulder is a presenting symptom and occurs within the specified time-frame;

(ii) Weakness:

(A) Clinical diagnosis in the absence of nerve conduction and electromyographic studies requires weakness in muscles supplied by more than one peripheral nerve.

(B) Nerve conduction studies (NCS) and electromyographic (EMG) studies localizing the injury to the brachial plexus are required before the diagnosis can be made if weakness is limited to muscles supplied by a single peripheral nerve.

(iii) Motor, sensory, and reflex findings on physical examination and the results of NCS and EMG studies, if performed, must be consistent in confirming that dysfunction is attributable to the brachial plexus; and

(iv) No other condition or abnormality is present that would explain the vaccine recipient's symptoms.

(7) *Thrombocytopenic purpura*. This term is defined by the presence of clinical manifestations, such as petechiae, significant bruising, or spontaneous bleeding, and by a serum platelet count less than 50,000/mm³ with normal red and white blood cell indices. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with other causes such as hypersplenism, autoimmune disorders (including alloantibodies from previous transfusions) myelodysplasias, lymphoproliferative disorders, congenital thrombocytopenia or hemolytic uremic syndrome. Thrombocytopenic purpura does not include cases of immune (formerly called idiopathic) thrombocytopenic purpura that are mediated, for example, by viral or fungal infections, toxins or drugs. Thrombocytopenic purpura does not include cases of thrombocytopenia associated with disseminated intravascular coagulation, as observed with bacterial and viral infections. Viral

infections include, for example, those infections secondary to Epstein Barr virus, cytomegalovirus, hepatitis A and B, human immunodeficiency virus, adenovirus, and dengue virus. An antecedent viral infection may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing. However, if culture or serologic testing is performed, and the viral illness is attributed to the vaccine-strain measles virus, the presumption of causation will remain in effect. Bone marrow examination, if performed, must reveal a normal or an increased number of megakaryocytes in an otherwise normal marrow.

(8) *Vaccine-strain measles viral disease*. This term is defined as a measles illness that involves the skin and/or another organ (such as the brain or lungs). Measles virus must be isolated from the affected organ or histopathologic findings characteristic for the disease must be present. Measles viral strain determination may be performed by methods such as polymerase chain reaction test and vaccine-specific monoclonal antibody. If strain determination reveals wild-type measles virus or another, non-vaccine-strain virus, the disease shall not be considered to be a condition set forth in the Table. If strain determination is not done or if the strain cannot be identified, onset of illness in any organ must occur within 12 months after vaccination.

(9) *Vaccine-strain polio viral infection*. This term is defined as a disease caused by poliovirus that is isolated from the affected tissue and should be determined to be the vaccine-strain by oligonucleotide or polymerase chain reaction. Isolation of poliovirus from the stool is not sufficient to establish a tissue specific infection or disease caused by vaccine-strain poliovirus.

(10) *Shoulder injury related to vaccine administration (SIRVA)*. SIRVA manifests as shoulder pain and limited range of motion occurring after the administration of a vaccine intended for intramuscular administration in the upper arm. These symptoms are thought to occur as a result of unintended injection of vaccine antigen or trauma from the needle into and around the underlying bursa of the shoulder resulting in an inflammatory reaction. SIRVA is caused by an injury to the musculoskeletal structures of the shoulder (e.g. tendons, ligaments, bursae, etc.). SIRVA is not a neurological injury and abnormalities on neurological examination or nerve conduction studies (NCS) and/or

electromyographic (EMG) studies would not support SIRVA as a diagnosis (even if the condition causing the neurological abnormality is not known). A vaccine recipient shall be considered to have suffered SIRVA if such recipient manifests all of the following:

(i) No history of pain, inflammation or dysfunction of the affected shoulder prior to intramuscular vaccine administration that would explain the alleged signs, symptoms, examination findings, and/or diagnostic studies occurring after vaccine injection;

(ii) Pain occurs within the specified time-frame;

(iii) Pain and reduced range of motion are limited to the shoulder in which the intramuscular vaccine was administered; and

(iv) No other condition or abnormality is present that would explain the patient's symptoms (e.g. NCS/EMG or clinical evidence of radiculopathy, brachial neuritis, mononeuropathies, or any other neuropathy).

(11) *Disseminated varicella vaccine-strain viral disease*. Disseminated varicella vaccine-strain viral disease is defined as a varicella illness that involves the skin beyond the dermatome in which the vaccination was given and/or disease caused by vaccine-strain varicella in another organ. For organs other than the skin, disease, not just mildly abnormal laboratory values, must be demonstrated in the involved organ. If there is involvement of an organ beyond the skin, and no virus was identified in that organ, the involvement of all organs must occur as part of the same, discrete illness. If strain determination reveals wild-type varicella virus or another, non-vaccine-strain virus, the viral disease shall not be considered to be a condition set forth in the Table. If strain determination is not done or if the strain cannot be identified, onset of illness in any organ must occur 7–42 days after vaccination.

(12) *Varicella vaccine-strain viral reactivation disease*. Varicella vaccine-strain viral reactivation disease is defined as the presence of the rash of herpes zoster with or without concurrent disease in an organ other than the skin. Zoster, or shingles, is a painful, unilateral, pruritic rash appearing in one or more sensory dermatomes. For organs other than the skin, disease, not just mildly abnormal laboratory values, must be demonstrated in the involved organ. There must be laboratory confirmation that the vaccine-strain of the varicella virus is present in the skin or in any other involved organ, for example by oligonucleotide or polymerase chain reaction. If strain determination reveals

wild-type varicella virus or another, non-vaccine-strain virus, the viral disease shall not be considered to be a condition set forth in the Table.

(13) *Vasovagal syncope*. Vasovagal syncope (also sometimes called neurocardiogenic syncope) means loss of consciousness (fainting) and postural tone caused by a transient decrease in blood flow to the brain occurring after the administration of an injected vaccine. Vasovagal syncope is usually a benign condition but may result in falling and injury with significant sequela. 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 with vasovagal syncope. 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, and seizures. Episodes of recurrent syncope occurring after the applicable time period are not considered to be sequela of an episode of syncope meeting the Table requirements.

(14) *Immunodeficient recipient*. Immunodeficient recipient is defined as an individual with an identified defect in the immunological system which impairs the body's ability to fight infections. The identified defect may be due to an inherited disorder (such as severe combined immunodeficiency resulting in absent T lymphocytes), or an acquired disorder (such as acquired immunodeficiency syndrome resulting from decreased CD4 cell counts). The identified defect must be demonstrated in the medical records, either preceding or postdating vaccination.

(15) *Guillain-Barré 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:

(A) Bilateral flaccid limb weakness and decreased or absent deep tendon reflexes in weak limbs;

(B) A monophasic illness pattern;

(C) An interval between onset and nadir of weakness between 12 hours and 28 days;

(D) Subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse; however, death may occur without a clinical plateau); and,

(E) The absence of an identified more likely alternative diagnosis.

(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:

(A) Bilateral ophthalmoparesis;

(B) Bilateral reduced or absent tendon reflexes;

(C) Ataxia;

(D) The absence of limb weakness (the presence of limb weakness suggests a diagnosis of AIDP, AMAN, or AMSAN);

(E) A monophasic illness pattern;

(F) An interval between onset and nadir of weakness between 12 hours and 28 days;

(G) Subsequent clinical plateau (the clinical plateau leads to either stabilization at the nadir of symptoms, or subsequent improvement without significant relapse; however, death may occur without a clinical plateau);

(H) No alteration in consciousness;

(I) No corticospinal track signs; and

(J) The absence of an identified more likely alternative diagnosis.

(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) To qualify as any subtype of GBS, there must not be a more likely alternative diagnosis for the weakness.

(vi) 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.

(d) *Glossary for purposes of paragraph (c) of this section*—(1) *Chronic encephalopathy*—(i) A chronic encephalopathy occurs when a change in mental or neurologic status, first manifested during the applicable Table time period as an acute encephalopathy or encephalitis, persists for at least 6 months from the first symptom or manifestation of onset or of significant aggravation of an acute encephalopathy or encephalitis.

(ii) Individuals who return to their baseline neurologic state, as confirmed by clinical findings, within less than 6 months from the first symptom or manifestation of onset or of significant aggravation of an acute encephalopathy or encephalitis shall not be presumed to have suffered residual neurologic damage from that event; any subsequent chronic encephalopathy shall not be presumed to be a sequela of the acute encephalopathy or encephalitis.

(2) *Injected* refers to the intramuscular, intradermal, or

subcutaneous needle administration of a vaccine.

(3) *Sequela* means a condition or event which was actually caused by a condition listed in the Vaccine Injury Table.

(4) *Significantly decreased level of consciousness* is indicated by the presence of one or more of the following clinical signs:

(i) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);

(ii) Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or

(iii) Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

(5) *Seizure* includes myoclonic, generalized tonic-clonic (grand mal), and simple and complex partial seizures, but not absence (petit mal), or pseudo seizures. Jerking movements or staring episodes alone are not necessarily an indication of seizure activity.

(e) *Coverage provisions.* (1) Except as provided in paragraph (e)(2), (3), (4), (5), (6), (7), or (8) of this section, this section applies to petitions for compensation under the Program filed with the United States Court of Federal Claims on or after [EFFECTIVE DATE OF THE FINAL REGULATION.]

(2) Hepatitis B, Hib, and varicella vaccines (Items VIII, IX, and X of the Table) are included in the Table as of August 6, 1997.

(3) Rotavirus vaccines (Item XI of the Table) are included in the Table as of October 22, 1998.

(4) Pneumococcal conjugate vaccines (Item XII of the Table) are included in the Table as of December 18, 1999.

(5) Hepatitis A vaccines (Item XIII of the Table) are included on the Table as of December 1, 2004.

(6) Trivalent influenza vaccines (Included in item XIV of the Table) are included on the Table as of July 1, 2005. All other seasonal influenza vaccines (Item XIV of the Table) are included on the Table as of November 12, 2013.

(7) Meningococcal vaccines and human papillomavirus vaccines (Items XV and XVI of the Table) are included on the Table as of February 1, 2007.

(8) Other new vaccines (Item XVII of the Table) will be included in the Table as of the effective date of a tax enacted to provide funds for compensation paid with respect to such vaccines. An amendment to this section will be published in the **Federal Register** to announce the effective date of such a tax.

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DEPARTMENT OF THE INTERIOR

Fish and Wildlife Service

50 CFR Part 17

[Docket No. FWS-HQ-IA-2013-0091; 96300-1671-0000-R4]

RIN 1018-AX84

Endangered and Threatened Wildlife and Plants; Revision of the Section 4(d) Rule for the African Elephant (*Loxodonta africana*)

AGENCY: Fish and Wildlife Service, Interior.

ACTION: Proposed rule.

SUMMARY: We, the U.S. Fish and Wildlife Service (Service), are proposing to revise the rule for the African elephant promulgated under section 4(d) of the Endangered Species Act of 1973, as amended (ESA), to increase protection for African elephants in response to the alarming rise in poaching of the species to fuel the growing illegal trade in ivory. The African elephant was listed as threatened under the ESA effective June 11, 1978, and at the same time a rule issued under section 4(d) of the ESA (a “4(d) rule”) was promulgated to regulate import and use of specimens of the species in the United States. This proposed rule would update the current 4(d) rule with measures that are appropriate for the current conservation needs of the species. We are proposing measures that are necessary and advisable to provide for the conservation of the African elephant as well as appropriate prohibitions from section 9(a)(1) of the ESA. Among other things, we propose to incorporate into the 4(d) rule certain restrictions on the import and export of African elephant ivory contained in the African Elephant Conservation Act (AfECA) as measures necessary and advisable for the conservation of the African elephant. We are not, however, revising or reconsidering actions taken under the AfECA, including our determinations in 1988 and 1989 to impose moratoria on the import of ivory other than sport-hunted trophies from both range and intermediary countries. We are proposing to take these actions under section 4(d) of the ESA to increase protection and benefit the conservation of African elephants, without unnecessarily restricting activities that have no conservation effect or are strictly regulated under other law.

DATES: In preparing the final decision on this proposed rule, we will consider

comments received or postmarked on or before September 28, 2015.

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

- *Electronically:* Go to the Federal eRulemaking Portal: <http://www.regulations.gov>. In the Search box, enter FWS-HQ-IA-2013-0091, which is the docket number for this rulemaking. You may submit a comment by clicking on “Comment Now!”

- *By hard copy:* Submit by U.S. mail or hand-delivery to: Public Comments Processing, Attn: FWS-HQ-IA-2013-0091; Division of Policy, Performance, and Management Programs; U.S. Fish and Wildlife Service; 5275 Leesburg Pike, MS: BPHC; Falls Church, VA 22041.

We will not accept email or faxes. We will post all comments on <http://www.regulations.gov>. This generally means that we will post any personal information you provide us (see the Public Comments section at the end of **SUPPLEMENTARY INFORMATION** for further information about submitting comments).

FOR FURTHER INFORMATION CONTACT: Craig Hoover, Chief, Wildlife Trade and Conservation Branch, Division of Management Authority; U.S. Fish and Wildlife Service; 5275 Leesburg Pike, MS: IA; Falls Church, VA 22041 (telephone, (703) 358-2093).

SUPPLEMENTARY INFORMATION:

Applicable Laws

In the United States, the African elephant is primarily protected and managed under the Endangered Species Act (ESA) (16 U.S.C. 1531 *et seq.*); the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES or Convention) (27 U.S.T. 1087), as implemented in the United States through the ESA; and the African Elephant Conservation Act (AfECA) (16 U.S.C. 4201 *et seq.*).

Endangered Species Act

Under the ESA, species may be listed either as “threatened” or as “endangered.” When a species is listed as endangered under the ESA, certain actions are prohibited under section 9 (16 U.S.C. 1538), as specified at 50 CFR 17.21. These include prohibitions on take within the United States, within the territorial seas of the United States, or upon the high seas; import; export; sale and offer for sale in interstate or foreign commerce; and delivery, receipt, carrying, transport, or shipment in interstate or foreign commerce in the course of a commercial activity.

The ESA does not specify particular prohibitions and exceptions to those