

401, 403, 404, 407, 414, 416, 3001–3011, 3201–3219, 3403–3406, 3621, 3622, 3626, 3632, 3633, and 5001.

■ 2. Revise the following sections of *Mailing Standards of the United States Postal Service*, International Mail Manual (IMM), as follows: New prices will be listed in the updated Notice 123, *Price List*.

**Joshua J. Hofer,**

*Attorney, Federal Compliance.*

[FR Doc. 2020–22886 Filed 10–13–20; 8:45 am]

BILLING CODE 7710–12–P

## POSTAL SERVICE

### 39 CFR Part 111

#### New Mailing Standards for Domestic Mailing Services Products

**AGENCY:** Postal Service™.

**ACTION:** Proposed rule.

**SUMMARY:** On October 9, 2020, the Postal Service (USPS®) filed a notice of mailing services price adjustments with the Postal Regulatory Commission (PRC), effective January 24, 2021. This proposed rule contains the revisions to *Mailing Standards of the United States Postal Service*, Domestic Mail Manual (DMM®) that we would adopt to implement the changes coincident with the price adjustments.

**DATES:** Submit comments on or before November 16, 2020.

**ADDRESSES:** Mail or deliver written comments to the Manager, Product Classification, U.S. Postal Service, 475 L'Enfant Plaza SW, Room 4446, Washington, DC 20260–5015. If sending comments by email, include the name and address of the commenter and send to [PCFederalRegister@usps.gov](mailto:PCFederalRegister@usps.gov), with a subject line of “January 2021 Domestic Mailing Services Proposal.” Faxed comments are not accepted.

All submitted comments and attachments are part of the public record and subject to disclosure. Do not enclose any material in your comments that you consider to be confidential or inappropriate for public disclosure.

You may inspect and photocopy all written comments, by appointment only, at USPS® Headquarters Library, 475 L'Enfant Plaza SW, 11th Floor North, Washington, DC 20260. These records are available for review on Monday through Friday, 9 a.m.–4 p.m., by calling 202–268–2906.

**FOR FURTHER INFORMATION CONTACT:** Jacqueline Erwin at (202) 268–2158, or Dale Kennedy at (202) 268–6592.

**SUPPLEMENTARY INFORMATION:** Proposed prices will be available under Docket

No. R2021–1 on the Postal Regulatory Commission's website at [www.prc.gov](http://www.prc.gov).

The Postal Service's proposed rule includes: Changes to prices, mail classification updates, and product simplification efforts.

#### Seamless Acceptance Incentive

Currently, mailers who present qualifying full-service mailings receive an incentive discount of \$.003 per piece for USPS Marketing Mail and First-Class Mail and \$.001 for Bound Printed Matter flats and Periodicals.

The Postal Service is proposing an incentive discount for mailers who mail through the Seamless Acceptance program, in addition to the full-service incentive discount.

Beginning on the day of their first mailing, following onboarding to the program the mailer or mail service provider, as applicable, will receive an incentive discount in addition to the full-service incentive discount. The mailer would be allowed to combine the Seamless and full-service incentive discounts. The Seamless incentive discount would be based on a mailer's customer registration ID (CRID). A Seamless mailer is defined by their status in *PostalOne!*. Moving to Seamless is defined as the status changing from “None” or “Seamless Parallel” to “Seamless Acceptance”.

The proposal would leave the full-service discount exactly as it is now and provide a \$.001 per piece incentive discount for Seamless. The maximum incentive discount per piece is \$.004 for USPS Marketing Mail and First-Class Mail and \$.002 for Bound Printed Matter flats and Periodicals.

Although exempt from the notice and comment requirements of the Administrative Procedure Act (5 U.S.C. 553(b), (c)) regarding proposed rulemaking by 39 U.S.C. 410(a), the Postal Service invites public comments on the following proposed revisions to *Mailing Standards of the United States Postal Service*, Domestic Mail Manual (DMM), incorporated by reference in the Code of Federal Regulations. See 39 CFR 111.1.

We will publish an appropriate amendment to 39 CFR part 111 to reflect these changes if our proposal is adopted.

#### List of Subjects in 39 CFR Part 111

Administrative practice and procedure, Postal Service.

Accordingly, 39 CFR part 111 is proposed to be amended as follows:

#### PART 111—[AMENDED]

■ 1. The authority citation for 39 CFR part 111 continues to read as follows:

**Authority:** 5 U.S.C. 552(a); 13 U.S.C. 301–307; 18 U.S.C. 1692–1737; 39 U.S.C. 101, 401, 403, 404, 414, 416, 3001–3011, 3201–3219, 3403–3406, 3621, 3622, 3626, 3632, 3633, and 5001.

■ 2. Revise the following sections of *Mailing Standards of the United States Postal Service*, Domestic Mail Manual (DMM), as follows:

#### Mailing Standards of the United States Postal Service, Domestic Mail Manual (DMM)

\* \* \* \* \*

#### Notice 123 (Price List)

[Revise prices as applicable.]

\* \* \* \* \*

We will publish an appropriate amendment to 39 CFR part 111 to reflect these changes.

**Joshua J. Hofer,**

*Attorney, Federal Compliance.*

[FR Doc. 2020–22887 Filed 10–13–20; 8:45 am]

BILLING CODE P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### 42 CFR Part 110

[Docket No. 2020–0003]

RIN 0906–AB22

#### Countermeasures Injury Compensation Program: Smallpox Countermeasures Injury Table

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

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Department of Health and Human Services (HHS) proposes adding a Smallpox Countermeasures Injury Table (Table) for designated covered smallpox countermeasures identified in a declaration. The proposed Smallpox Countermeasures Injury Table includes a list of smallpox countermeasures, proposed time intervals for the first symptom or manifestation of onset of injury, and Qualifications and Aids to Interpretation, which set forth the definitions and requirements necessary to establish the Table injuries.

**DATES:** Written comments and related material to this proposed rule must be received to the online docket via [www.regulations.gov](http://www.regulations.gov), or to the mail address listed in the **ADDRESSES** section below, on or before December 14, 2020.

**ADDRESSES:** You may submit comments on this proposed rule identified by HHS Docket No. HRSA–2020–0003, by any one of the following methods:

1. *Federal eRulemaking Portal (preferred):* [www.regulations.gov](http://www.regulations.gov).

Follow the website instructions for submitting comments.

2. *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, 5600 Fishers Lane, Room 13N82, Rockville, MD 20857. Mail must be postmarked by the comment submission deadline.

Because of staffing and resource limitations, and to ensure that no comments are misplaced, the Program cannot accept comments by facsimile (FAX) transmission. When commenting by any of the above methods, please refer to file code: #0906-AB22.

**FOR FURTHER INFORMATION CONTACT:**

Please visit the Countermeasures Injury Compensation Program's website, <http://www.hrsa.gov/cicp/>, or contact Tamara Overby, Acting Director, Division of Injury Compensation Programs, Healthcare Systems Bureau, HRSA, 5600 Fishers Lane, Room 08N146B, Rockville, MD 20857. Phone calls can be directed to (855) 266-2427. This is a toll-free number.

**SUPPLEMENTARY INFORMATION:**

**I. Public Participation**

HHS urges all interested parties to examine this regulatory proposal carefully and share your views, including data, to support your positions. We must consider all written comments received during the comment period before issuing a final rule. Subject to consideration of the comments received, the Secretary of Health and Human Services (the Secretary) intends to publish a final regulation.

If you are a person with a disability and/or a user of assistive technology who has difficulty accessing this document, please see the website: <https://www.hrsa.gov/about/508-resources.html> to obtain this information in an accessible format. Please visit <http://www.HHS.gov/regulations> for more information on HHS rulemaking and opportunities to comment on proposed and existing rules.

**II. Background and Purpose**

The Public Readiness and Emergency Preparedness Act (PREP Act) of 2005, enacted as Division C of the Department of Defense, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006 (Public Law 109-148), directs the Secretary to establish, through regulation, a Covered Countermeasures Injury Table (Table)

identifying serious physical injuries presumed to be directly caused by the administration or use of covered countermeasures identified in PREP Act declarations issued by the Secretary. The Secretary may only add injuries to a Table if it is determined based on "compelling, reliable, valid, medical and scientific evidence" that the administration or use of the covered countermeasure directly causes such covered injuries.<sup>1</sup> Such a Table informs the public about serious physical injuries supported by medical and scientific evidence known to be directly caused by covered countermeasures.

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

This notice of proposed rulemaking (NPRM) concerns only the compensation program authorized by the PREP Act, not the liability protections set forth therein. Specifically, the PREP Act authorizes the Secretary to establish and administer the Countermeasures Injury Compensation Program (CICP or the Program) to provide timely, uniform, and adequate compensation to certain individuals who develop serious physical injuries or to certain survivors of individuals who die as a direct result of the use or administration of a covered countermeasure identified in a declaration.<sup>3</sup> The Secretary delegated responsibility for establishing and administering the Program to HRSA.

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

injury or death, an individual must submit a timely Request for Benefits with the required information.

The Secretary published the interim final rule implementing the Program on October 15, 2010.<sup>4</sup> The final rule, published on October 7, 2011, explains the Program's policies, procedures, and requirements. Title 42 of the Code of Federal Regulations (CFR) § 110.20(a) states that individuals must establish that a covered injury occurred to be eligible for benefits under the Program. A covered injury is a death or a serious injury determined to have occurred as a direct result of the administration or use of a covered countermeasure. The Secretary has determined that the list includes: (1) An injury meeting the requirements of covered countermeasures placed on an injury table, unless the Secretary determines there is another more likely cause; or (2) an injury (or health complications) that is the direct result of the administration or use of a covered countermeasure. This includes serious aggravation of a pre-existing condition caused by a covered countermeasure.<sup>5</sup>

Serious injury means serious physical injury. Serious injuries may, in certain circumstances, be considered physical or biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function. As a general matter, only injuries that warranted hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability (whether or not hospitalization was warranted) will be considered serious injuries.<sup>6</sup>

The Secretary proposes adding a Smallpox Countermeasures Injury Table to subpart K of 42 CFR part 110 for designated covered smallpox countermeasures identified in declarations. The proposed Smallpox Countermeasures Injury Table includes a list of smallpox countermeasures, proposed time intervals for the first symptom or manifestation of onset of injury, and Qualifications and Aids to Interpretation, which set forth the definitions and requirements necessary to establish the Table injuries.

The Table proposed in this NPRM is limited to covered smallpox countermeasures. To date, the CICP published a Pandemic Influenza Countermeasures Injury Table.<sup>7</sup> Since the PREP Act mandates the

<sup>1</sup> Section 319F-4(b)(5)(A) of the Public Health Service Act, as amended (42 U.S.C. 247d-6e(b)(5)(A)).

<sup>2</sup> Section 319F-3(b) of the PHS Act (42 U.S.C. 247d-6d(b)).

<sup>3</sup> Section 319F-4(a) of the PHS Act (42 U.S.C. 247d-6e(a)).

<sup>4</sup> 75 FR 63656-63688; 42 CFR part 110.

<sup>5</sup> 42 CFR 110.3(g).

<sup>6</sup> 42 CFR 110.3(z).

<sup>7</sup> 80 FR 47411, August 7, 2015.

establishment of a Table identifying covered injuries that may be presumed to be directly caused by the administration or use of a covered countermeasure, the CICP may establish future Tables for other countermeasures relating to threats to health that pose or constitute potential public health emergencies. The PREP Act authorized the Secretary to create Tables for each covered countermeasure identified in a declaration if there is compelling, reliable, valid, medical and scientific evidence that the countermeasure directly causes a covered injury. Declarations have been issued with respect to countermeasures against pandemic influenza A viruses, anthrax, botulism, smallpox, acute radiation syndrome, Ebola, Zika, COVID-19, and nerve agents and certain insecticides (organophosphorus and/or carbamate). In the future, the Secretary may publish tables in the **Federal Register** through separate amendments to 42 CFR part 110 addressing additional covered countermeasures.

The CICP's Smallpox Countermeasures Injury Table is distinct from the Smallpox Vaccine Injury Table authorized under the Smallpox Emergency Personnel Protection Act of 2003 (SEPPA) (42 U.S.C. 239 *et seq.*). The SEPPA, enacted on April 30, 2003, authorized the Secretary to establish the Smallpox Vaccine Injury Compensation Program (SVICP). The SVICP provided benefits to certain persons who sustained a covered injury as the direct result of the administration of the smallpox vaccine or other covered countermeasure, and to certain individuals who sustained a covered injury as the direct result of accidental *vaccinia* inoculation (and/or death benefits to certain survivors of these individuals). The SVICP's implementing regulation was codified at 42 CFR part 102, and included a Smallpox Vaccine Injury Table. The SEPPA's Declaration Regarding Administration of Smallpox Countermeasures, expired on January 23, 2008, and was not renewed. Vaccine recipients and accidental *vaccinia* contacts had 1 and 2 years, respectively, to file a request for program benefits. The SVICP ended on January 23, 2010, and its outmoded regulations were rescinded on November 14, 2016. *See* 81 FR 62817–62818.

Relying instead on later-enacted legislation, based on a credible risk that the threat of exposure to variola virus, the causative agent of smallpox, constitutes a public health emergency, the Secretary issued a Declaration (73 FR 61869–61871) covering smallpox countermeasures under the Public Readiness and Emergency Preparedness

Act of 2005 (PREP Act), with an effective date of January 24, 2008. The PREP Act authorizes the establishment and administration of the CICP. The CICP's implementing regulation, at 42 CFR part 110, is based on the SVICP's regulation and provides similar benefits. On December 9, 2015, the PREP Act Declaration for smallpox countermeasures was amended and republished (80 FR 76546–76553), extending the effective time period to December 31, 2022, and deleting obsolete language referring to SEPPA.

#### *Definition of Covered Countermeasure*

A “covered countermeasure” is defined in the PREP Act and includes three categories.<sup>8</sup> The first category, consisting of “qualified pandemic or epidemic product[s],” is defined in section 319F–3(i)(7) of the PHS Act.<sup>9</sup> A qualified pandemic or epidemic product means a drug or device, as defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act), or a biological product, as defined in the PHS Act<sup>10</sup> that is: (i) Manufactured, used, designed, developed, modified, licensed, or procured to diagnose, mitigate, prevent, treat, or cure a pandemic or epidemic or to limit the harm such pandemic or epidemic might otherwise cause; (ii) manufactured, used, designed, developed, modified, licensed, or procured to diagnose, mitigate, prevent, treat, or cure a serious or life-threatening disease or condition caused by such a drug, biological product, or device; (iii) or a product or technology intended to enhance the use or effect of such a drug, biological product, or device.<sup>11</sup> To qualify as a pandemic or epidemic product, a drug, biologic, or device must be: (1) Approved or cleared under the Federal Food, Drug, and Cosmetic Act (FD&C Act) or licensed under the PHS Act; (2) the subject of research for possible use and subject to an exemption under sections 505(i) or 520(g) of the FD&C Act; or (3) authorized for emergency use in accordance with section 564, 564A, or 564B of the FD&C Act.

The second category includes “security countermeasures.” A security countermeasure, as defined in section 319F–2(c)(1)(B) of the PHS Act, is a drug or device<sup>12</sup>, as defined in the FD&C Act, or a biologic product, as defined in the PHS Act,<sup>13</sup> that the Secretary

determines is: (1) A priority to diagnose, mitigate, prevent harm or treat any biological, chemical, radiological, or nuclear agent identified as a material threat by the Secretary of Homeland Security, or to diagnose, mitigate, prevent harm or treat a condition that may result in adverse health consequences or death and may be caused by administering a drug, biological product, or device against such an agent; (2) is a necessary countermeasure to protect public health as determined by the Secretary of Health and Human Services;<sup>14</sup> and (3) is approved or cleared under the FD&C Act<sup>15</sup> or will likely be approved, cleared, or licensed within 10 years after the Department's determination that procurement of the countermeasure is appropriate or is authorized for emergency use under sections 564 of the FD&C Act.<sup>16</sup>

The final category consists of drugs,<sup>17</sup> biologics,<sup>18</sup> or devices<sup>19</sup> authorized for emergency use in accordance with section 564, 564A, or 564B of the FD&C Act.

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

#### *Covered Smallpox Countermeasures*

The Secretary issued two PREP Act declarations concerning smallpox countermeasures, pursuant to section 319F–3(b) of the PHS Act.<sup>20</sup> On December 9, 2015, the Secretary amended the smallpox countermeasures declaration issued on October 10, 2008<sup>21</sup>, pursuant to section 319F–3 of the PHS Act<sup>22</sup> to: (1) Include countermeasures authorized for use under section 564A and/or prepositioned under section 564B of the FD&C Act;<sup>23</sup> (2) clarify the description of covered countermeasures; (3) extend the effective time period of the declaration; (4) reformat the declaration;

<sup>14</sup> 42 U.S.C. 247d–6d(i)(1)(B), (c)(1)(B).

<sup>15</sup> 21 U.S.C. 301 *et seq.*

<sup>16</sup> 21 U.S.C. 360bbb–3, 360bbb–3a, 360bbb–3b.

<sup>17</sup> As defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)).

<sup>18</sup> As defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)).

<sup>19</sup> As defined in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

<sup>20</sup> *See* 73 FR 61869, October 10, 2008, as amended by 80 FR 76546, December 9, 2015.; 42 U.S.C. 247d–6d(b).

<sup>21</sup> 73 FR 61869 (October 10, 2008); <https://www.gpo.gov/fdsys/pkg/FR-2008-10-17/pdf/E8-24737.pdf>.

<sup>22</sup> 42 U.S.C. 247d–6d.

<sup>23</sup> 21 U.S.C. 360bbb–3a and 360bbb–3b.

<sup>8</sup> Section 319F–3(i)(1) of the PHS Act (42 U.S.C. 247d–6d(i)(1)).

<sup>9</sup> 42 U.S.C. 247d–6d(i)(7).

<sup>10</sup> 21 U.S.C. 321(g)(1), (h); 42 U.S.C. 262(i).

<sup>11</sup> Section 319F–3(i)(7)(A)(ii) of the PHS Act (42 U.S.C. 247d–6d(i)(7)(A)(ii)).

<sup>12</sup> 21 U.S.C. 321(g)(1), (h); 42 U.S.C. 262(i).

<sup>13</sup> 21 U.S.C. 321(g)(1), (h); 42 U.S.C. 262(i).

(5) modify or clarify terms of the declaration; and, (6) republish the declaration in its entirety, as amended.<sup>24</sup>

Covered countermeasures under the declaration are “any vaccine, including all components and constituent materials used in the administration of these vaccines, and all devices and their constituent components used in the administration of these vaccines; any antiviral; any other drug; any biologic; or any diagnostic or other device to identify, prevent or treat smallpox or orthopoxvirus or adverse events from such countermeasures.”<sup>25</sup> Moreover, these covered countermeasures “must be ‘qualified pandemic or epidemic products,’ or ‘security countermeasures,’ or drugs, biological products, or devices authorized for investigational or emergency use as those terms are defined in the PREP Act, the FD&C Act, and the PHS Act.”<sup>26</sup> The covered countermeasures subject to this declaration that will be included on the proposed Table include smallpox vaccines, *vaccinia* immunoglobulin, cidofovir, tecovirimat, brincidofovir, and smallpox infection diagnostic testing.

#### General Information

The Secretary proposes a Table for injuries directly resulting from the use or administration of covered smallpox countermeasures identified in the above-referenced declaration. The proposed Table lists serious physical injuries demonstrated by compelling, reliable, valid, medical and scientific evidence to be directly caused by the administration or use of the covered countermeasures (hereafter referred to as “evidence standard”).<sup>27</sup> Only injuries supported by this evidence standard are proposed for inclusion on the Table.

For each covered countermeasure, the proposed Table will include the covered injuries and/or conditions directly caused by such countermeasure and the applicable time intervals for the first symptom or manifestation of onset of injuries. The Program’s statute directs that covered injuries presumed to be caused by the administration or use of a covered countermeasure must be included on a Table.<sup>28</sup> The Secretary also proposes to indicate on the Table if no injuries or conditions qualify for a

Table presumption for a particular countermeasure at this time. This is to reflect that consideration was given regarding the possibility of Table injuries for these covered countermeasures. Claims related to any injuries alleged to be caused by these countermeasures will be considered on a case-by-case basis.

### III. Discussion of Proposed Rule

This NPRM proposes to amend the Program’s implementing regulation<sup>29</sup> and, if adopted, would establish a table of injuries resulting from the administration or use of smallpox covered countermeasures. Certain conditions that are currently not being proposed for inclusion on the Table also are discussed in this NPRM.

#### General Requirement of Serious Physical Injuries or Deaths

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

In general, only injuries or serious aggravation of injuries that warranted hospitalization (whether or not the person was actually hospitalized) or that led to a significant loss of function or disability will be considered serious physical injuries.<sup>30</sup> It is recognized that the term “disability” can be defined in many ways, and there are several definitions used by the federal government specific to various programs and services. To provide further clarity as to the type of disability that would qualify as a serious injury for the Program, under this NPRM, the term “disability” is defined as “a physical or mental impairment that substantially limits one or more major life activities of an individual.” This definition corresponds with the first listed definition of disability in the Americans with Disabilities Act, 42 U.S.C. 12102(1)(A). This definition was chosen because it is consistent with the Program’s existing authorities and adds further guidance by using a widely accepted definition familiar to the general public.

In addition, pursuant to 42 CFR 110.3(z), “physical biochemical alterations leading to physical changes

and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, be considered serious physical injuries.” According to the preamble to the CICIP Administrative Implementation interim final rule, 42 CFR part 110, serious physical injuries also include “instances in which there may be no measurable anatomic or structural change in the affected tissue or organ, but there is an abnormal functional change. For example, many psychiatric conditions are caused by abnormal neurotransmitter levels in key portions of the central nervous system. It is possible that certain serious psychiatric conditions will qualify as serious physical injuries if the psychiatric conditions are a manifestation of a physical biochemical abnormality in neurotransmitter level or type caused by a covered countermeasure. One way of determining that an abnormal physical change in neurotransmitter level is causing the injury would be a clinical challenge that demonstrates a positive clinical response to a medication that is designed to restore the balance of appropriate neurotransmitters necessary for normal function in an injured countermeasure recipient.”<sup>31</sup>

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

#### Serious Aggravation of Pre-Existing Conditions

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

<sup>24</sup> 80 FR 76546 (December 9, 2015); <https://www.gpo.gov/fdsys/pkg/FR-2015-12-09/pdf/2015-31092.pdf>.

<sup>25</sup> 80 FR 76546, 76552 (December 9, 2015).

<sup>26</sup> 80 FR 76546, 76552 (December 9, 2015).

<sup>27</sup> Section 319F-4(b)(5)(A) of the PHS Act (42 U.S.C. 247d-6e(b)(5)(A)).

<sup>28</sup> Section 319F-4(b)(5)(A) of the PHS Act (42 U.S.C. 247d-6e(b)(5)(A)).

<sup>29</sup> 42 CFR part 110.

<sup>30</sup> 42 CFR 110.3(z).

<sup>31</sup> 75 FR 63656, 63661.

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

#### *Table Time Intervals*

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

#### *Table Definitions and Requirements*

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

#### *Presumption Created for Table Injuries*

For purposes of this Program, a rebuttable presumption exists that a Table injury was directly caused by the administration or use of a covered countermeasure if the first symptom or manifestation of onset of an injury listed on the Table occurred within the timeframe indicated, and the Table's definitions and requirements are satisfied. By statute, this presumption only applies to Table injuries.<sup>32</sup> An individual may obtain this presumption

of causation by submitting medical documentation demonstrating the covered injury occurred, that it began within the time interval specified on the Table after administration or use of a covered countermeasure and all other applicable Table requirements and definitions are met. Nevertheless, it may be rebutted if, based on review of the relevant medical and scientific evidence, the Secretary determines the Table injury was more likely caused by other factors and not directly caused by the countermeasure.

#### *Non-Table Injuries*

Compensation may be available for individuals who: (1) Develop an injury not included on the Table, (2) develop an injury that is included on the Table but the injury began outside the allotted time interval provided by the Table, or (3) develop an injury that does not satisfy the definition or requirements included in the Qualifications and Aids to Interpretation that accompanies the Table with respect to such injury. In these cases, the injured countermeasure recipient does not receive the presumption of causation for a Table injury and must demonstrate that the use or administration of the covered countermeasure directly caused the injury. The regulation administratively implementing the Program includes more information about the requirements for such an injury.<sup>33</sup> For example, a temporal association between the administration or use of a covered countermeasure and onset of the injury (e.g., the injury occurs a certain time after the administration or use of the countermeasure) alone is not sufficient to show that an injury is the direct result of a covered countermeasure.<sup>34</sup> Proof of a causal association for the non-Table injury must be based on compelling, reliable, valid, medical and scientific evidence.

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

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

non-Table injuries on a case-by-case basis.

#### *Injuries Sustained as a Result of the Smallpox Virus*

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

#### *Amendments to the Proposed Table of Injuries*

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

#### *The Table in Effect at the Time a Claim is Filed*

The Table in effect when the Request for Benefits form is filed should be used, unless another Table is published after the claim is filed that provides greater benefit to the requester. If a new Table or an amendment to an existing Table would benefit a requester, as described in the following section, the requester may have an additional opportunity to file a Request for Benefits.

#### *Filing Deadlines and Table Additions or Amendments*

In accordance with 42 CFR 110.42(f), in the event that the Secretary issues a new Covered Countermeasures Injury Table or amends a previously published Table, requesters may have an extended filing deadline based on the effective date of the Table amendment. An

<sup>32</sup> Section 319F-4(b)(5)(A) of the PHS Act (42 U.S.C. 247d-6e(b)(5)(A)).

<sup>33</sup> 42 CFR 110.20(c).

<sup>34</sup> 42 CFR 110.20(c).

extended filing deadline will apply only if the Table amendment enables requesters to establish an injury when they could not establish one previously. If the Table proposed in this NPRM is adopted, any person who meets the Table requirements for a newly listed injury after receiving the smallpox vaccine would have 1 year from the effective date of the Table's adoption to file a Request for Benefits. This filing deadline applies regardless of whether the requester previously filed a Request for Benefits with the Program.

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

Eligible requesters have one year from the date of administration or use of a covered countermeasure to file a Request for Benefits. Also, if an injury is added to a countermeasure injury table, then a requester has 1 year from the effective date of publication of the table revision to file a Request for Benefits for that injury.

It is important to note that the additional filing deadline described in 42 CFR 110.42(f) is only available to persons whose Request for Benefits relates to a new or amended Table injury and otherwise meets the requirements of: (1) The new Table or the amendment(s) to a Table, (2) the Table time interval(s), (3) Table definitions, and (4) any other Table requirements. In this case, such persons may be eligible for the presumption of causation. Persons who sustained injuries not included on the new or amended Table, or those who do not meet all of the requirements for such a Table injury but may prove causation of the injury through other means, will not be afforded an additional 1-year filing deadline based on the Table amendment. Because the Table

amendment would not enable such individuals to establish a Table injury, they would be subject to the standard filing deadline described in 42 CFR 110.42(a) (e.g., 1 year from the date of administration or use of the covered countermeasure).

Eligible requesters have 1 year from the date of administration or use of a covered countermeasure to file a Request for Benefits. Also, if an injury is added to a countermeasure injury table, then the requester has 1 year from the effective date of publication of the table revision to file a Request for Benefits for that injury.

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

#### *Smallpox Countermeasures Injury Table*

The proposed Table lists serious covered injuries directly caused by covered smallpox countermeasures. Although the occurrence of many of the injuries included on the Table is rare, the Secretary is including such injuries on the Table to ensure that people who are otherwise eligible for benefits and/or compensation under the Program will receive the Table's presumption of causation. The Table presumption can be rebutted if the Secretary determines, based on a review of the relevant evidence, that an injury meeting the Table requirements was more likely caused by other factors and not directly caused by the smallpox countermeasure. Claims involving injuries that do not meet the requirements of the Table may qualify as non-Table injuries and will be reviewed on a case-by-case basis by the Program.

#### *Smallpox Background*

Smallpox is a highly contagious disease that may cause fever, a severe rash, and a high death rate. The *variola* virus causes smallpox disease. *Variola* is a large orthopoxvirus within the *Poxviridae* family. Other poxviruses that infect humans include *molluscum contagiosum*, *vaccinia* (the virus used in smallpox vaccine), and monkeypox.<sup>35</sup>

The *variola* virus usually enters the body through the respiratory system. The virus can also enter through the skin and, rarely, through the eyes, or crosses the placenta.<sup>36</sup> It then rapidly enters the regional lymph nodes. On the third or fourth day after infection, the virus is circulating in the blood even though the infected person may not show symptoms. The virus then spreads further into the spleen, bone marrow, and other lymph nodes. Increased virus levels within lymph tissue leads to secondary viremia (elevated virus levels in the bloodstream), which causes fever and the characteristic smallpox rash. During the 8th to 12th day after infection, secondary viremia occurs leading to severe illness.<sup>37</sup>

During the first week after the rash starts, patients are most infectious when sores in the mouth open and release large amounts of virus into the saliva. The ability to pass the infection to others has been estimated as being highest from 3 to 6 days after the onset of fever.<sup>38</sup> The period of infectiousness lasts until all the lesions have scabbed over and the scabs have fallen off. Although, viral particles can be detected in scabs, scabs are considered relatively non-infectious, since the viral particles are bound in the scab.<sup>39</sup> Once the smallpox infection resolves, the person cannot infect others.

Naturally occurring smallpox virus has been eliminated. The absence of endemic smallpox led to the halt of routine vaccination in the United States in 1972.<sup>40</sup> In 1980, the World Health Organization declared that the smallpox

<sup>35</sup> Zack S. Moore, Jane F. Seward and J. Michael Lane, "Smallpox." *Lancet* 367; 9508: (2006): 425.

<sup>36</sup> Frank Fenner et al. "Smallpox and its eradication." *World Health Organization*, Geneva: (1988): 182.

<sup>37</sup> Fenner et al. "Smallpox and its eradication." 188.

<sup>38</sup> Hiroshi Nishiura and Martin Eichner, "Infectiousness of smallpox relative to disease age: Estimates based on transmission network and incubation period." *Epidemiology and Infection* 135, no. 7 (2007): 1147.

<sup>39</sup> Fenner et al. "Smallpox and its eradication." 188.

<sup>40</sup> Richard B. Kennedy, Inna Ovsyannikova and Gregory A. Poland, "Smallpox vaccines for biodefense." *Vaccine* 5; 27 Supplement 4 (November 2009): D73.

vaccine was essential for the successful global eradication of smallpox virus.

Even though smallpox no longer occurs in nature because of the administration of the smallpox vaccine, concern exists that the smallpox virus could be used as a biological weapon. All of the known samples of *variola* virus in the world are kept in two designated laboratories. However, it is unknown if other samples of the virus exist outside those in these two laboratories. This creates the potential of an accidental or intentional release of the virus back into the environment and the need for the ability to provide mass vaccination against smallpox. The use of smallpox as a biological weapon is a concern for several reasons. First, much of the population is susceptible to infection because smallpox vaccination programs have stopped, and thus, the general population is not routinely given the smallpox vaccine. In addition, the virus is infectious via the respiratory system, requires only a small amount of the virus to cause infection, and is transmissible from person to person. Furthermore, the disease has a long asymptomatic incubation period and a high rate of morbidity and mortality. Also, very few treatments exist, and experience has shown that the presence of smallpox virus creates havoc and panic.<sup>41</sup> The ability of individuals to travel rapidly over great distances by air increases the risk of rapid dissemination of the disease. Additionally, the impact of smallpox on the general population would be greater today because the prevalence of immunosuppressed individuals is higher. This includes people living with Human Immunodeficiency Virus (HIV) and individuals taking certain medications that suppress their immune systems to ameliorate specific medical conditions.<sup>42</sup>

### Smallpox Vaccines

After confirmation of one or more human smallpox cases, the primary strategy for controlling the spread of disease involves the use of the smallpox vaccine in combination with other surveillance and containment activities. As demonstrated during the eradication campaign, the immune response generated by smallpox vaccination is one of the most effective tools for halting the transmission of smallpox.

<sup>41</sup> Tara O' Toole, Michael Mair and Thomas V. Inglesby, "Shining light on dark winter." *Clinical Infectious Disease* 34(7) (April 1, 2002): 972.

<sup>42</sup> Louisa E. Chapman, Gina T. Mootrey and Linda J. Neff, "Vaccination against smallpox in the post eradication era." *Clinical Infectious Disease* 15;46 Supplement 3: (March 2008): S155.

Smallpox vaccines are either replication-competent or replication-deficient. The replication-competent vaccines are administered via the intradermal scarification method and the virus in the vaccine reproduces within the vaccine recipient. This method uses a bifurcated needle that punctures the skin multiple times while placing a drop of live-attenuated *vaccinia* virus vaccine in the wound created by the needle. This method creates a vaccination site. There is a risk of transferring the *vaccinia* virus from the vaccination site to other parts of the individual's body or to others. This type of vaccine also has an increased risk of adverse side effects in individuals with immunodeficiencies or skin disorders.

A second type of vaccine involves the use of replication-deficient *vaccinia* virus. This vaccine contains a live-attenuated virus; and is administered subcutaneously; however, the viral agent does not reproduce in human cells. This reduces the risk of transferring the vaccine to other parts of the body or to others. Individuals with certain skin disorders or who are HIV-infected were included in clinical studies, the frequencies of solicited local and systemic adverse reactions among these adults were generally similar to those observed in healthy adults.

The current Food and Drug Administration (FDA) approved smallpox vaccines contain live *vaccinia* viruses that protect against smallpox disease. They do not contain *variola* virus, the causative agent of smallpox. The U.S. Government has three different smallpox vaccines available in the U.S. Strategic National Stockpile (SNS): Smallpox (*Vaccinia*) Vaccine Live (replication-competent), Smallpox and Monkeypox Vaccine, Live, Non-replicating (replication-deficient), and APSV (Aventis Pasteur Smallpox Vaccine) (replication-competent). Smallpox (*Vaccinia*) Vaccine Live and Smallpox and Monkeypox Vaccine, Live, Non-replicating are licensed by the FDA, whereas APSV, which is an investigational vaccine and is not licensed by the FDA, would be made available under an Investigational New Drug (IND) or under Emergency Use Authorization (EUA). Although an EUA cannot be issued until an emergency determination and declarations are in place, a product sponsor can submit and the FDA can review product data as pre-EUA submissions before a formal EUA request.<sup>43</sup> Such a pre-EUA submission

<sup>43</sup> Brett W. Petersen et al. "Clinical guidelines for smallpox vaccine use in a post-event vaccination program." *Morbidity and Mortality Weekly Report*:

does not imply that any specific set of qualifications has been met, but instead represents the initiation of a series of preliminary interactions between the FDA and a product sponsor to discuss potential suitability for EUA consideration.<sup>44</sup>

Dryvax, a type of smallpox vaccine, is no longer manufactured or used. It has been replaced by Smallpox (*Vaccinia*) Vaccine Live, which was derived from Dryvax. Smallpox (*Vaccinia*) Vaccine Live may cause myocarditis and pericarditis, conditions involving inflammation and swelling of the heart and surrounding tissues. Most of these cases are mild, resolve on their own, and do not have symptoms, but some can be very serious. Based on clinical studies, myocarditis and/or pericarditis occur in 1 in 175 adults who get this vaccine for the first time.<sup>45</sup>

In the Smallpox (*Vaccinia*) Vaccine Live clinical trial, 7 of the 2,983 first-time vaccine recipients were suspected of having myocarditis and/or pericarditis. Three of the 868 first-time recipients used the smallpox vaccine (Dryvax). No cases of myocarditis and/or pericarditis were reported among participants who had been previously vaccinated with a smallpox vaccine. In Smallpox (*Vaccinia*) Vaccine Live (replication-competent) clinical trials, among vaccinees naïve to *vaccinia*, 8 cases of suspected myocarditis and pericarditis were identified across both treatment groups, for a total incidence rate of 6.9 per 1,000 vaccinees (8 of 1,162). The rate for the Smallpox (*Vaccinia*) Vaccine Live (replication-competent) treatment group were similar: 5.7 (95 percent CI: 1.9–13.3) per 1,000 vaccinees (5 of 873 vaccinees) and for the Dryvax<sup>®</sup> group 10.4 (95 percent CI: 2.1–30.0) per 1,000 vaccinees (3 of 289 vaccinees). No cases of myocarditis and/or pericarditis were identified in 1,819 previously vaccinated subjects.<sup>46</sup> Commonly observed side effects included itching, sore arm, fever, headache, body ache, mild rash, and fatigue.<sup>47</sup>

*Recommendations and Reports* 64(2): (Feb 20, 2015): 11.

<sup>44</sup> U.S. Department of Health and Human Services, Food and Drug Administration, "Emergency Use Authorization of Medical Products and Related Authorities, Guidance for Industry and Other Stakeholders," January 2017; <https://www.fda.gov/media/97321/download>.

<sup>45</sup> "ACAM2000 (smallpox vaccine): Questions and answers." *United States Food and Drug Administration*, (March 23, 2018): 2.

<sup>46</sup> ACAM2000, Smallpox (*vaccinia*) vaccine, live. Package Insert, Emergent Product Development. Revised 03/2018, <https://www.fda.gov/media/75792/download>.

<sup>47</sup> Petersen et al. "Clinical guidelines for smallpox." 7.

Another smallpox vaccine available for use is Smallpox and Monkeypox Vaccine, Live, Non-replicating. This vaccine uses a modified *Vaccinia* Ankara virus in its composition. Smallpox and Monkeypox Vaccine, Live, Non-replicating is administered via subcutaneous injection. The vaccine virus is replication-deficient; therefore, Smallpox and Monkeypox Vaccine, Live, Non-replicating does not present a risk of secondary transmission. This vaccine requires two doses, 28 days apart. Clinical trials evaluating the safety of Smallpox and Monkeypox Vaccine, Live, Non-replicating found that among the smallpox vaccine-naïve subjects, serious adverse events (SAEs) were reported for 1.5 percent of Smallpox and Monkeypox Vaccine, Live, Non-replicating (replication-deficient) recipients and 1.1 percent of placebo recipients. Among the smallpox vaccine-experienced subjects enrolled in studies without a placebo comparator, SAEs were reported for 2.3 percent of Smallpox and Monkeypox Vaccine, Live, Non-replicating (replication-deficient) recipients. Across all studies, a causal relationship to Smallpox and Monkeypox Vaccine, Live, Non-replicating (replication-deficient) could not be excluded for four SAEs, all non-fatal, which included Crohn's disease, sarcoidosis, extraocular muscle paresis and throat tightness.<sup>48</sup>

APSV, sometimes called "WetVax" was manufactured from 1956 to 1957. It is a replication-competent vaccine. It has been maintained in cold storage since it was produced. It was manufactured from the same *vaccinia* virus strain as Dryvax. It contains live *vaccinia* virus without preservatives or antibiotics. Testing of samples indicate that it is safe to use from a bioburden (presence of bacteria within the sample) perspective. The vaccine is administered in a single dose with a bifurcated needle and the appropriate number of punctures at the vaccination site. The preferred site of vaccination is on the upper arm over the deltoid muscle. Once appropriately diluted, each vial contains approximately 500 doses of vaccine. It has a similar side effect profile as Dryvax and a safety profile similar to Dryvax and Smallpox (*Vaccinia*) Vaccine Live. It is thought to be 95 percent effective when used as pre-exposure prophylaxis. The most frequently encountered serious complications of APSV include: encephalitis, progressive *vaccinia* (PV),

<sup>48</sup> JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating, Package Insert, Bavarian Nordic A/S. Aug 2019. <https://www.fda.gov/medial/131078/download>.

and eczema vaccinatum.<sup>49</sup> APSV would be used if there is a shortage of Smallpox (*Vaccinia*) Vaccine, Live and of Smallpox and Monkeypox Vaccine, Live, Non-replicating.

Smallpox vaccination for pre-exposure prophylaxis using replication-competent vaccine is contraindicated in people with severe immunodeficiency (such as individuals undergoing bone marrow transplantation or those with primary or acquired immunodeficiency requiring isolation). A vaccine containing replication competent virus should be used with caution in the following groups: (1) Anyone who is allergic to the vaccine or any of its components; (2) anyone younger than 12 months of age; (3) people who have, or have had, certain skin conditions (especially eczema or atopic dermatitis); (4) people who have been diagnosed as having a heart condition, or having three or more known major cardiac risk factors; (5) women who are pregnant or planning to become pregnant within 4 weeks after vaccination; (6) persons with congenital or acquired immune deficiency disorders (e.g., HIV/AIDS, leukemia, lymphoma); and (7) persons using corticosteroid eye drops. Within these identified groups, the risk of vaccination must be weighed against the risk of potential smallpox virus exposure.<sup>50</sup>

Smallpox vaccination using replication-deficient vaccine has no absolute contraindication for administration, it should be noted, however, that this vaccine has not been studied in individuals less than 18 years old.<sup>51</sup> Warning and precautions for this product include: Severe allergic reactions; altered immunocompetence ("Immunocompromised persons, including those receiving immunosuppressive therapy, may have a diminished immune response.") and limitations of vaccine effectiveness.<sup>52</sup>

In a smallpox bioterrorism emergency, pregnant women at high risk of exposure may be advised to be vaccinated, since the risk of death and serious illness from smallpox in that situation would likely outweigh risks to the fetus from fetal *vaccinia* caused by replication-competent vaccines. A study of 376 women enrolled in the National

<sup>49</sup> Petersen et al. "Clinical guidelines for smallpox." 10.

<sup>50</sup> ACAM2000, Smallpox (*vaccinia*) vaccine, live. Package Insert, Emergent Product Development.

<sup>51</sup> JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating, Package Insert, Bavarian Nordic A/S. Aug 2019. <https://www.fda.gov/medial/131078/download>.

<sup>52</sup> JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating, Package Insert, Bavarian Nordic A/S. Aug 2019. <https://www.fda.gov/medial/131078/download>.

Smallpox Vaccine in Pregnancy Registry showed that women vaccinated during pregnancy with replication-competent vaccine did not have higher-than-expected rates of pregnancy loss, preterm birth, or birth defects compared with pregnant women not receiving the smallpox vaccine. Most of the women in the registry (77 percent) were vaccinated near the time of conception, before results of a standard pregnancy test would have been positive. No cases of fetal *vaccinia* were identified. A retrospective cohort study employing information from Department of Defense databases examined outcomes among 31,420 infants born to active-duty military women during 2003–2004. There were 7,735 infants born to women who had previously been vaccinated against smallpox. An additional 672 infants were delivered by women who had been vaccinated for smallpox in the first trimester of pregnancy. Analysis revealed that maternal smallpox vaccination during pregnancy was not associated with preterm or extreme preterm delivery.<sup>53</sup> Maternal smallpox vaccination during the first trimester was not significantly associated with overall birth defects.<sup>54</sup> Live born infants who experience a covered injury as the direct result of a covered countermeasure administered to or used by a pregnant woman, such as a smallpox vaccine, are eligible for compensation from the CICP.<sup>55</sup>

Serious adverse reactions to smallpox vaccination can occur.<sup>56</sup> It has been estimated that during mass vaccinations campaigns with replication-competent vaccines, 1 to 2 deaths and hundreds of complications severe enough to require hospitalization occurred for every 1 million people vaccinated. Estimates from the medical and scientific literature indicate that if the current population of the United States was vaccinated with the replication-competent smallpox vaccine, hundreds of deaths and thousands of hospitalizations could occur.<sup>57</sup> Statistics from the 1960s and 1970s documented the rate of serious complications after receipt of the smallpox vaccine. These rates may be higher today as more

<sup>53</sup> Margaret Ryan and Jane F. Seward, Pregnancy, birth, and infant health outcomes from the national smallpox vaccine in pregnancy registry, 2003–2006. *Clinical Infectious Disease* 2008;46 (Suppl 30): S222.

<sup>54</sup> Margaret Ryan, et al. Evaluation of preterm births and birth defects in liveborn infants of US military women who received smallpox vaccine. *Birth Defect Research (Part A): Clinical and Molecular Teratology* 82:2008, 533–539.

<sup>55</sup> 42 CFR 110.3(n)(3).

<sup>56</sup> Petersen et al. "Clinical guidelines for smallpox."

<sup>57</sup> Kennedy et al. "Smallpox Vaccines," D75.



individuals are immunocompromised, immunosuppressed or immunodeficient. However, the licensure of a vaccine with an improved safety profile is expected to decrease serious complications resulting from smallpox vaccination. Earlier studies primarily sought information only regarding what was already known to occur because of the administration of the smallpox vaccine. It is possible that previously unrecognized adverse reactions will become more evident with improved surveillance.

Minor adverse events following smallpox vaccination occur.<sup>58</sup> These include tenderness and erythema (redness) at the injection site and other localized reactions. With replication-competent vaccines, minor reactions also include allergic reactions to tape adhesives and “robust takes.” “Robust takes” are local reactions that are larger than expected and generally greater than 7.5 centimeters (cm), and are accompanied by some or all of the following signs and symptoms: Erythema, induration (firmness of the skin extending beyond the vaccination site), tenderness and warmth in the absence of secondary cellulitis (a bacterial infection of the skin). Robust takes are not generally considered a Table injury. In addition to localized reactions, systemic reactions such as fever of at least 100 °F, body aches, muscle pain, and local enlargement of the lymph nodes can occur and have been associated with replication-competent vaccines.

The *vaccinia* virus in the replication-competent smallpox vaccines is live and can be transmitted to other parts of the body of the vaccine recipient. For purposes of this NPRM, the term “vaccination” refers to the administration and receipt of the *vaccinia* virus through the smallpox vaccine and not through contact, whereas, the term “inoculation” refers to transmission of, and subsequent infection with, the *vaccinia* virus through a means other than smallpox vaccination. Autoinoculation occurs when vaccine recipients touch their vaccination site before it has healed and then touch another part of their body. Accidental or inadvertent, person-to-person inoculation occurs when a person or the vaccine recipient touches a vaccination site before it has healed and then touches another person.

The proposed Table lists the following injuries for the smallpox vaccines.

<sup>58</sup> ACAM2000, Smallpox (*vaccinia*) vaccine, live. Package Insert, Emergent Product Development.

### *Injuries Associated With Both Replication-Competent and Replication-Deficient Smallpox Vaccines*

#### A. Anaphylaxis

Anaphylaxis is a single discrete event that presents as a severe and potentially life threatening multi-organ reaction, particularly affecting the skin, respiratory tract, cardiovascular system, and the gastrointestinal tract. In an anaphylactic reaction, an immediate reaction generally occurs within minutes after exposure, and in most cases, the individual develops signs and symptoms within 4 hours after exposure to the antigen (substance causing the reaction). The immediate reaction leads to a combination of skin rash, mucus membrane swelling, leakage of fluid from the blood into surrounding tissues, restriction 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. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema (throat swelling) or bronchospasm and may be associated with cardiovascular collapse.<sup>59</sup>

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 additional complications. Anaphylaxis can be due to an exaggerated acute systemic hypersensitivity reaction. It is not an initial episode of a chronic condition, such as chronic 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.<sup>60</sup> In 2003, the Institute of Medicine (IOM) reported that evidence favors acceptance of a causal relationship between certain vaccines and anaphylaxis based on case reports and case series. The IOM 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 alternative causes.<sup>61</sup>

<sup>59</sup> 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.

<sup>60</sup> Jens U. Rugeberg et al. “Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data.” *Vaccine*. (August 2007): 5676.

<sup>61</sup> Institute of Medicine, “Immunization safety review vaccination and sudden unexpected death

Smallpox vaccines are currently prepared using various techniques that result in the final products containing a limited quantity of foreign protein that can induce immediate hypersensitivity reactions in some persons with severe protein mediated allergies. It is established that smallpox vaccines can cause anaphylaxis similar to that seen in other vaccines.<sup>62 63</sup>

A 1994 IOM Report supports the causal association between vaccines and a biologic gradient of host responses, ranging from true anaphylaxis to milder forms of hypersensitivity reactions. Biological gradient refers to the observation of a spectrum of responses from mild to severe. In the case of hypersensitivity reactions, the reported spectrum after the vaccine runs from mild skin manifestations to chest and throat tightness and cardiovascular events to full blown anaphylaxis. The IOM also stated that the onset of anaphylaxis generally occurs within a few hours of exposure.<sup>64</sup> Consistent with the time interval for the first manifestation of anaphylaxis after vaccines covered by the National Vaccine Injury Compensation Program and the CICP’s Pandemic Influenza Countermeasure Injury Table, the Secretary proposes an onset interval for the first symptom or manifestation of 0–4 hours for anaphylaxis to be covered under the proposed Table.

Based on the nature and timing of anaphylaxis, and the medical and scientific literature, the Program’s evidence standard has been met, and anaphylaxis is proposed for inclusion on the Table because it is a serious physical injury that may be directly caused by the administration or use of either the replication-competent or replication-deficient smallpox vaccine.

In rare cases of acute anaphylaxis, initial symptoms of the immediate reaction may present up to 12 hours after exposure. A slow evolving late phase hypersensitivity reaction is possible, with an onset that usually begins 4–8 hours after the immediate reaction ends. The medical literature contains reports of late phase onset up

in infancy.” *The National Academies Press*, (2003): 31.

<sup>62</sup> Joanne Cono, Christine G. Casey and David M. Bell, “Smallpox vaccination and adverse reactions. Guidance for clinicians.” *Morbidity and Mortality Weekly Report*, 52(RR04) (February 21, 2003): 2.

<sup>63</sup> Werner J. Pichler et al. “Drug hypersensitivity reactions: pathomechanism and clinical symptoms.” *Medical Clinics of North America* 94, (July 2010): 646.

<sup>64</sup> Institute of Medicine, “Adverse events associated with childhood vaccines evidence bearing on causality.” *The National Academies Press*, (1994): 22.

to 72 hours later.<sup>65</sup> The late phase reaction results from a different immunologic mechanism of action. The late phase reaction is part of a biphasic reaction. It is possible for the first immediate hypersensitivity reaction to be relatively mild, unrecognized, or not observed. There may be unusual cases in which the immediate reaction is delayed and/or cases that the immediate reaction is not recognized, with the first apparent manifestation occurring in the late phase. These unusual cases do not meet the requirements to be considered table injuries, and will be evaluated on a case-by-case basis based on the Program's evidence standard.

#### B. Vasovagal Syncope

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

In its 2012 report, *Adverse Effects of Vaccines*, the IOM concluded, based on mechanistic evidence (mechanism of action), that the evidence convincingly supports a causal relationship between the injection of a vaccine and vasovagal syncope. Vasovagal syncope after vaccination is usually not associated with serious injuries; however, some cases of vasovagal syncope will result in serious injury related to physical trauma from an associated fall or other related accidents.

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and vasovagal syncope may be a serious physical injury that may be directly caused by the administration or use of any injected smallpox vaccine.<sup>66</sup> Since most cases of vasovagal syncope occur within 1 hour of vaccination, syncope is proposed to be added to the Table with an onset interval for the first symptom or manifestation of 0–1 hour after vaccination with the injected smallpox vaccine.

<sup>65</sup> Rugeberg et al. "Anaphylaxis: case definition and guidelines." 5677.

<sup>66</sup> Institute of Medicine, *Adverse effects of vaccines: Evidence and causality*. (Washington, DC: The National Academies Press, 2012): 18.

### *Injuries Associated With Only Replication-Competent Smallpox Vaccines*

#### A. Skin Reactions

Certain skin reactions are associated with the administration of replication-competent smallpox vaccines. These include: (1) Significant local skin reaction, (2) Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), (3) inadvertent autoinoculation, (4) eczema vaccinatum, (5) generalized vaccinia, and (6) progressive vaccinia, previously termed "vaccinia necrosum."<sup>67</sup> Widespread skin reactions are larger than a simple skin reaction and include two groups. The first group includes significant skin reactions (such as SJS/TENS) and other nonspecific post-vaccination rashes with lesions that are thought to be free of the vaccinia virus. The second group includes adverse reactions thought to be caused by replicating vaccinia virus recovered from skin lesions, which can be associated with risk for autoinoculation or contact transmission.<sup>68 69 70 71 72 73</sup>

#### 1. Significant Local Skin Reaction

A significant local skin reaction is, for purposes of the Table, an unexpected and extreme response to the inoculation of the vaccinated person. The expected onset of this injury is the initial skin lesion at the smallpox vaccination or inoculation site. The replication-competent smallpox vaccine is administered through a multiple puncture technique known as scarification. The dose of vaccine is placed on a needle, which is then penetrated multiple times into the skin, commonly, in the upper arm.<sup>74</sup> Other sites for vaccine administration may be selected utilizing this same technique. The vaccinia virus in the vaccine replicates and causes damage in the

<sup>67</sup> Aysegul Nalca and Elizabeth E. Zumbrun, "ACAM2000: The new smallpox vaccine for United States strategic national stockpile," *Drug Design, Development and Therapy* 4. (2010): 76.

<sup>68</sup> Cono et al. "Smallpox vaccination and adverse reaction." 2.

<sup>69</sup> Cono et al. "Smallpox vaccination and adverse reactions." 3.

<sup>70</sup> Lane and Goldstein, "Adverse Events." 191–192.

<sup>71</sup> Kent A. Sepkowitz, "How contagious is vaccinia?" *New England Journal of Medicine* 348(5) (January 30, 2003): 443–445.

<sup>72</sup> Vincent A. Fulginiti et al. "Smallpox vaccination: a review, part II. Adverse events." *Clinical Infectious Disease* 37 (July 15, 2003): 252.

<sup>73</sup> Ellen R. Wertheimer et al. "Contract transmission of vaccinia virus from smallpox vaccinees in the United States, 2003–2011." *Vaccine* 30. (2012): 986.

<sup>74</sup> Richard B. Kennedy et al. *Vaccines*. (Philadelphia: Elsevier-Saunders, 2013): 730.

cells resulting in a localized lesion.<sup>75</sup> This can result in a typical local skin reaction in a naïve (first-time) vaccine recipient composed of a papule, which develops 3 to 4 days post-vaccination. The papule then goes on to mature into a vesicle and a pustule over the next 4 to 5 days. The vaccine lesion is generally at its maximum size by day 8 post-vaccination. The primary lesion is surrounded by erythema and inflammation, and regional lymphadenopathy is generally present. The scab formed by the healing pustule separates by day 21 post-vaccination. The cutaneous reaction in individuals being revaccinated may be reduced in severity or entirely absent. In previously immunized individuals who fail to develop a skin response with the second immunization, no additional smallpox immunizations are required.<sup>76</sup>

Cono et al. found that approximately 10 percent of first time vaccinees will go on to develop a large vaccination reaction, defined as a reaction greater than 10 cm in diameter at the site of the inoculation. This is a normal variant within the population.<sup>77</sup>

In an examination of the data generated in the most recent mass smallpox vaccination program completed in the U.S. with HHS and the U.S. Department of Defense (DoD) in 2003 and 2004, using replication-competent vaccine, significant local skin reactions leading to hospitalization were not identified.<sup>78</sup> Of the nearly 770,000 individuals (both first time and revaccinated) vaccinated during this program, there were no reported cases of local skin reaction requiring hospitalization. The improved pre-screening of smallpox vaccine recipients is thought to have reduced the incidence of significant local skin reactions.<sup>79</sup>

In the 2003 Grabenstein and Winkenwerder study, the data indicates that 16 of 450,000 military patients vaccinated were hospitalized due to the uncertainty of the communicability of their skin conditions after receiving the replication-competent smallpox

<sup>75</sup> Xiaolin Tan et al. "Failure of the smallpox vaccine to develop a skin lesion in vaccinia virus-naïve individuals is related to differences in antibody profiles before vaccination, not after." *Clinical and Vaccine Immunology* 19(3) (March 2012): 418.

<sup>76</sup> ACAM2000, Smallpox (vaccinia) vaccine, live. Package Insert, Emergent Product Development.

<sup>77</sup> Cono et al. "Smallpox vaccination and adverse reaction." 5.

<sup>78</sup> Gregory A. Poland, John D. Grabenstein and John M. Neff, "The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program." *Vaccine* 23 (February 4, 2005): 2079.

<sup>79</sup> Poland et al. "The US smallpox vaccination program." 2081.

vaccine. After additional evaluation, each patient was returned to duty. The authors also describe 36 cases of suspected mild generalized *vaccinia*; each of these patients were treated and released. Of these 36 patients, nine were hospitalized. These hospitalizations were attributed to providers who were seeing smallpox vaccinated patients for the first time being overly cautious. Each of these patients were treated and returned to duty. A single service member developed erythema multiforme major after receiving multiple vaccines. This was seen as a possible reaction to the replication-competent smallpox vaccine.<sup>80</sup>

A revaccination program that occurred in Israel in 2002 and 2003 provided replication-competent smallpox vaccinations to 21,000 first responders and utilized a different vaccine strain than the one used in the U.S. Many of the vaccine recipients experienced local swelling and pain. However, only one individual was hospitalized with a diagnosis of cellulitis at the injection site.<sup>81</sup>

The severity of adverse reactions following vaccination can vary based upon factors such as the immune status of the individual and a positive or negative history of past exposure to the smallpox vaccine. Typically, those with a potentially higher level of immunity, because of previous exposure to the vaccine, may develop a reduced response to revaccination. Vaccination site lesions generally resolve with the separation of the overlaying scab within 21 days post-vaccination.<sup>82</sup> This 21-day period is the expected timeframe of a normal immune response and the time in which reactions associated with the vaccine should have occurred and been resolved.<sup>83</sup>

Skin reactions that occur because of receiving the replication-competent smallpox vaccine are generally self-limiting and resolve without intervention. Minor scarring or minor local reactions do not constitute a Table injury. A robust take does not constitute a Table injury.

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and significant local skin reactions are serious physical injuries that may be

<sup>80</sup> John D. Grabenstein and William Winkenwerder, "US Military smallpox vaccination program experience." *Journal of the American Medical Association* 289(24) (June 25, 2003): 3280.

<sup>81</sup> Emilia Anis et al. "Smallpox revaccination of 21,000 first responders in Israel: lessons learned." *International Journal of Infectious Disease* 13 (August 6, 2009): 406.

<sup>82</sup> Lane et al. "Adverse Events." 190.

<sup>83</sup> Kennedy et al. "Smallpox and *vaccinia*." 730.

directly caused by the use of the replication-competent smallpox vaccine. As explained above, the expected time interval between exposure and onset of injury for the first symptom or manifestation is 1–21 days.<sup>84</sup>

A Table injury in a recipient requires sufficient evidence in the medical records of the occurrence of a significant local skin reaction at the vaccination or inoculation site. The presence of a scar resulting from the significant local skin reaction would not be considered a Table injury unless the scar is of sufficient severity to warrant hospitalization or lead to a significant loss of function or disability.

## 2. SJS/TEN

SJS and TEN, are acute hypersensitivity reactions that affect skin, mucus membranes, and sometimes internal organs (systemic toxicity). As mentioned in the previous section, the terms Erythema Multiforme (EM) and SJS have been historically linked to TEN and are often confused by clinicians even today. It is now recognized that EM is a different disease from SJS and TEN.<sup>102</sup> Although SJS and TEN were once thought to be separate conditions, they are now considered part of a continuum. SJS is on the less severe end of the spectrum and TEN represents the more severe end.<sup>85</sup> SJS/TEN is the most commonly used term to refer to the spectrum of conditions that include SJS, SJS/TEN overlap, and TEN. The difference between SJS, SJS/TEN overlap, and TEN is defined by the degree of skin detachment. SJS is defined as skin involvement of less than 10 percent. TEN is defined as skin involvement of greater than 30 percent. SJS/TEN is defined as overlap of 10–30 percent skin involvement.<sup>86</sup> For the purposes of the Table, the term SJS/TEN will be used to refer to the SJS and TEN disease spectrum, consistent with its use in recent scientific articles.<sup>87 88 89</sup> SJS/TEN is a rare condition that affects

<sup>84</sup> Kennedy et al. "Smallpox and *vaccinia*." 730.

<sup>85</sup> National Institutes of Health, U.S. National Library of Medicine, "Steven-Johnson syndrome/toxic epidermal necrolysis." (September 10, 2019): 1–2.

<sup>86</sup> Marianne Lerch et al. "Current Perspectives on Stevens-Johnson syndrome and Toxic Epidermal Necrolysis." *Clinical Reviews in Allergy & Immunology*. Feb 2018;54(1):147–176.

<sup>87</sup> Roni P. Dodiuk-Gad et al. "Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: An Update." *American Journal of Clinical Dermatology*. Dec 2015;16(6):475–493.

<sup>88</sup> National Institutes of Health, U.S. National Library of Medicine, "Stevens-Johnson syndrome." 1.

<sup>89</sup> Lerch et al. "Current Perspectives on Stevens-Johnson syndrome and Toxic Epidermal Necrolysis." 147–176.

1–2 people per million, per year. SJS/TEN is most commonly triggered by medication, but it is also seen in individuals experiencing infections with *Mycoplasma pneumoniae* and cytomegalovirus. In many cases, no cause of SJS/TEN is ever identified.<sup>90</sup> Although rare, generalized hypersensitivity reactions have been documented with the use of live attenuated vaccines, such as the replication-competent smallpox vaccine, as the body reacts to the presence of an identified foreign protein.<sup>91 92 93</sup>

SJS/TEN frequently begins with flu-like symptoms. Shortly thereafter, the skin begins to blister and peel creating painful open areas on the skin, mouth, airways, and potentially the urinary tract and genitals. In SJS/TEN, mucosal involvement generally predominates. Mucosal lesions generally occur at more than one location and manifest as painful lesions in sites, such as the mouth or eyes. Skin rash or lesions in SJS/TEN usually consist of red raised areas, blisters, and ulcerations. Open areas created by SJS/TEN can lead to fluid loss and make the person susceptible to infection. Because of the damage that occurs to the skin and mucus membranes, SJS/TEN is considered a life threatening condition. Serious complications of SJS/TEN include pneumonia, sepsis, shock, multiple organ failure, and death. Approximately 10 percent of individuals with SJS/TEN will die from the condition.<sup>94</sup> For those who survive SJS/TEN, the potential long-term complications include skin color changes, skin and mucosal dryness, excessive sweating, hair loss, impaired taste, difficulty urinating, and genital abnormalities. Some individuals develop chronic dry eye leading to photophobia (light sensitivity) and vision impairment.<sup>95</sup>

A 1968 survey identified 48 cases of EM among 572 patients identified with

<sup>90</sup> National Institutes of Health, U.S. National Library of Medicine, "Stevens-Johnson syndrome." 1.

<sup>91</sup> Adena E. Rosenblatt and Sarah L. Stein, "Cutaneous reactions to vaccines." *Clinics in Dermatology* 33(3). (2015): 327.

<sup>92</sup> J. Michael Lane et al. "Deaths attributed to smallpox vaccinations, 1959 to 1966, and 1968." *Journal of the American Medical Association* 212(3) (April 20, 1970): 441.

<sup>93</sup> Ashish Chopra et al. "Stevens-Johnson syndrome after immunization with smallpox, anthrax and tetanus vaccines." *Mayo Clinic Proceedings* 79(9) (September 2004): 1193.

<sup>94</sup> National Institutes of Health, U.S. National Library of Medicine, "Stevens-Johnson syndrome." 1.

<sup>95</sup> National Institutes of Health, U.S. National Library of Medicine, "Stevens-Johnson syndrome." 1.

adverse reactions to the replication-competent smallpox vaccine; however, it was noted that this may actually be an under representation of the actual total number of SJS cases.<sup>96</sup> At the time of the study, EM and SJS were considered synonyms for the same condition or conditions on the same spectrum of disease. The United States Armed Forces vaccinated 450,293 of its members from December 2002, to May 2003, and reported one case of severe EM, defined as SJS, during this period.<sup>97</sup>

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and SJS/TEN is a serious physical injury that may be directly caused by the use of the replication-competent smallpox vaccine.<sup>98</sup> For SJS/TEN to be a Table injury, both skin and mucus membrane rash or lesions must be present. Two or more mucosal sites must be involved and the distribution of the rash must be widespread.<sup>99</sup> <sup>100</sup> The proposed onset interval for the first symptom or manifestation is 4–28 days after vaccination. The earliest time of onset, 4 days post-vaccination, is consistent with other conditions that cause SJS/TEN.<sup>101</sup> <sup>102</sup> The 28-day mark represents the point at which any immune response in the form of SJS/TEN would have occurred.<sup>103</sup> <sup>104</sup> <sup>105</sup>

<sup>96</sup>J Michael Lane et al. "Complications of smallpox vaccination, 1968\* National Surveillance in the United States." *The New England Journal of Medicine* 281 (22) (November 27, 1969): 1205.

<sup>97</sup>Chopra et al. "Stevens-Johnson syndrome." 1196.

<sup>98</sup>Rosenblatt et al. "Cutaneous Reactions to Vaccinations," 327.

<sup>99</sup>Chopra et al. "Stevens-Johnson Syndrome after Immunization with Smallpox, Anthrax, and Tetanus Vaccines." 1195.

<sup>100</sup>Heng et al. "Epidermal necrolysis: 60 years of errors and advances." 1252.

<sup>101</sup>Dodiuk-Gad et al. "Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: An Update." 475, 477.

<sup>102</sup>Maja Mockenhaupt, Cecile Viboud, Ariane Dunant, Luigi Naldi, Sima Halevy, Jan Nico Bouwens Bavinck, Alexis Sidoroff, Jurgen Schneck, Jean-Claude Roujeau and Antoine Flahault. Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: Assessment of Medication Risks with Emphasis on Recently Marketed Drugs. The Euro SCAR Study. *Journal of Investigative Dermatology*. January 2008; 128(1):35–44.

<sup>103</sup>Dodiuk-Gad et al. "Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: An Update." 477.

<sup>104</sup>B. Sassolas, C. Haddad, M. Mockenhaupt, A. Dunant, Y. Liss, K. Bork, UF Hausteiner, D. Vieluf, JC Roujeau and H. Le Louet. "ALDEN, an Algorithm for Assessment of Drug Causality in Stevens-Johnson syndrome and Toxic Epidermal Necrolysis: Comparison with Case-Control Analysis" *Nature*. July 2010;88(1): 60–68.

<sup>105</sup>Cono et al. "Smallpox Vaccination and Adverse Reactions." 3.

### 3. Inadvertent Autoinoculation (IA) (Self-Inoculation)

Unintentional transfer of replication-competent *vaccinia* virus, which includes transfer from the vaccination site to elsewhere on the vaccine recipient's body, is called inadvertent autoinoculation (IA) or self-inoculation. IA is the most common adverse event associated with the smallpox vaccine.<sup>106</sup>

Smallpox vaccine recipients or contacts can transfer replication-competent *vaccinia* virus to their hands or fomites (inanimate objects that carry infection), which become a source for infection elsewhere on the body. The Program does not cover injuries caused by the transfer of the *vaccinia* virus to individuals who are not primary vaccine recipients. Other than ocular (eyes), the most common sites are the face, nose, mouth, lips, genitalia, and anus.<sup>107</sup> Lesions at IA sites progress through the same stages (e.g., papular, vesicular, pustular, crusting, and scab) as the vaccination site. When IA occurs greater than 5 days post-vaccination, the developing immune response might reduce the lesions and their progression. Persons at highest risk for IA are children ages 1–4 years and those with disruption of the epidermis, such as abrasions and burns.<sup>108</sup>

Ocular *vaccinia* infections result from the transfer of *vaccinia* from the vaccine site or other lesion containing *vaccinia* to or near the eye. Infections can be clinically mild to severe and can lead to vision loss.<sup>109</sup> <sup>110</sup>

IA was a frequently reported complication of early smallpox vaccination programs. Proper adherence to aseptic technique with dressing changes, hand washing, and the use of hand sanitizers with greater than 60 percent alcohol content help to reduce the frequency of IA, but it still remains a complication of replication-competent smallpox vaccines. Treatment is based on the number of transfer sites or the size of the resulting lesions.<sup>111</sup>

During the 2002–2004 HHS and DoD smallpox vaccination program, 101 of the 770,000 individuals vaccinated reported cases of IA. This number represents both ocular and non-ocular forms of IA. The study did not provide

<sup>106</sup>Kennedy et al. "Smallpox and *vaccinia*." 738.

<sup>107</sup>Lane et al. "Adverse Events." 191.

<sup>108</sup>Kennedy et al. "Smallpox and *vaccinia*." 741.

<sup>109</sup>Frederick Ruben and J. Michael Lane, "Ocular *vaccinia*: an epidemiologic analysis of 348 cases." *Archives of Ophthalmology* 84 (July 1970): 47.

<sup>110</sup>Danielle M. Tack et al. "Unintentional transfer of *vaccinia* virus associated with smallpox vaccines." *Human Vaccines & Immunotherapeutics* 9:7 (July 2013): 1491.

<sup>111</sup>Fulginiti et al. "Smallpox vaccination: a review, Part II." 256.

information regarding the rate of hospitalization.<sup>112</sup>

In the 2002–2003 Israeli replication-competent smallpox immunization effort to revaccinate 21,000 first responders, there were 221 identified cases of IA. This represents a 1 percent incident rate within this group of vaccine recipients. The study did not provide details regarding the extent of the IA, and although some individuals were hospitalized as a result of receiving vaccines, the article does not make clear if these hospitalizations were the result of IA or other causes.<sup>113</sup>

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and IA is a serious physical injury that may be directly caused by the use of the replication-competent smallpox vaccine. Therefore, IA is proposed to be added to the Table with an onset interval for the first symptom or manifestation of onset of 1–21 days for the first symptom or manifestation to occur after vaccination since the live *vaccinia* virus can be transferred from the vaccination site to another location on the vaccine recipient's body at any time during this period. By day 21 post-vaccination, the vaccination site should be healed, and the scab should have become dislodged and fallen off.<sup>114</sup> <sup>115</sup> <sup>116</sup> <sup>117</sup> For the purpose of this regulation, the inadvertent or intentional inoculation of other persons by the vaccine recipient is not considered a covered injury. Only individuals who were administered the smallpox vaccine will be eligible for benefits.<sup>118</sup>

### 4. Generalized *Vaccinia*

Generalized *vaccinia* (GV) is caused by the systemic spread of replication-competent *vaccinia* from the site of vaccination with the smallpox vaccine.<sup>119</sup> It presents as a disseminated vesicular or pustular rash and is usually benign and self-limited among immunocompetent hosts. GV may be accompanied by fever and can produce skin lesions anywhere on the body. GV can also appear as a regional form characterized by extensive vesiculation

<sup>112</sup>Poland et al. "The US smallpox vaccination program: a review." 2079.

<sup>113</sup>Anis et al. "Smallpox revaccination of 21,000." 406.

<sup>114</sup>Cono et al. "Smallpox Vaccination and Adverse Reactions." 3.

<sup>115</sup>Lane et al. "Adverse Events." 191.

<sup>116</sup>Kennedy et al. "Smallpox and *vaccinia*." 738.

<sup>117</sup>Wertheimer et al. "Contract transmission of *vaccinia* virus." 985.

<sup>118</sup>See sections 319F–4(b)(4), (e)(2), and (e)(5) of the PHS Act (42 U.S.C. 247d–6e(b)(4), (e)(2), and (e)(5)).

<sup>119</sup>Kennedy et al. "Smallpox and *vaccinia*." 738.

around the vaccination site or as an eruption localized to a single body region (e.g., arm or leg). The skin lesions of GV are thought to contain virus spread through the blood stream. First-time vaccinees are at higher risk for GV than re-vaccinees. GV is often more severe among persons with underlying immunodeficiency who might have been inadvertently vaccinated; these patients might benefit from early intervention with *vaccinia* immunoglobulin (VIG). GV should not be confused with multiple inadvertent inoculations that might occur in the presence of acute or chronic exfoliative, erosive, or blistering skin disease. GV is different from eczema *vaccinatum* (EV), which typically occurs in persons with a history of atopic dermatitis and is often associated with systemic illness.<sup>120</sup>

In GV, the initial lesions usually appear approximately a week after immunization on unimmunized skin. These new lesions have a similar appearance to the initial immunization but are generally smaller and heal quickly to a scar (within 5–6 days). In extremely rare cases, lesions have been seen to reoccur at 4 to 6 week intervals for up to 1 year unless treatment with VIG stops the recurrence.<sup>121</sup>

In the U.S., from January 24 through August 8, 2003, 38,257 civilian health care workers received the smallpox vaccination using replication-competent smallpox vaccine. During this period, HHS reported there were two suspected cases and one confirmed case of GV within the group of vaccine recipients.<sup>122</sup>

In the DoD smallpox vaccination program (770,000 vaccinated), as of January 4, 2005, there were 35 suspected cases of GV. All of these cases were described in the literature as mild, and all individuals made a full recovery.<sup>123</sup>

GV is a known, but rare, complication of receiving the replication-competent smallpox vaccine, and its level of severity varies from person to person. The literature indicates the risk of developing GV is significantly reduced with obtaining a complete history and excluding individuals at risk for developing the condition. It is presently

not possible to predict completely who may develop GV, but Smallpox (*Vaccinia*) Vaccine Live is contraindicated for use in individuals with severe immunodeficiency.<sup>124</sup> The treatment of GV may require hospitalization and the use of *vaccinia* immunoglobulin intravenous (VIGIV).

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and GV is a serious physical injury that may be directly caused by the administration or use of the replication-competent smallpox vaccine.<sup>125 126 127 128 129</sup> Therefore, GV is proposed to be added to the Table with an onset interval of 6–9 days for the first symptom or manifestation to occur after vaccination as supported by the compelling, reliable and valid medical and scientific literature.<sup>130</sup> The literature supports this timeframe as the first symptoms of GV generally occur approximately one week after immunization. Because GV entails the systemic spread of *vaccinia* virus throughout the body causing an immune response and then the subsequent development of satellite lesions on unvaccinated skin, the onset of symptoms typically does not occur prior to 6 days post vaccination. Cases of GV with an onset occurring outside this timeframe will be considered as non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

##### 5. Eczema *Vaccinatum* (EV)

Eczema *vaccinatum* (EV) is the acute onset of widespread painful vesicles and pustules that occur in individuals who receive the smallpox vaccine and who have a history of atopic dermatitis. Persons with a history of atopic dermatitis are at highest risk for eczema *vaccinatum*. However, not all individuals who have a history of atopic dermatitis and are vaccinated against smallpox with a replication-competent vaccine will go on to develop EV. This phenomenon is well documented in the

medical literature, but is not completely understood.<sup>131</sup>

EV may occur as the result of implantation of the *vaccinia* virus into broken or diseased skin. After implantation, the virus spreads from cell to cell creating extensive lesions. The amount of spread is dependent on the amount of abnormal skin and the individual's immune system.<sup>132</sup> Once viremia is established, lesions can develop in unbroken skin.<sup>133</sup> Positive viral cultures of the lesions are diagnostic of EV.<sup>134</sup> Cases of EV have also been reported in individuals with a history of atopic dermatitis but whose condition appeared to resolve over time and who had intact skin at the time of vaccination.<sup>135 136</sup>

Onset of the characteristic lesions can occur concurrently or shortly after the occurrence of the reaction at the vaccination site. There is generally no visible reaction at the vaccination site before day 3 or 4 post vaccination. On approximately day 3 to 4, a papule forms, which progresses to a vesicle by day 5 to 6, which forms a pustule by day 7 to 9.<sup>137</sup> In EV, these lesions occur in areas away from the primary vaccination site, often initially on non-intact skin, and they may progress to areas of intact skin. EV lesions follow the same Jennerian progression (progression of dermatological lesions through the various stages of development and resolution) as the vaccination site in a vaccine recipient. Confluent (flowing together) or erosive (wearing away) lesions can occur. The rash is often accompanied by fever and lymphadenopathy and affected persons are frequently systemically ill. EV tends to be most severe among first-time replication-competent vaccine recipients, unvaccinated close contacts of vaccine recipients, and young children.<sup>138</sup>

Early diagnosis of EV and the administration of VIGIV, within 1 or 2 days of diagnosis, is helpful in reducing the associated morbidity and

<sup>131</sup> Jennifer L. Reed, Dorothy E. Scott, and Mike Bray. "Eczema *vaccinatum*." *Clinical Infectious Disease* 54(6) (March 15, 2012): 834.

<sup>132</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II. 256–258.

<sup>133</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II. 256–258.

<sup>134</sup> Rosenblatt et al. "Cutaneous Reactions to Vaccinations." 328.

<sup>135</sup> Reed et al. "Eczema *vaccinatum*." 835.

<sup>136</sup> Vincent Fulginiti et al. "Smallpox vaccination: a review, Part I. Background, vaccination technique, normal vaccination and revaccination, and expected normal reactions." *Clinical Infectious Disease* 37. (July 15, 2003): 244.

<sup>137</sup> Fulginiti et al. "Smallpox vaccination: a review Part I." 248.

<sup>138</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 258.

<sup>120</sup> Cono et al. "Smallpox Vaccination and Adverse Reactions." 2.

<sup>121</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II. 261.

<sup>122</sup> Centers for Disease Control and Prevention. "Update: Adverse events following civilian smallpox vaccination, United States, 2003." *Morbidity and Mortality Weekly Report* 52(34) (August 29, 2003): 819.

<sup>123</sup> Poland et al. "The US smallpox vaccination program." 2079–2080.

<sup>124</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 261.

<sup>125</sup> Cono et al. "Smallpox Vaccination and Adverse Reactions." 12–13.

<sup>126</sup> Rosenblatt et al. "Cutaneous Reactions to Vaccinations." 328.

<sup>127</sup> Kennedy et al. "Smallpox and *vaccinia*." 738.

<sup>128</sup> Poland et al. "The US smallpox vaccination program." 2079.

<sup>129</sup> Claudia Vellozzi et al. "Generalized *vaccinia* progressive *vaccinia*, and eczema *vaccinatum* are rare following smallpox (*vaccinia*) vaccination: United States surveillance, 2003." *Clinical Infectious Disease* 41(5) (September 1, 2005): 689.

<sup>130</sup> Cono et al. "Smallpox Vaccination and Adverse Reactions." 12.

mortality.<sup>139 140</sup> The fatality rate for those experiencing EV ranges from 5 to 40 percent both with and without treatment, respectively.<sup>141 142</sup> Complications of EV include secondary infections caused by fungus and bacteria, septic shock, and fluid and electrolyte imbalances.<sup>143</sup> Historical reports from the era of universal vaccination for smallpox showed greater rates for developing EV with varying severity.<sup>144</sup> In the most recent DoD and HHS smallpox vaccination programs, there were no documented cases of EV in primary vaccine recipients.<sup>145</sup> This is attributed to improved pre-screening of potential smallpox vaccine recipients and excluding those thought to be at risk of developing EV. Attenuated smallpox vaccine may reduce the risk of developing EV in those individuals with a history of atopic dermatitis. However, the potential of developing EV from receiving the smallpox vaccine must be weighed against the potential of being exposed to the smallpox virus and then developing smallpox infection.<sup>146</sup>

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and EV is a serious physical injury that may be directly caused by the administration or use of the replication-competent smallpox vaccine.<sup>147 148 149</sup> EV is proposed to be added to the Table with an onset interval for the first symptom or manifestation of onset of 3–21 days after vaccination. Three days would be the minimum time to mount an immune response and develop symptoms. With treatment, using VIGIV, no additional lesions should occur after 21 days.

Although EV can occur as the result of inadvertent transfer of the *vaccinia* virus to non-*vaccinia* vaccine recipients,<sup>150</sup> for the purpose of this regulation, the inadvertent or intentional inoculation of other persons by the vaccine recipient and the subsequent development of EV is not

considered a covered injury. Only those individuals who actually were administered the smallpox vaccine will be eligible for benefits.<sup>151</sup>

#### 6. Progressive *Vaccinia*

Progressive *vaccinia* (PV) also known as *vaccinia necrosum*, *vaccinia gangrenosa* or disseminated *vaccinia*, is a rare, severe, and potentially fatal complication of receiving replication-competent smallpox vaccine. Its frequency of occurrence is estimated to be 3 to 5 cases per million vaccinated.<sup>152</sup> PV results when a vaccination site fails to heal after 14 to 21 days in the presence of a minimal inflammatory response and when *vaccinia* virus replication persists.<sup>153</sup> Of all of the adverse skin conditions associated with smallpox vaccine, PV is the most severe and life threatening.<sup>154</sup> PV occurs as the result of a T-cell deficiency within the immune system of the vaccine recipient while the "B" cell function remains intact. As a result, the progression and manifestation of this condition are limited to the skin without viremic spread.<sup>155</sup> The skin surrounding the vaccination site becomes *vaccinia* infected due to cell-to-cell spread, the primary lesion (vaccination site) becomes larger in diameter, and secondary metastatic *vaccinia* lesions can occur in areas away from the primary immunization site. As the lesions increase in size, they leave dead skin behind the leading edge of the expanding lesion.

The onset of symptoms and rate of progress are based on the individual level of T-cell deficiency, but with an expected onset of 3 to 21 days after vaccination.<sup>156</sup> Primary lesions that fail to heal by day 21 post-vaccination should be suspicious for PV.<sup>157</sup>

Lesions can appear necrotic (dead), fungated (ulcerated), piled-up, or well demarcated (clear margins). Concomitant bacterial superinfection can also occur. Fungal and parasitic infections have also been documented in patients diagnosed with PV. Progression of PV can lead to toxic or septic shock and disseminated intravascular coagulation (DIC), a blood clotting disorder, generally ending with

death.<sup>158</sup> A diagnosis of PV is made by the appearance and progression of the lesions at the primary vaccination site and other subsequent satellite lesions.<sup>159</sup> Management of PV should include aggressive therapy with VIGIV. Cidofovir has been included in some recommendations as a potential second-line agent that might be used under an investigational protocol if the patient does not respond to VIGIV or if supplies of VIGIV are exhausted. In addition, case management should include intensive monitoring, and tertiary-level supportive care.<sup>160</sup> More recently, recommendations<sup>161</sup> have been posted suggesting tecovirimat (recently approved as a smallpox treatment) brincidofovir, and cidofovir as antivirals that might be used under certain circumstances to treat certain vaccine complications if treatment with VIGIV alone is inadequate or if VIGIV is not readily available. Tecovirimat and brincidofovir were used as part of multifactorial interventions in a case of PV though the contribution of any one intervention to the patient's outcome could not be assessed.<sup>162</sup>

During the most recent DoD and HHS smallpox vaccination program where approximately 770,000 individuals were vaccinated, using replication-competent vaccines, there were no documented cases of PV. The study results indicate improved screening techniques prior to delivering the vaccine and withholding vaccinations from those at greatest risk of developing an adverse event contributed to this result.<sup>163</sup>

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and PV is a serious physical injury that may be directly caused by the administration or use of the replication-competent smallpox vaccine.<sup>164 165 166 167</sup> PV is proposed to be added to the Table with an onset interval for the first symptom

<sup>139</sup> Cono et al. "Smallpox vaccination and adverse reactions." 13.

<sup>140</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 256–258.

<sup>141</sup> Rosenblatt et al. "Cutaneous reactions to vaccinations." 328.

<sup>142</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 256.

<sup>143</sup> Rosenblatt et al. "Cutaneous reactions to vaccinations." 328.

<sup>144</sup> Reed et al. "Eczema *vaccinatum*." 832.

<sup>145</sup> Poland et al. "The US smallpox vaccination program." 2079.

<sup>146</sup> Reed et al. "Eczema *vaccinatum*." 838.

<sup>147</sup> Cono et al. "Smallpox vaccination and adverse reactions." 13.

<sup>148</sup> Rosenblatt et al. "Cutaneous reactions to vaccinations." 328.

<sup>149</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 256–258.

<sup>150</sup> Lane et al. "Adverse events." 191.

<sup>151</sup> 42 CFR part 110.

<sup>152</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 253.

<sup>153</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>154</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>155</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>156</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>157</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>158</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

<sup>159</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 265.

<sup>160</sup> Cono et al. "Smallpox vaccination and adverse reactions." 14.

<sup>161</sup> <https://www.cdc.gov/smallpox/clinicians/vaccine-medical-management6.html>.

<sup>162</sup> E. Lederman et al. "Progressive *vaccinia*: Case description and laboratory-guided therapy with *vaccinia* immune globulin, ST-246, and CMX001." *Journal of Infectious Disease*, 206 (November 1, 2012) 1372–1385.

<sup>163</sup> Poland et al. "The US smallpox vaccination program." 2079.

<sup>164</sup> Cono et al. "Smallpox vaccination and adverse reactions." 13.

<sup>165</sup> Lane et al. "Adverse Events." 191.

<sup>166</sup> Rosenblatt et al. "Cutaneous reactions to vaccinations." 328.

<sup>167</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 263.

or manifestation of onset of 3–21 days after vaccination.

#### B. The Post-Vaccinial Encephalopathy (PVE), Encephalitis, and Encephalomyelitis Spectrum (PVEM)

PVEM is a spectrum of overlapping conditions that includes post-*vaccinia* encephalopathy, encephalitis, and encephalomyelitis, and, for the purposes of this NPRM, is treated as one injury. Encephalopathy, encephalitis, and encephalomyelitis are inflammations of the parenchyma (the functional tissue of an organ) of the central nervous system, the brain and spinal cord generally due to an infectious or post-infectious etiology. These conditions have been reported after receiving the replication-competent smallpox vaccine and have been causally associated with the replication-competent smallpox vaccine.<sup>168</sup> In addition to the replication-competent smallpox vaccine, more than one hundred viruses have been identified as causing encephalitis, and there are no known predictors for those individuals who will go on to develop encephalitis.<sup>169</sup> Of the conditions on the PVEM spectrum, the literature discusses PVE in depth.

In early vaccination campaigns in Great Britain, Europe, and the United States, cases of PVE were reported after receipt of the smallpox vaccine with varying rates of occurrence based on the type of vaccine used by each country.<sup>170 171</sup> The Great Britain incidence of PVE decreased when they changed the type of replication-competent smallpox vaccine they were using to the Lister strain.<sup>172 173</sup> Rates for PVE in Dutch military recruits were as high as 1 in 4,000 vaccinated, whereas in U.S. military recruits, the rate was estimated to be 1 in 100,000 vaccinated.<sup>174</sup> Statistics from the 1960s in the U.S. suggest the rates of PVE could range from 9 to 59 in 1 million vaccinated.<sup>175</sup> Among the more than 700,000 DoD vaccine recipients, three

cases of PVE occurred.<sup>176</sup> Complications from vaccination were much less frequent in previously vaccinated individuals than those who were *vaccinia*-naïve.

Literature indicates there are two subtypes of PVE associated with the smallpox vaccine. First, microglial encephalitis results in the demyelination of the subcortical white matter and clinically resembles acute disseminated encephalomyelitis (ADEM). Second, the cytotoxic form presents with cerebral edema (swelling of the brain), infiltration of white blood cells into the meningeal tissues and hemorrhages around the small blood vessels of the brain.<sup>177 178</sup>

A confirmed diagnosis of PVE requires demonstration of CNS inflammation by histopathology or neuroimaging. A suspected diagnosis is made by clinical features alone.<sup>179 180</sup> The clinical symptoms of PVE generally begin 7 to 14 days post-vaccination. Clinically significant findings may be identified on magnetic resonance imaging (MRI) as early as day 5 post-vaccination with multifocal lesions noted throughout the white matter. Cerebral spinal fluid may be positive for *vaccinia* virus, but this does not universally occur. The initial symptoms of PVE may include headache, vomiting, drowsiness, and fever in mild cases. Severe cases may include these same symptoms, as well as paralysis, incontinence, urinary retention, coma, and seizures. There is no effective treatment for PVE, only supportive care. Approximately 25 percent of patients with PVE will die, and 1/3 of the survivors will experience a broad spectrum of residual neurological conditions that include mental impairment and paralysis.<sup>181 182</sup>

The pathophysiology of CNS adverse reactions attributed to replication-competent smallpox vaccination is not completely understood, but it is thought to represent some type of autoimmune process involving the white matter of

the CNS.<sup>183</sup> Direct infection of the CNS by *vaccinia* virus may result in acute cytotoxic neuronal damage and inflammation. However, laboratory evidence of virus replication is often lacking; inflammatory changes are attributed instead to immune response mechanisms.

Histopathological findings of PVE are often similar to those found with acute disseminated encephalomyelitis (or post-infectious encephalomyelitis). However, a diagnosis of acute disseminated encephalomyelitis is characterized by a longer interval of onset after immunization and by MRI findings suggesting acute demyelination.<sup>184</sup> Demyelination occurs as the result of an immune response in which the membrane that covers the nerves begins to breakdown. Demyelination interferes with nerve signal transmission.

PVE is diagnosed by excluding other causes of the symptoms prior to associating them with the vaccine.<sup>185</sup> Cerebral spinal fluid examination may show an increased number of white blood cells and increased protein, but this is not always the case.<sup>186</sup>

Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and PVEM (including PVE, encephalitis, and encephalomyelitis) are serious physical injuries that may be directly caused by the administration or use of the replication-competent smallpox vaccine. The expected onset interval for the first symptom or manifestation is 5–14 days after vaccination.<sup>187 188</sup>

#### C. Vaccinial Myocarditis, Pericarditis or Myopericarditis (MP)

For purposes of the NPRM, MP is *vaccinia* myocarditis, pericarditis, or myopericarditis. Myocarditis is an inflammation of the heart muscle without blockage of the coronary arteries, and pericarditis is an inflammation of the fibrous sack surrounding the heart muscle. Myopericarditis is the term used when the two conditions occur

<sup>168</sup> Cornelius Van Dam et al. "Severe post *vaccinia* encephalitis with acute disseminated encephalomyelitis: recovery with early intravenous immunoglobulin, high-dose steroids, and *vaccinia* immunoglobulin." *Clinical Infectious Disease* 48(4) (February 15, 2009): e47.

<sup>169</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

<sup>170</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

<sup>171</sup> Kennedy et al. "Smallpox and *vaccinia*." 738.

<sup>172</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

<sup>173</sup> Kennedy et al. "Smallpox and *vaccinia*." 738.

<sup>174</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

<sup>175</sup> Van Dam et al. "Severe post *vaccinia* encephalitis." e47.

<sup>176</sup> Van Dam et al. "Severe post *vaccinia* encephalitis." e47.

<sup>177</sup> Van Dam et al. "Severe post *vaccinia* encephalitis." e47.

<sup>178</sup> James J. Sejvar et al. "Neurologic adverse events associated with smallpox vaccination in the United States, 2002–2004." *Journal of the American Medical Association* 294(21) (December 7, 2005): 2744.

<sup>179</sup> Cono et al. "Smallpox vaccination and adverse reactions." 15.

<sup>180</sup> Stuart N. Isaacs and Harvey M. Friedman. "Vaccinia virus as the smallpox vaccine." *UpToDate* (June 03, 2015): 5.

<sup>181</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

<sup>182</sup> Kennedy et al. "Smallpox vaccines for biodefense." 738.

<sup>183</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 268.

<sup>184</sup> John Neff et al. "Monitoring the safety of a smallpox vaccination program in the United States: report of the joint smallpox vaccine safety working group of the advisory committee on immunization practices and the armed forces epidemiological board." *Clinical Infectious Disease* 46 (Supplement 3) (2008): S261.

<sup>185</sup> Cono et al. "Smallpox vaccination and adverse reactions." 15.

<sup>186</sup> Cono et al. "Smallpox vaccination and adverse reactions." 14.

<sup>187</sup> Cono et al. "Smallpox vaccination and adverse reactions." 14.

<sup>188</sup> Fulginiti et al. "Smallpox vaccination: a review, Part II." 267.

simultaneously. Severe cases of myopericarditis can result in dilated cardiomyopathy (DCM) characterized by an enlarged and weakened heart muscle. Myocarditis and pericarditis can cause palpitations, shortness of breath, fever, sweats, or chest pain and can be diagnosed by an abnormal electrocardiogram (ECG), imaging studies (echocardiogram), histopathology, or elevated cardiac enzymes. Myocardial dysfunction in cases of myopericarditis may result from direct viral injury or from a triggered immune response that targets the myocardium or pericardium. In mouse models of infectious myocarditis, the virus is only rarely isolated from the myocardium. The absence of direct infection of the myocardium suggests immune-mediated injury as the predominant pathogenic mechanism.

Inflammatory processes can be caused by a number of viral infections and autoimmune disorders and have *sequelae* ranging from self-limiting asymptomatic disease to DCM, resulting in fulminant (severe and sudden) congestive heart failure and possibly death. Myocarditis is blamed for causing up to 20 percent of all cases of sudden death among military recruits. Although cardiac events after the administration or use of replication-competent smallpox vaccine were reported in the literature before 2003, they were largely unrecognized during the worldwide eradication campaign and were thought to occur very rarely. Only six cases of cardiac complications after replication-competent smallpox vaccination with the New York City Board of Health (NYCBH) strain of *vaccinia* were reported in the United States before 2003.<sup>189</sup> In the past decade, cardiac complications following live *vaccinia* vaccination have been detected more often due to the availability of more sophisticated diagnostic techniques. Cardiac complications resulting from live *vaccinia* vaccination range in severity from mild to fatal and include myocarditis, pericarditis, arrhythmias, and DCM.<sup>190</sup>

Of 730,580 U.S. Armed Forces personnel vaccinated with the discontinued vaccine, Dryvax, 86 cases of myopericarditis with moderate or severe clinical presentation occurred in otherwise healthy vaccine recipients.<sup>191</sup>

<sup>189</sup> Juliette Morgan et al. "Myocarditis, pericarditis, and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, January–October 2003." *Clinical Infectious Disease* 46 Supplement 3 (2008): S242.

<sup>190</sup> Nalca et al. "ACAM200™: The New Smallpox vaccine." 76.

<sup>191</sup> Poland et al. "The US smallpox vaccination program." 2079.

The single fatal case of myocarditis was in a female. The report calculated a rate of myopericarditis 7.5-fold higher than the expected background rate among 347,516 primary vaccine recipients with the expected rate being 2.16 per 100,000 vaccinated as opposed to the observed rate of 16.11 per 100,000 vaccinated.<sup>192</sup>

Of 37,901 HHS vaccine recipients, 21 civilians were diagnosed with mild cases of myopericarditis (at a rate of 554 per million), all of which resolved without further complication.<sup>193</sup> Additionally, four DoD and three HHS cases of DCM occurred among previously healthy subjects, with two requiring heart transplants.<sup>194</sup>

The occurrence of the vast majority of cardiac adverse events within 30 days of the smallpox vaccination, and clustering within 7–12 days post-vaccination, provides compelling, reliable, valid, medical and scientific evidence of a direct link between vaccination with live *vaccinia* virus and incidence of *vaccinia* associated cardiac complications consisting of *vaccinia* myocarditis, pericarditis and myopericarditis (MP). Based on a review of the medical and scientific literature, the Program's evidence standard has been met, and MP is a serious physical injury that may be directly caused by the administration or use of the replication-competent smallpox vaccine. Therefore, MP is proposed to be added to the Table with an onset interval for the first symptom or manifestation of 0–21 days after vaccination.<sup>195</sup> <sup>196</sup> Although clustering occurs 7–12 days post-vaccination, symptoms may begin within 24 hours of vaccination.<sup>197</sup> The literature does not indicate that cardiac manifestations have occurred beyond 21 days post-vaccination based on immune response.<sup>198</sup>

Anecdotal reports of ischemic heart disease, such as angina pectoris or myocardial infarction (heart attacks), occurring in a few individuals following receipt of the smallpox vaccine have

<sup>192</sup> Poland et al. "The US smallpox vaccination program." 2079.

<sup>193</sup> Morgan et al. "Myocarditis, pericarditis, and dilated cardiomyopathy." S246.

<sup>194</sup> Neff et al. "Monitoring the safety of a smallpox vaccination program." S262.

<sup>195</sup> Centers for Disease Control and Prevention, "Cardiac adverse events following smallpox vaccination—United States, 2003." *Morbidity and Mortality Weekly Report* 52(12) (March 28, 2003): 250.

<sup>196</sup> Dimitri C. Cassimatis et al. "Smallpox vaccination and myopericarditis: a clinical review." *Journal of the American College of Cardiology* 43(9) (May 5, 2004): 1505.

<sup>197</sup> Centers for Disease Control and Prevention, "Cardiac adverse." 3.

<sup>198</sup> Lane et al. "Adverse events." 190.

been published in the literature.<sup>199</sup> However, these reports are not compelling, reliable, valid, medical and scientific evidence demonstrating that the replication-competent smallpox vaccine directly causes ischemic heart disease. Therefore, the Secretary does not propose to add ischemic heart disease to the Table, and claims for this injury will be considered non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

#### Other Conditions of Special Interest to Smallpox Vaccination

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

##### A. Secondary Infection

Secondary infections resulting from loss of skin integrity because of receiving a replication-competent vaccine are common. All instances of secondary infection will be considered non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

##### B. Serum Sickness

Serum sickness is a systemic, immune complex-mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins. It is a classic example of a type III hypersensitivity reaction caused by antigen-antibody complexes. The symptoms of serum sickness generally begin 7–12 days after injection of the foreign material, but may appear as late as 3 weeks afterward. Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Reactions originally described as serum sickness—like are now attributed to drug allergy, triggered in particular by antibiotics (*e.g.*, penicillin, cefaclor), and, rarely, to other agents, such as human immune globulin, humanized monoclonal antibodies, and insect venom. The Program is not aware of compelling, reliable, valid, medical and scientific evidence in literature demonstrating the smallpox vaccine directly causes serum sickness. Therefore, the Secretary does not propose to add serum sickness to the

<sup>199</sup> Centers for Disease Control and Prevention, "Cardiac adverse." 2.



Table, and claims for this injury will be considered non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

#### C. Shoulder Injury Related to Vaccine Administration (SIRVA)

Shoulder Injury Related to Vaccine Administration (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. The symptoms occur in the arm in which the vaccine was administered because 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 not a neurological injury.

The smallpox vaccine is administered via a bifurcated (two-pronged) needle into the deep epidermis when administering Smallpox (*Vaccinia*) Vaccine Live, replication-competent or, in the case of Smallpox and Monkeypox Vaccine, Live, Non-replicating replication-deficient, via a subcutaneous (under the skin) injection. Both injections generally take place over the deltoid or triceps muscles. As the smallpox vaccine is administered in a manner other than an intramuscular injection and neither the vaccine nor the needle reaches the internal structures of the shoulder, there is no compelling, reliable, valid, medical and scientific evidence of a direct causal association between the smallpox vaccination and SIRVA. Therefore, the Secretary does not propose to add SIRVA to the Table at this time, and claims for this injury will be considered non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

#### D. Subdeltoid Bursitis

Subdeltoid bursitis (*e.g.*, deltoid bursitis, subacromial bursitis) is an inflammation of the bursa located between the deltoid muscle and the capsule of the shoulder joint. A bursa is a closed fluid-containing sac that reduces friction between bones and tendons, or bones and skin. The bursa extends below the deltoid muscle, and it is possible for a deep injection given high in the shoulder to enter the bursa inadvertently causing an inflammatory bursitis. Subdeltoid bursitis can result in debilitating pain or immobility.

As stated above, the smallpox vaccine is administered via a bifurcated (two-pronged) needle into the deep epidermis or via a subcutaneous (under the skin) injection. Both injections generally take place over the deltoid or triceps

muscles. Since the smallpox vaccine is administered in a manner other than an intramuscular injection and neither the vaccine nor the needle reaches the subdeltoid space, there is no compelling, reliable, valid, medical and scientific evidence of a direct causal association between the smallpox vaccination and subdeltoid bursitis. Therefore, the Secretary does not propose to add subdeltoid bursitis to the Table at this time. However, claims for this injury will be considered non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

#### E. EM

EM is a typically mild and self-limiting mucocutaneous reaction characterized by target lesions on the skin and mucous membranes.<sup>200</sup> Historically, EM comprised a disease spectrum that was classified by increasing degrees of severity. The spectrum included a minor form (EM minor) and a more severe or major form (EM major), SJS, TEN completed the spectrum as the most severe form of the disease. The unifying clinical features of these diseases that placed them under the EM spectrum were target lesions, similar mucosal features and epidermal necrosis. However, current evidence suggests that EM, SJS, and TEN are not in the same continuum. SJS and TEN are the same disease differing only in the area of involvement and severity of systemic findings. EM and SJS/TEN differ in their cause, clinical presentation, pathology and therapy.<sup>201</sup>

EM is almost always infectious in origin, with herpes simplex virus (HSV) as the infectious agent in 70–80 percent of cases.<sup>202</sup> Drugs have been estimated to induce EM in less than 10 percent of cases. The most common precipitators are non-steroidal anti-inflammatory drugs, sulfonamides, anti-epileptics and antibiotics.<sup>203</sup> The interpretation of the literature on drug-induced EM is complicated by previous classification of SJS/TEN as part of the EM spectrum. This is true for studies involving smallpox and EM. A 1968 study noted that EM accounted for 13 percent of all complications associated with the replication-competent smallpox vaccine or a rate of 165 cases of EM per 1

million persons vaccinated.<sup>204</sup> In 1977, an Australian study of 938 adverse events related to the replication-competent smallpox vaccine identified 87 cases of EM, which represented 9.3 percent of all of the reported complications.<sup>205</sup> Neither of these studies specified the severity of EM or mentioned SJS/TEN.

EM most often manifests as both skin and mucosal lesions, but may also exhibit skin lesions alone. Occasionally, EM presents only with mucous membrane involvement. Skin lesions most commonly appear in a symmetrical distribution on the extremities (acral distribution) and spread centripetally (toward the center). Skin lesions are usually asymptomatic though some patients experience itching and burning. Oral mucous lesions are common. Mucosal lesions can also be found in other sites (such as genital area and eyes) but are less common.<sup>206</sup> In most patients, EM is a transient condition that spontaneously resolves without long-term morbidity. EM lesions usually appear over the course of 3 to 5 days and resolve in approximately 2 weeks. Skin lesions do not scar, but post-inflammatory hyperpigmentation may remain months after resolution. Rarely, patients experience complications, such as fluid and electrolyte abnormalities, or those with eye involvement can have scarring and visual impairment.<sup>207</sup>

Based on a review of the medical and scientific literature, EM is a physical injury that may be directly caused by the use of the replication-competent smallpox vaccine. However, since EM is typically a mild and self-limiting condition, it is not considered a serious injury based on the Program's standards. Therefore, the Secretary does not propose to add EM to the Table and claims for this injury will be considered non-Table injuries and evaluated on a case-by-case basis, based on the Program's evidence standard.

#### Non-Vaccine Countermeasures

In addition to the smallpox vaccine, there are other potential countermeasures that might be used either for smallpox or to treat adverse

<sup>204</sup> J. Michael Lane et al. "Complications of smallpox vaccination, 1968: Results of ten statewide surveys." *Journal of Infectious Disease* 122(4) (October 1, 1970): 305.

<sup>205</sup> B.J. Feery, "Adverse reactions after smallpox vaccinations." *Medical Journal of Australia* 2 (August 6, 1977): 181.

<sup>206</sup> J. Clark Huff, William Weston, and Marcia Tonnesen. "Erythema multiforme: A critical review of characteristics, diagnostic criteria and causes." *Journal of the American Academy of Dermatology* 8(6) (June 1983): 763–775.

<sup>207</sup> Huff et al. Erythema multiforme, 767–768.

<sup>200</sup> P. Michele Williams and Robert J. Conklin.

"Erythema multiforme: A review and contract from Stevens-Johnson syndrome/toxic epidermal necrolysis." *Dental Clinics of North America* 2005; 49: 67–76.

<sup>201</sup> Williams et al. "Erythema multiforme." 68.

<sup>202</sup> Williams et al. "Erythema multiforme." 68.

<sup>203</sup> David Wetter. "Erythema multiforme: Pathogenesis, clinical features and diagnosis." 2019 UpToDate.

events following vaccination including *vaccinia* immunoglobulin intravenous (VIGIV), cidofovir, tecovirimat, and brincidofovir. The Secretary proposes to add VIGIV, cidofovir, tecovirimat and brincidofovir to the Table as covered countermeasures.

#### *Vaccinia* Immunoglobulin Intravenous (VIGIV)

*Vaccinia* immunoglobulin intravenous (VIGIV) is a medication that is used to treat some of the complications (adverse side effects) of receiving the smallpox vaccine. It is not indicated for treatment of smallpox infection. Immunoglobulins are a class of medication used to treat many autoimmune diseases and primary immune deficiency, infections, and complications from the smallpox vaccine. Although the clinical use of, and experience with, VIGIV is limited, this product is derived in the same way as other types of immunoglobulins and is thought to have the same side effects and potential complications. As a result, the possible adverse side effects are thought to be similar to other immunoglobulins (class effect).

VIGIV is harvested from the plasma of persons vaccinated with *vaccinia* virus and who have had a sufficient immune response to produce antibodies in an effort to prevent smallpox infection. Individuals who were vaccinated, as part of their immune response, develop antibodies after vaccination, and those antibodies are collected within donated plasma. The plasma is processed into VIGIV. VIGIV may help in ameliorating some complications of *vaccinia* immunization including eczema *vaccinatum*, progressive *vaccinia*, or severe generalized *vaccinia*. It may also be used to treat autoinoculation to the eye or eyelid. VIGIV is not thought to be effective in treating PVE. The current VIGIV product is administered intravenously.

The following injuries have been associated with the use of immunoglobulins: (a) anaphylaxis, (b) transfusion related acute lung injury, (c) acute renal failure, (d) drug-induced aseptic meningitis, (e) hemolysis, and (f) thrombosis.<sup>208</sup>

#### A. Anaphylaxis

A general discussion of anaphylaxis is in the Anaphylaxis section under the Smallpox Vaccine heading of this NPRM. *Vaccinia* immune globulin is a product derived from human plasma and as such, it contains human proteins

<sup>208</sup> David J. Hamrock, "Adverse events associated with intravenous immunoglobulin therapy." *International Immunopharmacol* 6 (2006): 535.

and antibodies. According to the literature, the use of VIGIV poses a risk of anaphylaxis when used in individuals who have an immunoglobulin A (IgA) deficiency and who go on to form immunoglobulin E (IgE) antibodies against IgA or who have had a previous allergic reaction to human antibody/blood products.<sup>209 210 211</sup> The number of individuals with IgA deficiency varies based on geographic location. Estimates of IgA deficiency range from 1 in 400 to 1 in 3,000 within the U.S. Approximately 30–40 percent of this population also has anti-IgA antibodies. It is possible to reduce the amount of IgA in VIGIV. However, it is not possible to eliminate the antibody, and only very small amounts are necessary to cause anaphylaxis.<sup>212</sup>

Based on the unique nature of the presentation and timing of anaphylaxis, the consensus in the medical community regarding causation based on IgA antibody reactions, and the existing medical literature, anaphylaxis is proposed for inclusion on the Table because it is a serious physical injury that may be directly caused by the administration or use of VIGIV, as supported by the Program's evidence standard. Consistent with the time interval for the first manifestation of anaphylaxis after exposure to a foreign protein and as established in the 1994 IOM clinical case definition of anaphylaxis<sup>213</sup>, the Secretary proposes including anaphylaxis as an injury on the Table with an onset interval of 0–4 hours for the first symptom or manifestation to occur after the administration or use of VIGIV.<sup>214</sup> This timeframe is consistent with other medications or blood derived products that may induce anaphylaxis.<sup>215</sup>

In rare cases of acute anaphylaxis, initial symptoms of the immediate reaction may present up to 12 hours after exposure. A slow evolving late phase hypersensitivity reaction is possible, with an onset that usually begins 4–8 hours after the immediate reaction ends. The medical literature contains reports of late phase onset up

<sup>209</sup> Centers for Disease Control and Prevention (CDC). "Smallpox supplemental fact sheet: Investigational *vaccinia* immune globulin (VIG) information." (March 10, 2009): 1.

<sup>210</sup> Hamrock, "Adverse events associated." 535.

<sup>211</sup> Patrick Chérin et al. "Management of adverse events in the treatment of patients with immunoglobulin therapy: a review of evidence." *Autoimmunity Reviews* 15 (September 16, 2015): 75.

<sup>212</sup> Hamrock, "Adverse events associated." 539.

<sup>213</sup> Institute of Medicine, "Immunization safety review vaccination." 5.

<sup>214</sup> Rugeberg et al. "Anaphylaxis." 5677–5678.

<sup>215</sup> Rugeberg et al. "Anaphylaxis." 5677–5678.

to 72 hours later.<sup>216</sup> The late phase reaction results from a different immunologic mechanism of action. The late phase reaction is part of a biphasic reaction. It is possible for the first immediate hypersensitivity reaction to be relatively mild, unrecognized, or not observed. There may be unusual cases in which the immediate reaction is delayed and/or cases that the immediate reaction is not recognized, with the first apparent manifestation occurring in the late phase. These unusual cases do not meet the requirements to be considered table injuries, and will be evaluated on a case-by-case basis based on the Program's evidence standard.

#### B. Transfusion-Related Acute Lung Injury (TRALI)

Transfusion-related acute lung injury (TRALI) is defined as the onset of respiratory distress within 6 hours after receipt of plasma containing blood products in non-critically ill patients. However, in critically ill patients, the literature states that it may take as long as 72 hours to develop TRALI post-transfusion.<sup>217</sup> As VIGIV is derived from human plasma, VIGIV may precipitate TRALI.

TRALI is a form of non-cardiac pulmonary edema identified by chest x-ray and characterized by severe respiratory distress, pulmonary edema, hypoxia (oxygen starvation), and fever in the presence of normal left ventricular function.<sup>218</sup> A patient experiencing TRALI may require mechanical ventilation to treat the respiratory distress, pulmonary edema, and hypoxia. The use of mechanical ventilation is associated with other injuries and complications, such as lung trauma and tracheal stenosis. TRALI has been identified as a major cause of mortality in those individuals receiving plasma-containing transfusions.<sup>219</sup>

Although not completely understood, it is believed that the basis of TRALI rests in a host antibody response to receiving blood products that contain plasma, via transfusion. The host receives a transfer of donor anti-leukocyte antibodies (antibodies that act against the patient's white blood cells) within the plasma and then develops a reaction causing the activation of the endothelial cells and pulmonary neutrophils leading to capillary leakage

<sup>216</sup> Rugeberg et al. "Anaphylaxis: case definition and guidelines." 5677.

<sup>217</sup> Alexander P.J. Vlaar and Nicole P. Juffermans, "Transfusion-related acute lung injury: a clinical review." *Lancet* 328 (May 1, 2013): 984.

<sup>218</sup> "*Vaccinia* immune globulin intravenous (human)" [package insert]. Cangene Corporation, Frederick, MD; (2010): 7.

<sup>219</sup> Vlaar et al. "Transfusion-related acute." 984.

and pulmonary edema (fluid in the lungs).<sup>220</sup> The patient then goes on to develop the classic symptoms of TRALI.<sup>221</sup>

Based on the unique nature of the presentation and timing of TRALI together with consensus in the medical community regarding causation, and the existing scientific and medical literature, the Program's evidence standard has been met, and TRALI is as a serious physical injury proposed to be added to the Table. The Secretary proposes including TRALI as an injury on the Table with an onset interval of 0–72 hours for the first symptom or manifestation to occur after the administration or use of VIGIV.<sup>222</sup>

#### C. Acute Renal Failure

Acute renal failure (ARF) is the sudden inability of the kidneys to filter waste products from the blood stream. This leads to the build-up of waste products and fluid in the body and can lead to a metabolic derangement (chemical imbalance), fluid overload, and death, if not identified and treated early. Acute renal failure can occur over a matter of hours or days and can generally be treated and reversed if diagnosed early. The use of immunoglobulin has been identified as a factor leading to the development of ARF. Between 1985 and 1998, the FDA received 120 reports of patients developing ARF associated with the use of immunoglobulins.<sup>223</sup> The majority of cases of renal failure were associated with the use of immunoglobulins that contained sucrose as a stabilizing agent. The sucrose caused swelling within the kidney and the loss of renal function.<sup>224</sup> VIGIV does not contain sucrose, but rather maltose, which may decrease the incidents of ARF but not eliminate the risk of developing the condition completely.<sup>225</sup>

The factors that may contribute to or precipitate ARF when using VIGIV include: (1) Pre-existing renal insufficiency or use of VIGIV in patients at risk of developing renal insufficiency due to diabetes; (2) age older than 65 years; (3) volume depletion (dehydration); (4) paraproteinemia (high

amount of paraprotein in the blood); (5) sepsis; (6) a faster rate of immunoglobulin infusion; and (7) the concomitant use of nephrotoxic (kidney toxic) drugs.<sup>226 227 228</sup>

Based on existing scientific and medical literature, the Program's evidence standard has been met, and ARF is as a serious physical injury proposed to be added to the Table. The onset of ARF with the use of VIGIV begins with the onset of renal insufficiency, progressing to renal failure, and occurs within 0–10 days after receiving VIGIV. Therefore, the Secretary proposes adding ARF to the Table as an injury associated with the use of VIGIV with a time of onset within 10 days for the first symptom or manifestation to occur after the administration or use of VIGIV.<sup>229 230 231 232 233</sup>

#### D. Drug-Induced Aseptic Meningitis

Drug-induced aseptic meningitis (DIAM) is an inflammation of the linings of the brain (meninges) that is not caused by a bacteria or virus, but by a drug or medication. The symptoms of meningitis include severe headache, nuchal (neck) rigidity, drowsiness, fever, photophobia (light sensitivity), painful eye movements, nausea, and vomiting. Discontinuation of the medication leads to a resolution of the symptoms. It is postulated that DIAM occurs because of an immunological hypersensitivity reaction to a specific medication.<sup>234</sup> In the case of immunoglobulins, DIAM may be precipitated by the immunologically active components within the plasma or because of the stabilizers used within

the product.<sup>235</sup> The symptoms of DIAM may reoccur with another exposure to the offending agent. Drugs that can cause DIAM include immunoglobulins, non-steroidal anti-inflammatory drugs (NSAIDs), drugs delivered via the intrathecal route (into the spinal canal) and antibiotics.<sup>236 237</sup>

The incidence of DIAM is estimated to occur in approximately 1 percent of patients receiving immunoglobulins. Most patients who experience immunoglobulin-associated DIAM recover completely within 5 days of stopping the medication and without *sequelae* or permanent injury.<sup>238</sup> It appears that individuals with a history of migraine headaches have an increased risk for developing immunoglobulin associated DIAM.<sup>239</sup> In addition, the dose delivered may contribute to the development of DIAM. Doses of immunoglobulin given at 2 g/kg/cycle appeared to precipitate aseptic meningitis when compared to smaller doses.<sup>240</sup>

Based on existing scientific and medical literature, the Program's evidence standard has been met, and DIAM is a serious physical injury proposed to be added to the Table. As noted by Jolles et al., the anticipated time of onset for the first symptom or manifestation to occur is within 48 hours after the administration or use of the first dose of VIGIV and no more than 48 hours after the administration or use of the last dose of VIGIV.<sup>241</sup> Therefore, the Secretary proposes adding DIAM within this time of onset interval as a Table injury.

#### E. Hemolysis

Hemolysis is the physical breakdown of red blood cells (RBCs) either through natural attrition or as caused by external factors. An RBC's natural life cycle ranges from 110 to 120 days. This cycle coincides with the production of RBCs within the bone marrow, which maintains homeostasis (steady state). The RBC's function is to transport oxygen throughout the body in the hemoglobin contained within the RBCs. Additionally, the RBCs contain the majority of the body's potassium stores. When RBCs break down faster than their natural life cycle, the bone marrow

<sup>226</sup> Cono et al. "Smallpox vaccination and adverse reactions." 18.

<sup>227</sup> *Vaccinia* immune globulin intravenous package insert.

<sup>228</sup> Hamrock, "Adverse events associated." 538.

<sup>229</sup> H.I.A. Sati, R. Ahya and H.G. Watson, "Incidence and associations of acute renal failure complicating high-dose intravenous immunoglobulin therapy." *British Journal of Haematology* 113 (January 4, 2001): 557.

<sup>230</sup> Doreen Bianchi-Winward and Mary T. Brophy, "Acute renal failure after administration of intravenous immunoglobulin: review of the literature and case report." *Pharmacotherapy* 15(6) (1995): 766.

<sup>231</sup> Yelena M. Itkin and Toby C. Trujillo, "Intravenous immunoglobulin-associated acute renal failure: case series and literature review." *Pharmacotherapy* 25(6) (2005): 889.

<sup>232</sup> N. Gupta et al. "Intravenous gammaglobulin-associated acute renal failure." *American Journal of Hematology* 66 (2001): 1552.

<sup>233</sup> Thomas G. Cantu et al. "Acute renal failure associated with immunoglobulin therapy." *American Journal of Kidney Disease* 25(2) (February 1995): 228.

<sup>234</sup> Stephen Jolles, W.A. Carrock-Sewell and Carol Leighton, "Drug-induced aseptic meningitis." *Drug Safety* 3 (March 2000): 216.

<sup>235</sup> Jolles et al. "Drug-induced." 221.

<sup>236</sup> German Moris and Juan Carlos Garcia-Monoco, "The challenge of drug-induced aseptic meningitis revisited." *Journal of the American Medical Association* 174(9) (September 2004): 1511.

<sup>237</sup> Jolles et al. "Drug-induced." 217.

<sup>238</sup> Cherin et al. "Management of adverse events." 75.

<sup>239</sup> Hamrock, "Adverse events associated." 537.

<sup>240</sup> Hamrock, "Adverse events associated." 537.

<sup>241</sup> Jolles et al. "Drug-induced." 221.

<sup>220</sup> Vlaar et al. "Transfusion-related acute." 985.

<sup>221</sup> Robert S. Makar, Amy Powers and Christopher Stowell, "Reducing transfusion-related acute lung injury risk: evidence for and approaches to transfusion-related acute lung injury mitigation." *Transfusion Medicine Reviews* 26(4) (October 2012): 305.

<sup>222</sup> Vlaar et al. "Transfusion-related acute." 984.

<sup>223</sup> M. Jennifer Cheng and Colleen Christmas, "Special consideration with the use of intravenous immunoglobulin in older persons." *Drugs Aging* 28(9) (2011): 732.

<sup>224</sup> Hamrock, "Adverse events associated." 538.

<sup>225</sup> Hamrock, "Adverse events associated." 538.

cannot produce new cells fast enough to maintain RBC levels, resulting in anemia. The body is unable to transport oxygen effectively, and the person develops hypoxia (oxygen starvation). Additionally, the rapid breakdown of the cell releases large amounts of potassium into the blood stream, which can cause abnormal heart rhythms. Breakdown of RBCs also releases large amounts of hemoglobin which may result in renal damage. In severe cases of hemolysis, a blood transfusion may be required to correct the resulting anemia.<sup>242</sup>

Conditions that contribute to hemolysis include immune reactions, infections, toxins, poisons, hemodialysis, and medications. Immunoglobulins cause hemolysis in certain individuals due to blood group antibodies. These antibodies cause RBCs to be coated with immune globulin, which leads to an anti-globulin reaction and hemolysis.<sup>243</sup> Individuals with non-group O type blood may be more susceptible to hemolysis in conjunction with the use of immunoglobulin.<sup>244</sup> There may also be a relationship between hemolysis and the total accumulative amount of immunoglobulin received by an individual. Individuals who have received a larger accumulative dose of immunoglobulin had a greater likelihood of developing hemolysis.<sup>245</sup>

Based on existing scientific and medical literature, the Program's evidence standard has been met, and development of hemolysis after the use or administration of VIGIV is a serious physical injury proposed to be added to the Table. As noted by Berg, et al., the onset of hemolysis associated with the use of VIGIV is anticipated to develop between 12 hours and 14 days from the administration of VIGIV.<sup>246 247</sup>

Therefore, the Secretary proposes adding hemolysis as a Table injury with a time of onset from 12 hours to 14 days for the first symptom or manifestation to occur after the administration or use after of VIGIV.<sup>248</sup>

<sup>242</sup> Cherin et al. "Management of adverse events." 78.

<sup>243</sup> *Vaccinia* immune globulin intravenous package insert.

<sup>244</sup> Cherin et al. "Management of adverse events." 78.

<sup>245</sup> Cherin et al. "Management of adverse events." 78.

<sup>246</sup> Zohra Daw et al. "Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis." *Transfusion* 48(8) (August 2008): 1598.

<sup>247</sup> Scott Winiacki et al. "Complementary use of passive surveillance and mini-sentinel of better characterize hemolysis after immune globulin." *Transfusion* 55 (July 2015): s30.

<sup>248</sup> Roger Berg et al. "Hemolytic events associated with intravenous immune globulin therapy: a

Other Conditions of Special Interest to VIGIV

#### A. Thrombotic Events

A thrombotic event involves the formation of a blood clot within a blood vessel. This clot restricts flow of blood back to the heart and lungs in the area distal to (behind) the clot. Once formed the clot poses a risk of dislodging, becoming an embolism, floating to a smaller blood vessel in the brain, lung, or heart and causing tissue death in one of these areas resulting in a stroke, pulmonary embolism, or heart attack, respectively. People with a history of atherosclerosis (blood vessel disease), multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders (blood clotting disorders), prolonged periods of immobilization and known or suspected hyperviscosity (thickening of the blood) are at increased risk of thrombus formation.<sup>249 250 251 252 253</sup> Additional risk factors for forming a thrombus include smoking, obesity, pregnancy, and the use of oral contraceptives.<sup>254</sup>

Medical and scientific literature supports an association between the use of VIGIV and thrombotic events. There are a number of predisposing factors, which may increase an individual's risk of developing a thrombus in association with the use of immunoglobulins. Since multiple external factors play a role in the development of a thrombus, a timeframe for the onset of a thrombotic event after the use of VIGIV that meets the Program's evidence standard cannot be determined. Therefore, claims for thrombotic events associated with the use of VIGIV will be considered a non-table injury and evaluated on a case-by-case basis based on the Program's evidence standard.

#### B. Interference With Blood Glucose Testing

As noted above, VIGIV uses maltose, a disaccharide or sugar, in its

qualitative analysis of 263 cases reported to four manufacturers between 2003 and 2012." *Transfusion* 55 (July 2015): S40.

<sup>249</sup> Cangene Corporation, "*Vaccinia* immune globulin intravenous package insert." (2005): 6.

<sup>250</sup> Hamrock, "Adverse events associated." 538–539.

<sup>251</sup> Cherin et al. "Management of adverse events." 76–77.

<sup>252</sup> Gregory W. Daniel et al. "Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010." *Transfusion* 52 (October 2012): 2117.

<sup>253</sup> Cheng et al. "Special considerations with the use." 733.

<sup>254</sup> Mayo Clinic, "Diseases and conditions-Deep vein thrombosis (DVT). (August 10, 2018). Available from <https://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/symptoms-causes/syc-20352557>.

composition. Some forms of blood glucose monitoring equipment may falsely identify the presence of maltose as an elevated blood glucose level. Treating this false reading by providing supplemental insulin could result in hypoglycemia (low blood sugar) in patients receiving VIGIV.<sup>255</sup>

There is compelling, reliable, valid, medical and scientific evidence that the use of VIGIV may lead to false measurements of elevated blood glucose levels if the appropriate testing methods are not used. However, these falsely elevated blood glucose levels in and of themselves are not harmful unless treated inappropriately. Since false test results alone do not meet the Program's definition of a serious injury, the Secretary does not propose adding interference with blood glucose testing as a Table injury with the use of VIGIV. However, claims of hypoglycemia resulting from the treatment of falsely elevated blood glucose levels will be considered a non-Table injury and will be evaluated on a case-by-case basis based on the Program's evidence standard.

#### C. Infectious Contamination

As immunoglobulins generally and VIGIV specifically are products derived from human blood plasma, there is a risk, however slight, of the product being contaminated with human viruses. Prior to donating plasma, all donors are tested for certain infectious diseases. Additionally, during the processing of plasma into VIGIV, it undergoes treatment to remove and or kill infectious organisms. It is possible, however, that an individual could potentially obtain a blood-borne infection from receiving VIGIV.<sup>256</sup>

The medical literature supports the theoretical possibility of infectious contamination of VIGIV; however, as there is no compelling, reliable, valid, medical or scientific evidence linking VIGIV to a specific infection meeting the Program's definition of a serious injury, each claim for unintended infections caused by the receipt of VIGIV will be considered on a case-by-case basis based on the Program's evidence standard.

#### Cidofovir

Cidofovir is a medication that is only approved to treat cytomegalovirus retinitis in HIV-infected persons. However, it has been included in some recommendations as a potential second-line agent that might be used under an

<sup>255</sup> Cangene Corporation, "*Vaccinia* immune globulin intravenous package insert." (2005): 6.

<sup>256</sup> Cangene Corporation, "*Vaccinia* immune globulin." 7–8.

investigational protocol when treatment with VIGIV is not sufficient or not available to treat adverse events related to the smallpox vaccine, based on studies in animals.<sup>257</sup> It might sometimes be used (preferably under an IND protocol) for serious vaccine adverse events, such as eczema vaccinatum or progressive *vaccinia*, if other potential countermeasures are not available or not working. Reports indicate some activity in the laboratory against *vaccinia* and variola viruses, but there is currently no human data showing efficacy against any poxvirus infection. Cidofovir is injected through a needle into the vein. The co-administration of intravenous fluids (fluids given through the vein) and probenecid have been shown to decrease the renal side effects of cidofovir. Cidofovir is a pregnancy category "C" meaning that can cause severe birth defects in pregnant women. Cidofovir is excreted in breast milk, therefore, nursing mothers should not receive cidofovir or discontinue nursing.<sup>258</sup>

The major adverse events associated with the use of cidofovir are kidney injury that can lead to kidney failure and a decreased number of white blood cells, which may in turn lead to increased susceptibility to infections. Additionally, the following have been reported with the use of cidofovir: Decreased pressure in the eye, swelling and tenderness of the eye, and buildup of acid in the body that can result in liver abnormalities and inflammation of the pancreas that can result in death. Other symptoms include fever, infection, pneumonia, shortness of breath, and nausea with vomiting.

At this time, the Secretary is not proposing to add any injuries to the Table related to the use of cidofovir. Claims of injuries associated with the use of cidofovir will be considered as a non-Table injury and evaluated on a case-by-case basis based on the Program's evidence standard.

#### Conditions of Special Interest to Cidofovir

##### Acute Renal Failure

Acute renal failure (ARF), associated with the use of cidofovir, can occur after as few as one or two doses and in some cases has been reported as resulting in dialysis or contributing to death. It is believed that cidofovir is toxic to the

epithelial cells of the kidney, and this combined with other factors can lead to the development of ARF.<sup>259</sup> The factors that may contribute to, or precipitate, ARF when using cidofovir include: (1) Pre-existing renal insufficiency or use of cidofovir in patients at risk of developing renal insufficiency; (2) increased baseline serum creatinine concentration greater than 1.5 mg/dL, baseline creatinine clearance less than 55mL/min; (3) baseline urine protein concentration greater than 100 mg/dL, 2+ proteinuria (protein in the urine); or (4) glycosuria (glucose or sugar in the urine) and concomitant use of nephrotoxic drugs.<sup>260</sup>

The compelling, reliable, valid, medical and scientific evidence, regarding the clinical use of this medication in treating the complications of smallpox vaccination, and other types of infections, indicates that there is an increased risk of developing ARF with the use of cidofovir. However, the literature does not establish an exact time of onset for the possible development of ARF after using cidofovir. The increased risk of developing ARF is individually based and may be influenced by the patient's age, fluid status, baseline renal function, and the level of infection at the time the medication is administered. Because an exact timeframe for the onset of ARF with the use of cidofovir cannot be established by compelling, reliable, and valid medical and scientific evidence, the Secretary does not propose including ARF after the use of cidofovir as a Table injury. Claims for ARF associated with the use of cidofovir will be considered a non-Table injury and evaluated on a case-by-case basis based on the Program's evidence standard.

##### Other Conditions

The following injuries have been associated with the use of cidofovir: neutropenia (abnormally low concentration of the white blood cells, neutrophils), decreased intraocular pressure and metabolic acidosis (an imbalance of the acid/base balance within the body).<sup>261</sup> Although documented in medical case studies, most of these data were collected from patients with significant co-morbidities, including organ transplants, and/or who were taking other medications, such as immunosuppressants. There is

insufficient compelling, reliable, valid, medical and scientific evidence that these injuries are directly caused by cidofovir. Therefore, the Secretary does not propose to add these injuries to the Table at this time. Claims for these injuries associated with cidofovir will be considered on a case-by-case basis as non-Table injuries.

##### Tecovirimat

Tecovirimat is a small-molecule antiviral oral drug that has been approved for the treatment of smallpox under the Animal Rule<sup>262</sup> which in certain instances allows for approval based on adequate and well-controlled animal efficacy studies. An intravenous formulation is presently under development. Although extensively tested in animal models, the drug has had no efficacy testing in humans due to the eradication of naturally occurring smallpox, but an acceptable safety profile has been demonstrated in healthy human volunteers. It is also possible that it would be used as an investigational treatment for certain serious *vaccinia* vaccine adverse events. In a clinical trial with 359 participants receiving tecovirimat, 21 individuals reported minor adverse side effects.<sup>263</sup> Due to the limited information regarding possible adverse reactions associated with tecovirimat, there is presently no compelling, reliable, valid, medical and scientific evidence of any injury directly caused by tecovirimat. Therefore, the Secretary does not propose to add any injuries to the Table as associated with tecovirimat at this time, and claims for injuries associated with it will be considered a non-Table injury and evaluated on a case-by-case basis based on the Program's evidence standard.

##### Brincidofovir

Brincidofovir is a broad-spectrum antiviral agent, which has activity in the laboratory against a number of double stranded DNA (dsDNA) viruses and has been under investigation for its potential clinical utility. It might be used as an investigational treatment of some serious *vaccinia* vaccine complications and is under development for possible use against smallpox, but its role in treating any of these infections has not been established. Brincidofovir is a nucleotide analog of the drug, cidofovir; however, brincidofovir is likely to demonstrate a different spectrum of

<sup>257</sup> Cono et al. "Smallpox vaccination and adverse reactions." 14.

<sup>258</sup> Mylan Institutional LLC. Cidofovir package insert. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56541229-8c1a-4550-8951-2415ed08e7e9>.

<sup>259</sup> Hassane Izzedine, Vincent Launay-Vacher and Gilbert Deray, "Antiviral drug-induced nephrotoxicity." *American Journal of Kidney Diseases* 45(5) (May 2005): 804.

<sup>260</sup> Mylan Institutional LLC. Cidofovir package insert.

<sup>261</sup> Cono et al. "Smallpox vaccination and adverse reactions." 19–20.

<sup>262</sup> See 21 CFR part 314 Subpart I.

<sup>263</sup> U.S. Food and Drug Administration. "Drug Trial Snapshot: TPOXX." (July 13, 2018): 1–2.

toxicity when compared to cidofovir.<sup>264</sup> Specifically, gastrointestinal toxicity (including severe diarrhea) and hepatotoxicity have been observed in clinical trials of brincidofovir; however, most of these data were collected from patients with significant co-morbidities, including patients' post-stem cell or solid organ transplantation who were taking other medications, such as immunosuppressants.<sup>265</sup>

Due to the challenges inherent in evaluating the available safety data regarding possible adverse reactions associated with brincidofovir, there is no compelling, reliable, valid, medical and scientific evidence of any injury directly caused by brincidofovir. Therefore, the Secretary does not propose to add any injuries to the Table as associated with brincidofovir at this time, and claims for injuries associated with it will be considered a non-Table injury and evaluated on a case-by-case basis based on the Program's evidence standard.

#### Smallpox Infection Diagnostic Testing Devices

Presently, there is no compelling, reliable, valid, medical and scientific evidence demonstrating a causal association between smallpox infection diagnostic testing devices and any serious injuries. Therefore, the Secretary does not propose to add any injuries to the Table as associated with diagnostic testing devices at this time. Any claims of injury from the use or administration of smallpox infection diagnostic testing devices will be considered as non-Table injuries and evaluated on a case-by-case basis based on the Program's evidence standard.

The Program will not compensate claims merely because a diagnostic test provides inaccurate results, such as failure to diagnose the presence of a smallpox infection or yielding a positive result of a smallpox infection that is not present. The Program also cannot compensate for injuries that are the direct result of the covered condition or disease for which the countermeasure was administered or used, and that are not the direct result of the administration or use of the covered countermeasure (for example, if the

covered countermeasure is ineffective).<sup>266</sup>

#### Other Proposed Changes to Section 42 CFR 110.100

In light of the proposed additions related to the inclusion of the Smallpox Countermeasure Injury Table, this NPRM also proposes changes to section 110.100. First, revisions are proposed to the introductory text of paragraph (b). These revisions are intended to clarify that paragraph (b) relates to the Pandemic Influenza Countermeasure Injury Table in paragraph (a). The NPRM also proposes to revise paragraph (c) by deleting the current language and replacing it with the proposed Smallpox Countermeasures Injury Table. The language in current paragraph (c) indicates that the Secretary publishes information about certain covered countermeasures in the **Federal Register**. The Secretary proposes to delete the current language in paragraph (c) because it is unnecessary and for accuracy as, when declarations are updated, the language becomes out of date. Finally, the NPRM proposes to add paragraph (d) to include the Smallpox Countermeasures Injury Table's qualifications and aids to interpretation (table definitions and requirements).

#### Impact on Family Well-Being

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

### IV. Statutory and Regulatory Requirements

#### A. Executive Orders 12866, 13563, and 13771: Regulatory Planning and Review

HHS examined the impact of this proposed rule as required by Executive Order 12866 on Regulatory Planning and Review (September 30, 1993), Executive Order 13563 on Improving Regulation and Regulatory Review (January 18, 2011), the Congressional

Review Act (5 U.S.C. 804(2)), the Regulatory Flexibility Act (RFA) (September 19, 1980, Pub. L. 96-354), section 202 of the Unfunded Mandates Reform Act of 1995 (March 2, 1995; Pub. L. 104-4), section 654(c) of the Treasury and General Government Appropriations Act of 1999, and Executive Order 13132 on Federalism (August 4, 1999).

Executive Order 12866 requires all regulations reflect consideration of alternatives, costs, benefits, incentives, equity, and available information. Regulations must meet certain standards, such as avoiding an unnecessary burden. Regulations that are "significant" because of cost, adverse effects on the economy, inconsistency with other agency actions, effects on the budget, or novel legal or policy issues, require special analysis. In 2011, President Obama supplemented and reaffirmed Executive Order 12866.

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

Executive Order 13771 (January 30, 2017) requires that the costs associated with significant new regulations "to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." The designation of this rule, if finalized, will be informed by public comments received; however, if finalized as proposed, this rule would be neither regulatory nor deregulatory for purposes of E.O. 13771. There are no additional costs; the proposed rule, if finalized, will only change how HRSA expends the appropriated funds.

#### Summary of Impacts

In this NPRM, the Secretary proposes a Table identifying serious physical

<sup>264</sup> Lawrence C. Trost et al. "The efficacy and pharmacokinetics of brincidofovir for the treatment of lethal rabbitpox virus infection: A model of smallpox disease." *Antiviral Research* 117 (2015): 115.

<sup>265</sup> Francisco Marty et al. "A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation." *Biology of Blood and Marrow Transplant* 25(2019) 369-381.

<sup>266</sup> See 42 CFR 110.20(d).

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

Rather than showing that a serious physical injury or death directly resulted from an injury included on the Table, individuals may, in the alternative, receive compensation if they can show that a covered countermeasure caused an injury or death. This NPRM is based upon legal authority.

The Secretary has determined that minimal resources are required to implement the provisions included in this NPRM. Therefore, in accordance with the Regulatory Flexibility Act of 1980 (RFA) and the Small Business Regulatory Enforcement Fairness Act of 1996, which amended the RFA, the Secretary certifies that this NPRM will not have a significant impact on a substantial number of small entities.

The Secretary also determined that this NPRM does not meet the criteria for a major rule as defined by Executive Order 12866 and would have no major effect on the economy or federal expenditures. The Secretary determined that this NPRM is not a "major rule" within the meaning of the statute providing for Congressional Review of Agency Rulemaking, 5 U.S.C. 801.

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.

**B. Unfunded Mandates Reform Act of 1995**

The Secretary determined that this NPRM will not have effects on state, local, or tribal governments or on the private sector such as to require consultation under the Unfunded Mandates Reform Act of 1995. This NPRM comports with the 2011 supplemental requirements.

**C. Executive Order 13132—Federalism**

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

**D. Collection of Information**

This NPRM has no information collection requirements.

**List of Subjects in 42 CFR Part 110**

Biologics, Immunization.

Dated: August 24, 2020.

**Thomas J. Engels,**

*Administrator, Health Resources and Services Administration.*

Approved: September 14, 2020.

**Alex M. Azar II,**

*Secretary, Department of Health and Human Services.*

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

**PART 110—COUNTERMEASURES INJURY COMPENSATION PROGRAM**

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

**Authority:** 42 U.S.C. 247d–6e.

■ 2. Amend § 110.100 by revising paragraph (b) introductory text and paragraph (c), and adding paragraph (d) to read as follows:

**§ 110.100 Injury Tables.**

\* \* \* \* \*

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

\* \* \* \* \*

(c) *Smallpox countermeasures injury table.*

Table 1 to paragraph (c)

Covered countermeasures under declarations	Serious physical injury (illness, disability, injury, or condition) <sup>1</sup>	Time interval (for first symptom or manifestation of onset of injury after administration or use of covered countermeasure, unless otherwise specified)	
I. Smallpox Vaccines Replication-Deficient.	A. Anaphylaxis .....	A. 0–4 hours.	
	B. Vasovagal Syncope .....	B. 0–1 hour.	
	II. Smallpox Vaccines Replication-Competent.	A. Anaphylaxis .....	A. 0–4 hours.
		B. Vasovagal Syncope .....	B. 0–1 hour.
		C. Significant Local Skin Reaction .....	C. 1–21 days.
		D. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.	D. 4–28 days.
		E. Inadvertent Autoinoculation .....	E. 1–21 days.
		F. Generalized <i>Vaccinia</i> .....	F. 6–9 days.
		G. Eczema <i>Vaccinatum</i> .....	G. 3–21 days.
		H. Progressive <i>Vaccinia</i> .....	H. 3–21 days.
I. Post- <i>vaccinia</i> Encephalopathy, Encephalitis or Encephalomyelitis (PVEM).		I. 5–14 days.	
J. <i>Vaccinia</i> Myocarditis, Pericarditis, or Myopericarditis (MP).		J. 0–21 days.	
III. <i>Vaccinia</i> Immunoglobulin Intravenous (VIGIV).	A. Anaphylaxis .....	A. 0–4 hours.	
	B. Transfusion-Related Acute Lung Injury (TRALI) .....	B. 0–72 hours.	
	C. Acute Renal Failure (ARF) .....	C. 0–10 days.	
	D. Drug-Induced Aseptic Meningitis (DIAM) .....	D. Within 48 hours after the first dose and up to 48 hours after the last dose of VIGIV.	

Covered countermeasures under declarations	Serious physical injury (illness, disability, injury, or condition) <sup>1</sup>	Time interval (for first symptom or manifestation of onset of injury after administration or use of covered countermeasure, unless otherwise specified)
IV. Cidofovir .....	E. Hemolysis .....	E. 12 hours to 14 days.
V. Tecovirimat .....	A. No Condition Covered <sup>2</sup> .....	A. Not Applicable.
VI. Brincidofovir .....	A. No Condition Covered <sup>2</sup> .....	A. Not Applicable.
VII. Smallpox Infection Diagnostic Testing Devices.	A. No Condition Covered <sup>2</sup> .....	A. Not Applicable.

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

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

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

(1) *Anaphylaxis*. Anaphylaxis is an acute, severe, and potentially lethal systemic reaction that occurs as a single discrete event with simultaneous involvement of two or more organ systems. Most cases resolve without *sequelae*. Signs and symptoms begin within 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) *Vasovagal syncope*. Vasovagal syncope (also sometimes called neurocardiogenic syncope) means loss of consciousness (fainting) and loss of postural tone caused by a transient decrease in blood flow to the brain occurring after the administration of an injected countermeasure. Vasovagal syncope is usually a benign condition, but may result in falling and injury with significant *sequelae*. Vasovagal syncope may be preceded by symptoms, such as nausea, lightheadedness, diaphoresis (sweating), and/or pallor. Vasovagal syncope may be associated with transient seizure-like activity, but recovery of orientation and consciousness generally occurs simultaneously. Loss of consciousness resulting from the following conditions will not be considered vasovagal syncope: Organic heart disease, cardiac arrhythmias, transient ischemic attacks, hyperventilation, metabolic conditions,

neurological conditions, psychiatric conditions, seizures, trauma, and situational as can occur with urination, defecation, or cough. This list is not complete as other conditions that are not associated with the vaccine also may cause loss of consciousness. Episodes of recurrent syncope occurring after the applicable timeframe are not considered to be *sequelae* of an episode of syncope meeting the Table requirements.

(3) *Significant local skin reaction*. Significant local skin reaction is an unexpected and extreme response at the vaccination or inoculation site that results in a significant scar that is serious enough to require surgical intervention. The onset of this injury is the initial skin lesion at the vaccination site that generally occurs with replication-competent smallpox vaccinations. Minor scarring or minor local reactions do not constitute a Table injury. A robust take, defined as an area of redness at the vaccination site that exceeds 7.5 cm in diameter with associated swelling, warmth and pain, is generally considered an expected response to the vaccination or inoculation. A robust take, in itself, does not constitute a Table injury, even when the redness and swelling involves the entire upper arm with associated enlargement and tenderness of the glands (lymph nodes) in the underarm (axilla).

(4) *Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN)*. SJS/TEN is a spectrum of acute hypersensitivity reactions that affects skin, mucous membranes, and sometimes, internal organs (systemic toxicity) associated with the use or administration of replication-competent smallpox vaccines. For purposes of the Table, both skin and mucous membrane rash or lesions must be present. Rash or lesion distribution must be widespread. Rash must not have a symmetric acral distribution (affecting arms, hands, legs or feet). Two or more mucosal sites must

be involved. Mucosal lesions generally manifest as painful lesions in sites, such as the mouth or eyes. Skin rash or lesions in SJS/TEN usually consist of red or purple raised areas (erythematous macules), blisters, and ulcerations.

(5) *Inadvertent Autoinoculation (IA)*. IA is the spread of *vaccinia* virus from an existing vaccination site to a second location usually by scratching the vaccination site and subsequently spreading the virus, which produces a new *vaccinia* lesion on the same person who received the vaccination. IA is the most common adverse event associated with the replication-competent smallpox vaccine.

(6) *Generalized Vaccinia (GV)*. GV is a *vaccinia* infection that occurs from the spread of *vaccinia* from an existing vaccination or inoculation site, with the use or administration of a replication-competent smallpox vaccine, to otherwise normal skin, resulting in multiple new areas of *vaccinia* rash or lesions. The *vaccinia* is believed to be spread through the blood. The rash or lesions, characterized by multiple blisters (vesicles or pustules) generally evolve in a similar sequence or manner as the original vaccination site.

(7) *Eczema Vaccinatum (EV)*. EV is the transmission or the spread of *vaccinia* virus from a vaccination site, after the use or administration of a replication-competent smallpox vaccine, to skin that has been affected by, or is currently affected with, eczema or atopic dermatitis. EV is characterized by lesions that include multiple blisters (vesicles or pustules), which generally evolve in a similar sequence or manner as the original vaccination site. The lesions may come together to form larger lesions. Lesions may also spread to patches of skin that have never been involved with eczema or atopic dermatitis. The new lesions, if cultured, will be positive for *vaccinia* virus. A person with EV may become severely ill with signs and symptoms that involve the whole body (systemic illness), such



as fever, malaise, or enlarged glands (lymph nodes).

(8) *Progressive Vaccinia (PV)*. PV is the failure to initiate the healing process in an initial vaccination or inoculation site, after the use or administration of a replication-competent smallpox vaccine, by 21 days after exposure to *vaccinia*, with progressive ulceration or necrosis at the vaccination site leading to a large destructive ulcer. PV is seen in people who are immunocompromised (have an impaired immune system) and is characterized by a complete or near complete lack of inflammation or absence of inflammatory cells in the dermis of the skin at the vaccination site. The diagnosis of PV may be made before 21 days after exposure, especially in a known immunocompromised individual who develops a lesion at the vaccination site. PV may spread through the blood to any location in the body. No one who experiences a significant healing process of the vaccination site within 21 days after receipt of the replication-competent smallpox vaccine or exposure to *vaccinia* has PV.

(9) *Post-vaccinial Encephalopathy, Encephalitis, and Encephalomyelitis (PVEM)*. PVEM is a spectrum of overlapping conditions that includes post-vaccinial encephalopathy, encephalitis, and encephalomyelitis, and, for the purposes of this Table, is treated as one injury. For the purposes of the Table, PVEM is an autoimmune central nervous system injury that occurs after the use or administration of a replication-competent smallpox vaccine. In rare cases, the *vaccinia* virus is isolated from the central nervous system. Manifestations usually occur abruptly and may include fever, vomiting, loss of appetite (anorexia), headache, general malaise, impaired consciousness, confusion, disorientation, delirium, drowsiness, seizures, language difficulties (aphasia), coma, muscular incoordination (ataxia), urinary incontinence, urinary retention, and clinical signs consistent with inflammation of the spinal cord (myelitis), such as paralysis or meningismus (meningeal irritation). Long-term central nervous system impairments, such as paralysis, seizure disorders, or developmental delays are known to occur as *sequelae* of the acute PVEM. No clinical criteria, radiographic findings, or laboratory tests are specific for the diagnosis of PVEM. Symptoms that occur before 5 days or more than 14 days after receiving the smallpox vaccine should not be attributed to it. In addition, encephalopathy caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a

genetic disorder, or trauma would not meet this Table definition.

(10) *Vaccinial Myocarditis, Pericarditis, or Myopericarditis (MP)*. For purposes of the Table, MP is *vaccinial* myocarditis, pericarditis, or myopericarditis. *Vaccinial* myocarditis is defined as an inflammation of the heart muscle (myocardium) because of receiving the replication-competent smallpox vaccine. *Vaccinial* pericarditis is defined as an inflammation of the covering of the heart (pericardium) because of receiving the smallpox vaccine. *Vaccinial* myopericarditis is defined as an inflammation of both the heart muscle and its covering because of receiving the smallpox vaccine. The inflammation associated with MP may range in severity from very mild (subclinical) to life threatening. In many mild cases, myocarditis is diagnosed solely by; transient electrocardiographic (EKG) abnormalities (e.g., ST segment and T wave changes), increased cardiac enzymes, or mild echocardiographic abnormalities. Arrhythmias, abnormal heart sounds, heart failure, and death may occur in more severe cases. Pericarditis generally manifests with chest pain, abnormal heart sounds (pericardial friction rub), EKG abnormalities (e.g., ST segment and T wave changes), and/or increased fluid accumulation around the heart. A Table injury of MP requires sufficient evidence in the medical records of the occurrence of acute MP.

(11) *Transfusion-Related Acute Lung Injury (TRALI)*. TRALI is defined as the onset of respiratory distress within 6 hours in non-critically ill patients, and 72 hours in critically ill patients, after receipt of blood products containing plasma, in this case, VIGIV. The relative level of illness will be determined on a case-by-case basis after reviewing the medical records and the medical history. The respiratory distress is the result of receiving a plasma containing transfusion (VIGIV) and subsequently developing pulmonary edema, respiratory distress, and hypoxia. TRALI occurs as the result of an antibody response in the host to the donor antibodies within the plasma product. Pulmonary edema is non-cardiac in nature and does not occur more than 72 hours after receiving VIGIV. Pulmonary edema occurring more than 72 hours after receiving a blood product containing plasma (VIGIV) or associated with cardiac dysfunction is not TRALI and is excluded as a countermeasure-related injury. TRALI has been identified as a major cause of mortality in those individual receiving plasma-containing transfusions. A Table injury for TRALI has occurred in a recipient if

there is sufficient evidence in the medical record of an occurrence of TRALI and the pulmonary edema is not caused by cardiac dysfunction or other causes and occurs within 72 of receiving a blood product containing plasma, in this case VIGIV.

(12) *Acute Renal Failure (ARF)*. ARF is the sudden loss of the kidneys' ability to perform their main function of eliminating excess fluids and electrolytes (salts), as well as waste material from the blood. ARF, which is also called acute kidney injury, develops rapidly over a few hours or a few days. ARF can be fatal and requires intensive treatment; however, ARF may be reversible. ARF may cause permanent loss of kidney function, or end-stage renal disease necessitating dialysis or transplant. A Table injury for ARF has occurred if there is sufficient evidence in the medical record of an occurrence of ARF within the identified timeframe and the individual received the associated countermeasure (VIGIV).

(13) *Drug-Induced Aseptic Meningitis (DIAM)*. DIAM is an inflammation of the meninges (linings of the brain) that is not caused by a bacteria or virus, but is caused by a drug or medication. The symptoms of meningitis include severe headache, nuchal (neck) rigidity, drowsiness, fever, photophobia (light sensitivity), painful eye movements, nausea, and vomiting. Discontinuation of the medication leads to a resolution of the symptoms. DIAM is thought to occur because of an immunological hypersensitivity reaction to a specific medication. In the case of immunoglobulins, DIAM may be precipitated by the immunologically active components within the plasma or because of the stabilizers used within the product. The symptoms of DIAM may reoccur with another exposure to the offending agent. A Table injury for DIAM has occurred in a recipient if there is sufficient evidence in the medical record of an occurrence of DIAM within the identified timeframe and the individual received the associated countermeasure (VIGIV). DIAM occurring in the absence of the use of VIGIV, or DIAM occurring with the use of VIGIV outside the established timeframe of onset, which is any time after the first dose and up to 48 hours after the last dose of this medication, is not a Table injury.

(14) *Hemolysis*. Hemolysis is the physical breakdown of red blood cells (RBCs) either through natural attrition or as caused by external factors. The RBC's function is to transport oxygen throughout the body in the hemoglobin contained within the RBC. Additionally, the RBCs contain the majority of the

body's potassium stores. With hemolysis, the body is unable to transport oxygen effectively, and the person develops hypoxia. Additionally, the rapid breakdown of the cell releases large amounts of potassium into the blood stream, which can cause abnormal heart rhythms and cardiac arrest. In severe cases of hemolysis, a blood transfusion may be required to correct the resulting anemia. A Table injury for hemolysis has occurred if there is sufficient evidence in the medical record of an occurrence of hemolysis, and the patient received the associated countermeasure (VIGIV). Hemolysis occurring in the absence of the use of VIGIV and outside of the timeframe of 12 hours to 14 days after receiving VIGIV is not a Table injury. Hemolysis occurring from a more likely alternative diagnosis, such as infections, toxins, poisons, hemodialysis, or medications, is not a Table injury. This list of conditions that can cause hemolysis, not associated with VIGIV, is not exhaustive, and all additional diagnoses within the medical documentation will be evaluated.

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## DEPARTMENT OF COMMERCE

### National Oceanic and Atmospheric Administration

#### 50 CFR Part 665

[Docket No. 201008-0267]

RIN 0648-BJ84

#### Pacific Island Fisheries; 2020-2023 Hawaii Kona Crab Annual Catch Limit and Accountability Measure

**AGENCY:** National Marine Fisheries Service (NMFS), National Oceanic and Atmospheric Administration (NOAA), Department of Commerce.

**ACTION:** Proposed rule; request for comments.

**SUMMARY:** This proposed rule would establish annual catch limits (ACLs) of 30,802 pound (lb) and annual catch targets (ACTs) of 25,491 lb of main Hawaiian Islands (MHI) Kona crab in 2020, 2021, 2022, and 2023. The proposed rule would also establish in-season and post-season accountability measures (AMs). The proposed action supports the long-term sustainability of the Hawaii Kona crab fishery.

**DATES:** NMFS must receive comments by November 5, 2020.

**ADDRESSES:** You may submit comments on this document, identified by NOAA-

NMFS-2020-0091, by either of the following methods:

- **Electronic Submission:** Submit all electronic public comments via the Federal e-Rulemaking Portal. Go to <https://www.regulations.gov/docket?D=NOAA-NMFS-2020-0091>, click the "Comment Now!" icon, complete the required fields, and enter or attach your comments.

- **Mail:** Send written comments to Michael D. Tosatto, Regional Administrator, NMFS Pacific Islands Region (PIR), 1845 Wasp Blvd., Bldg. 176, Honolulu, HI 96818.

**Instructions:** NMFS may not consider comments sent by any other method, to any other address or individual, or received after the end of the comment period. All comments received are a part of the public record and will generally be posted for public viewing on <https://www.regulations.gov> without change. All personal identifying information (e.g., name, address, etc.), confidential business information, or otherwise sensitive information submitted voluntarily by the sender will be publicly accessible. NMFS will accept anonymous comments (enter "N/A" in the required fields if you wish to remain anonymous).

NMFS prepared a draft environmental assessment (EA) that describes the potential impacts on the human environment that could result from the proposed ACL and AM. The draft EA and other supporting documents are available from [www.regulations.gov](http://www.regulations.gov).

**FOR FURTHER INFORMATION CONTACT:** Kate Taylor, NMFS PIRO Sustainable Fisheries, 808-725-5182.

**SUPPLEMENTARY INFORMATION:** NMFS and the Council manage the Kona crab fishery in the U.S. Exclusive Economic Zone (generally 3-200 nm from shore) around Hawaii through the Fishery Ecosystem Plan for the Hawaiian Archipelago (FEP) under the authority of the Magnuson-Stevens Fishery Conservation and Management Act (Magnuson-Stevens Act). The FEP contains a process for the Council and NMFS to specify ACLs, ACTs, and AMs; that process is codified at Title 50, Code of Federal Regulations, § 665.4 (50 CFR 665.4). The regulations require NMFS to specify an ACL and AM for each stock and stock complex of management unit species (MUS) in an FEP, as recommended by the Council, and considering the best available scientific, commercial, and other information about the fishery. If a fishery exceeds an ACL, the regulations require the Council to take action, which may include reducing the ACL for the subsequent fishing year by the amount of the

overage, or other appropriate action. The specification of an ACT, which is set below the ACL, can help ensure that the catch does not exceed the ACL. When used, an ACT also serves as the basis for invoking accountability measures.

The Council recommended that NMFS specify ACLs of 30,802 lb and ACTs of 25,491 lb for MHI Kona crab for each of the 2020-2023 fishing years. The fishing year for Kona crab is the calendar year. The Council based its recommendation on a 2018 benchmark stock assessment of MHI Kona crab, published in 2019, and in consideration of the best available scientific, commercial, and other information about the fishery. The stock assessment estimated the overfishing limit for Kona crab to be 33,989 lb. The proposed ACLs and ACTs are associated with a 38 percent and 20 percent risk of overfishing, respectively. These levels are more conservative than the 50 percent risk threshold allowed under NMFS guidelines for National Standard 1 of the Magnuson Stevens Act. Catch from State and Federal waters will count toward catch limits. NMFS does not anticipate that the fishery would reach the proposed limit in any fishing year, or that fishing for Hawaii Kona crab would be constrained during the fishing year.

NMFS proposes to implement both in-season and post-season AMs. Under the in-season AM (which is new for this fishery), when NMFS projects that the catch of Kona crab will reach the ACT, we would close the commercial and non-commercial fisheries for Kona crab in Federal waters for the remainder of the year. For the post-season AM, if NMFS and the Council determine after the end of each fishing year that the catch exceeded the ACL, NMFS would reduce the ACL and ACT in the subsequent fishing year by the amount of the overage. In the event that the catch exceeds the ACT, but is below the ACL, a post-season correction would not be applied. NMFS will use the best scientific information available to monitor the ACT and ACL, such as the monthly catch reporting required by State of Hawaii Commercial Marine License (CML) holders. Since NMFS does not issue Federal fishing permits to fish for Kona crab and instead relies on the CML, we have no way to directly inform fishermen of an in-season closure or post-season adjustment. NMFS will provide advance notice to fishermen and the public through available print and online publications if we implement an in-season closure or a post-season correction. We will also request the State of Hawaii notify CML