



DEPARTMENT OF HEALTH AND HUMAN SERVICES

42 CFR Part 100

RIN # 0906-AB00

National Vaccine Injury Compensation Program

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

ACTION: Notice of proposed rulemaking.

SUMMARY: The Secretary has made findings as to intussusceptions that can reasonably be determined in some circumstances to be caused or significantly aggravated by rotavirus vaccines. Based on these findings, the Secretary proposes to amend the Vaccine Injury Table (Table) by regulation. These proposed regulations will apply only for petitions for compensation under the National Vaccine Injury Compensation Program (VICP) filed after the final regulations become effective. The Secretary is seeking public comment on the proposed revisions to the Table.

DATES: Written comments must be submitted on or before [INSERT DATE 180 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. A public hearing on this proposed rule will be held before the end of the public comment period. A separate notice will be published in the Federal Register to provide the details of this hearing. Subject to consideration of the comments received, the Secretary intends to publish a final regulation.

ADDRESSES: You may submit comments in one of three ways, as listed below. The first is the preferred method. Please submit your comments in only *one* of these ways to minimize the receipt of duplicate submissions.

1. **Federal eRulemaking Portal.** You may submit comments electronically to <http://www.regulations.gov>. Click on the link “Submit electronic comments on HRSA regulations with an open comment period.” Submit your comments as an attachment to your message or cover letter. (Attachments should be in Microsoft Word or WordPerfect; however, Microsoft Word is preferred).
2. **By regular, express, or overnight mail.** You may mail written comments to the following address only: Health Resources and Services Administration, Department of Health and Human Services: Attention: HRSA Regulations Officer, Parklawn Building, Room 14-101, 5600 Fishers Lane, Rockville, MD 20857. Please allow sufficient time for mailed comments to be received before the close of the comment period.
3. **Delivery by hand (in person or by courier).** If you prefer, you may deliver your written comments before the close of the comment period to the same address: Parklawn Building, Room 14-101, 5600 Fishers Lane, Rockville, MD 20857. Please call in advance to schedule your arrival with one of our HRSA Regulations Office staff members at telephone number (301) 443-1785. This is not a toll-free number.

Because of staffing and resource limitations, and to ensure that no comments are misplaced, HRSA cannot accept comments by facsimile (FAX) transmission. In commenting, by any of the above methods, please refer to file code (HRSA # 0906-AB00). All comments received on a timely basis will be available for public inspection without charge, including any personal information provided, in Room 14-101 of the Health Resources and Services Administration’s offices at 5600 Fishers Lane, Rockville, MD., on Monday through Friday of each week from 8:30 a.m. to 5 p.m. (excluding federal holidays). Phone: (301) 443-1785. This is not a toll-free number.

FOR FURTHER INFORMATION CONTACT: Please visit the National Vaccine Injury Compensation Program’s website, <http://www.hrsa.gov/vaccinecompensation/>, or contact Dr. Catherine Shaer, Acting Chief Medical Officer, National Vaccine Injury Compensation Program, Healthcare Systems Bureau, Health Resources and Services Administration, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, MD 20857. Phone calls can be directed to (855) 266-2427. This is a toll-free number.

SUPPLEMENTARY INFORMATION:

Background

Under Title XXI of the Public Health Service (PHS) Act, individuals who demonstrate a vaccine-related injury or death may receive compensation through the National Vaccine Injury Compensation Program (VICP). To gain entitlement to compensation in the VICP, a petitioner must demonstrate that the injured or deceased individual received a vaccine set forth in the Vaccine Injury Table (a “covered vaccine”) and sustained a vaccine-related injury or death. A petitioner can prove a vaccine-related injury or death in two ways: 1) The petitioner can show that the vaccine recipient suffered an injury listed in the Vaccine Injury Table corresponding with the vaccine received, and that the onset of such injury occurred within the time period specified in the Table (a “Table injury”). As set out in sections 2111(c)(1)(C)(i), 2113(a)(1)(B), and 2114(a) of the PHS Act, a Table injury or death is given the legal presumption that it was caused by the vaccination. 2) If the petitioner cannot demonstrate a Table injury, the petitioner can prevail by proving, by a preponderance of the evidence, that the vaccine caused the injury or death (an “off-Table injury”). In either case, a petitioner must also show that the injury was sufficiently severe by demonstrating that such person suffered the residual effects of the injury for more than 6 months; died from the administration of the vaccine; or that the alleged injury

resulted in inpatient hospitalization and surgical intervention. Section 2111(c) of the PHS Act. If the petitioner can prove a Table injury or off-Table injury, the petitioner is entitled to compensation unless it is affirmatively shown by the Secretary that the injury was caused by some factor unrelated to the vaccination.

Under section 2114(e)(2) of the PHS Act, when the Centers for Disease Control and Prevention (CDC) recommends a vaccine for routine administration to children, the Secretary is required to amend the Vaccine Injury Table to include such vaccine. Coverage becomes effective when an excise tax is imposed on the vaccine. Additionally, the Secretary is authorized to include specific adverse events on the Table with respect to each covered vaccine, including the time period when the first symptoms or manifestations of onset or other significant aggravation of such adverse event may occur. Under section 2114(c) of the PHS Act, the Secretary may make such modifications to the Table by promulgating regulations, with notice and opportunity for a public hearing, and at least 180 days of public comment.

Coverage for Rotavirus Vaccines on the Vaccine Injury Table

The general category of rotavirus vaccines was added for coverage under the VICP, effective October 22, 1998. The prerequisites for adding rotavirus vaccines to the VICP were satisfied by the enactment of the Omnibus Consolidated and Emergency Supplemental Appropriations Act of 1999, Pub. L. 105-277 (October 21, 1998), which imposed an excise tax of 75 cents per dose on “any vaccine against rotavirus gastroenteritis,” and the publication of the CDC recommendation of the vaccine for “routine use in children” in the “Morbidity and Mortality Weekly Report” (MMWR), 1999:48 (March 19, 1999).

When the general category of rotavirus vaccines was added to the Table, it was added with “no condition specified.” 64 FR 40517. In other words, at the time rotavirus vaccines were

first included for coverage under the Program, the Secretary had not identified any adverse events to include in the Table. Therefore, individuals who received the rotavirus vaccine did not receive a legal presumption of causation for any claimed injury and were required to prove that the vaccine actually caused the claimed injury.

History of Rotashield Vaccine

On August 31, 1998, the Food and Drug Administration (FDA) licensed a live, oral, rhesus-based rotavirus tetravalent vaccine (trade name “Rotashield”) for use in infants between the ages of 6 weeks and 1 year. Distribution of the vaccine began on October 1, 1998. At the time, this was the only U.S.-licensed rotavirus vaccine on the market. Following a review by the Advisory Committee on Immunization Practices (ACIP), the CDC published its rotavirus recommendation in the March 19, 1999, issue of the MMWR (1999:48), calling for doses to be administered at 2, 4, and 6 months of age, with the first dose to be administered between 6 weeks and 6 months. The series was not to be initiated in children who were 7 months of age or older due to an increased rate of febrile (fever) reactions after the first dose among older infants.

Over the next eight months, the Secretary’s Vaccine Adverse Event Reporting System (VAERS) began receiving reports of intussusception (a type of bowel obstruction that occurs when the bowel folds into itself) in infants receiving the Rotashield vaccine after the first dose. Based on an analysis of 15 reports, the CDC, in the July 16, 1999, issue of the MMWR, recommended that health care providers and parents postpone use of this rotavirus vaccine. The CDC undertook additional epidemiological studies to determine if there was a true association between the vaccine and intussusception. Also, at that time, the manufacturer, in consultation with the FDA, voluntarily ceased further distribution of the vaccine. Upon further consideration, and following consultation with CDC officials in preparation for the upcoming ACIP meeting,

the manufacturer announced the withdrawal of the Rotashield vaccine (which was still the only U.S.-licensed rotavirus vaccine at that time) from the market on October 15, 1999, and requested the immediate return of all doses of the vaccine.

At its October 22, 1999, meeting, the ACIP reviewed scientific data from several sources, including a 19-state case-control study which showed a statistically significant rate of intussusception among recipients of the live, oral, rhesus-based rotavirus vaccine in the 2 week period following vaccine administration, with the highest risk period in the 3-14 days after the first dose of vaccine, and a much smaller risk in the same time period after dose two. Beyond 14 days, there did not appear to be more cases than might occur by chance alone. The ACIP concluded that intussusception occurs with significantly increased frequency in the first 14 days following administration of the Rotashield vaccine and withdrew its recommendation for use of this vaccine in infants. The CDC adopted and published the Committee's decision in the November 5, 1999, issue of the MMWR.

By December 2000, VAERS had received over 100 reports of confirmed intussusception cases, 58 of which had onset within 7 days of vaccine receipt. Of the cases reported, approximately one-half required surgical intervention. Nearly all of the other cases of bowel obstruction were relieved through barium enema, a radiological procedure used to both diagnose and often rectify the telescoped bowel segment, or resolved spontaneously without any intervention. At least one death associated with rotavirus vaccine was reported to VAERS.

The Secretary reviewed the epidemiological data, and in a notice of proposed rulemaking published on July 13, 2001, the Secretary announced his findings that the condition of intussusception could reasonably be determined in some circumstances to be caused by vaccines containing live, oral, rhesus-based rotavirus (66 FR 36735). Based on those findings, the

Secretary proposed to amend the Table by adding the specific category of vaccines containing live, oral, rhesus-based rotavirus as a distinct category, with intussusception listed as a covered Table injury. This proposal was based on data indicating a strong association between Rotashield and intussusception in the two weeks following vaccination.

In a final rule published July 25, 2002 (67 FR 48558), the Secretary made final the changes proposed in the earlier notice. After these amendments, the Table included two categories of rotavirus vaccines. The first, the general category of rotavirus vaccines, did not include an associated injury. This category of vaccines was effective as of October 22, 1998, the effective date of the excise tax imposed for rotavirus vaccines. See 42 CFR 100.3(a), 100.3(c)(3). The second, more specific category of vaccines containing live, oral, rhesus-based rotavirus, contained an associated injury of intussusception with an onset interval of 0–30 days. The live, oral, rhesus-based rotavirus vaccine was covered in the VICP effective October 22, 1998, but the Table injury could only be claimed by those petitioners that had the vaccine administered on or before August 26, 2002 (the effective date of the final rule adding this category of vaccine), and beginning on August 26, 1994, the period of the eight-year “look back” prescribed in the statute. Because the manufacturer of the only U.S.-licensed rotavirus vaccine at the time voluntarily ceased distribution of the vaccine in July 1999, and because the CDC recommended that this vaccine no longer be routinely administered to children in the United States in October 1999, the Secretary concluded that it was unlikely that potential claims under this specific category would arise after the rule's publication. Because of this, the final rule limited the Table injury of intussusception to live, oral, rhesus-based rotavirus vaccines administered on or before the effective date of the final rule (August 26, 2002). Individuals who sought compensation for injuries related to such a vaccine administered after the effective date of

the final rule were not entitled to the presumption of a Table injury for intussusception, but such individuals could still file claims under the Table's general category for rotavirus vaccines.

Through an interim final rule published October 9, 2008 (73 FR 59528), the Secretary removed the specific category of vaccines containing live, oral, rhesus-based rotavirus from the Table. Given the applicable statute of limitations and the fact that this category limited its application to vaccines administered on or before August 26, 2002, the Secretary believed that any potential Table claim under this category would have been time-barred, so no persons could have had claims under that category.

Subsequent Rotavirus Vaccines

On February 3, 2006, the FDA licensed a pentavalent human-bovine reassortant rotavirus vaccine (trade name “RotaTeq”). Following a review by ACIP, the CDC published its recommendation for routine vaccination of U.S. infants with three doses of this rotavirus vaccine administered orally at ages 2, 4, and 6 months (MMWR 2006:55; RR12). On April 3, 2008, the FDA licensed a monovalent rotavirus vaccine derived from the human rotavirus strain (trade name “Rotarix”). In June 2008, the CDC updated its recommendation to include use of the newly licensed Rotarix (MMWR 2009:58; RR02). The prelicensure clinical trials for RotaTeq examined 70,000 infants, and did not identify an increased risk of intussusception in the 1-42 days post immunization. In addition, the prelicensure clinical trials for Rotarix examined over 60,000 infants, and found no increased risk in the 1-31 days after vaccination with either dose. Because of the prior association of intussusception with Rotashield, multiple post-marketing studies regarding RotaTeq, Rotarix, and intussusception were conducted to evaluate the possibility of a small risk of intussusception as utilization increased.

RotaTeq Scientific History

In February 2007, the FDA notified health care providers and consumers about 28 post-marketing reports of intussusception following administration of RotaTeq. The notification stated that of the reported 28 cases of intussusception, the number that may have been caused by the vaccine, or occurred by coincidence, was unknown. The FDA issued this notification both to encourage the reporting of any additional cases of intussusception that may have occurred in the past or will occur in the future after administration of RotaTeq, and to remind people that intussusception may be a potential complication of RotaTeq.

In 2008, the Vaccine Safety Datalink (VSD) published their experience from the first 111,521 doses of RotaTeq given from 2006 to 2007, and in 2012, the VSD and the CDC published data in “The Journal of the American Medical Association” (JAMA), from 786,725 doses of RotaTeq given from 2006 to 2010. There was no identifiable risk in the 1–7 day or 1–30 day periods following administration of RotaTeq in either analysis. The final post-marketing study of RotaTeq in the U.S. was performed by Merck and found no association with intussusception and RotaTeq. Post-marketing clinical trials of RotaTeq performed after U.S. licensure included two smaller efficacy studies from Africa and Asia. The African study had no cases of intussusception in either vaccine or placebo groups, and the Asian study had one case 97 days following the third dose of the placebo, and no cases in the vaccine group.

A 2011 post-marketing study of RotaTeq published in “Vaccine,” from the Australian National Immunization Program, suggests an association between RotaTeq and intussusception. Approximately 295,000 doses of RotaTeq were given in two states. In 1–3 month old infants, the expected number of intussusception cases was exceeded for the 1–7 and 1–21 day periods following the first dose of RotaTeq. In the 1–7 days following the first dose, three cases were found, compared to an expected 0.57 cases (relative risk of 5.26 [confidence interval (CI), 1.1-

15.4]). (Relative risk is the ratio of the chance of a disease developing among members of a population exposed to a factor compared with a similar population not exposed to the factor.) [Confidence Intervals are a measure of estimation that represents the possible range of values in a population estimated from a given sample drawn from that population (in this case ranging from a relative risk value of 1.1 to 15.4)].

When the 1–21 day interval following the first dose was examined, six cases of intussusception were found, compared to an expected 1.71 cases (relative risk 3.5 [CI, 1.3-7.6]). There was no increase from the expected cases after dose two of RotaTeq, and actually a decrease from expected cases after dose three. Also important to note is that there was no evidence of increased risk of intussusception when examining the entire period of 1–9 months of age.

Rotarix Scientific History

Rotarix was given in the other two states evaluated in the Australian post-marketing study, totaling approximately 302,000 doses. The study demonstrated an increased risk in both the 1–7 day and the 1–21 day windows following the first dose of Rotarix (relative risk of 3.45 [CI 0.7-10] and 1.53 [CI, 0.4-3.9], respectively). Neither of these risks showed statistical significance. There were no excess cases of intussusception associated with dose two of Rotarix. Similar to RotaTeq, the number of observed cases in the post-vaccine windows was small, with three cases observed in the 1-7 days after first dose vaccination versus 0.9 cases expected for the 1–3 month old infants. Since Rotarix constitutes a small percentage of total rotavirus vaccine given in the U.S. (3 million doses of Rotarix versus 35 million doses of RotaTeq as of 2010), comparable U.S. post-licensure studies of Rotarix are not currently available.

Post-marketing studies (case series and case-control analysis) performed in Mexico and Brazil, and published in “The New England Journal of Medicine” in 2011, identified an association between Rotarix and intussusception. In Mexico, there was an increased rate of intussusception during the 1-7 day period after the first dose of Rotarix with an incidence rate ratio of 5.3 (CI, 3-9.3). (Incidence rate ratio compares two incidence rates. Incidence rate is the number of new cases per population in a given time period.) There was no increase in the rate 1–7 days after the second dose, but a small increase by a factor of two was identified in the second and third week following the second dose. This contrasts with the Brazil data where there was no increase in the rate of intussusception found after the first dose of Rotarix, but a small elevation of the rate was identified 1–7 days following the second dose (incidence ratio of 2.6 [CI, 1.3-5.2]). The reason behind the variation between the data from Mexico and Brazil is unclear, but one potential explanation could be a result of Brazil’s administering Rotarix and the oral polio virus vaccine (OPV) together, which has been shown to decrease the immunogenicity of the first dose of Rotarix, perhaps making the second dose function more like the initial dose.

The commentary in “The New England Journal of Medicine” in 2011 regarding the Rotarix data from Mexico and Brazil summarized the small attributable risk of intussusception as 1/51,000 vaccinated infants in Mexico and 1/68,000 vaccinated infants in Brazil. [Attributable risk is the difference in rate of a condition (intussusception in this case) between an exposed population (those who received rotavirus vaccine in this case) and an unexposed population.] The article raised the possibility that any live, oral, rotavirus vaccine, along with natural rotavirus infection, could carry a detectable risk of intussusception, although the risk is demonstrably quite low, based on the available studies. It is also biologically plausible that the different vaccines have differing intrinsic risks of intussusception based on the distinct strains in

each vaccine, and that the same vaccine could manifest different risks in different populations. It is also possible that with small risks overall (resulting in a small number of excess intussusception cases in the specific narrow age groups receiving vaccine) and variability in background numbers of cases of intussusception year to year, an increase in overall burden of intussusception in infants aged < 1 year may not be detectable. The article raised the point that the small increase of intussusception after vaccination does not seem to increase the overall burden of intussusception, and that perhaps the rotavirus vaccination has a preventive role in long-term intussusception risk.

Because of these findings, the prescribing information in the U.S. for Rotarix was amended in September 2010 to reflect the above increased risk and the potential implications for U.S. infants. (GlaxosmithKline Biologicals Package Insert (PI) and Patient Package Information (PPI)). The PI and PPI were further amended in February 2011 to include “history of intussusception” as a contraindication to vaccination. (Statement available for viewing at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm245491.htm>). A “history of intussusception” was also made a contraindication for Rotateq in July 2011.

In addition, a large post-marketing surveillance study of intussusception in Mexico published in “The Pediatric Infectious Disease Journal” in July 2012 reported an “attributable risk of 3 to 4 additional cases of intussusception per 100,000 vaccinated infants after receipt if Rotarix.

CDC Response

In November 2010, the CDC issued a statement noting that some, but not all, studies suggest RotaTeq and Rotarix may possibly cause a small increase in the risk of intussusception; however, the CDC concluded that the benefits of these vaccines far outweigh this possible risk.

The CDC continues to recommend routine rotavirus vaccination of U.S. infants to prevent severe rotavirus disease in U.S. infants and children. (Statement available for viewing at <http://www.cdc.gov/vaccines/vpd-vac/rotavirus/intussusception-studies-acip.htm>).

The FDA's mini-sentinel "Post-Licensure Rapid Immunizations Safety Monitoring Program" (PRISM) is currently performing a study to assess the risk of intussusception from both Rotarix and RotaTeq vaccines in the United States. This self-controlled and case-centered study targets approximately 1 million infants. Results are expected late in 2012.

Proposed Rule

The Secretary has reviewed all the currently available data regarding the Rotarix and RotaTeq vaccines and the risk of intussusception. The background of the Rotashield experience in the U.S. and the recently published literature from Mexico, Brazil, and Australia supports a small attributable risk of intussusception after the first and second doses of Rotarix and RotaTeq (with a greater amount of data supporting an association with the first dose of both vaccines). Therefore, the Secretary proposes that the injury of intussusception be added to the general Table category of "rotavirus vaccines" to allow a presumption of causation for claims that meet the requirements set forth in the Table for that injury. Current U.S. studies of RotaTeq do not show a statistically identifiable risk of intussusception, but the number of study patients exposed to the vaccine in the U.S. may not be large enough (even with the results expected from the ongoing PRISM study) to rule out a very small attributable risk to the vaccine. Platforms like VSD in the U.S. have not been able to evaluate the possible small risk associated with Rotarix to date because of the low numbers of doses of Rotarix administered in settings captured by the surveillance program. To allow for a generous timeframe, the Secretary proposes that the Table injury for intussusception have an onset interval of 1–21 days under sections 2114(c) and (e) of

the PHS Act, since evidence shows the increased risk within the 1–7 days following immunization with peaks in the fourth and fifth days.

The Qualifications and Aids to Interpretation section of the table will define the injury of “intussusception” as the invagination of a segment of intestine into the next segment of intestine, resulting in bowel obstruction, diminished arterial blood supply, and blockage of the venous blood flow. This is characterized by a sudden onset of abdominal pain that may be manifested by anguished crying, irritability, vomiting, abdominal swelling, and/or passing of stools mixed with blood and mucus. The definition for presumption of vaccine causation only applies to the first and second dose of vaccine, and excludes intussusception occurring with or after the third dose. The third dose of rotavirus vaccines lacks sufficient evidence showing risk.

The definition also delineates the alternative causes of intussusception which, if present in a case, would prevent it from qualifying as a Table injury. The alternative causes were classified into four categories: infectious diseases; anatomic lead points; anatomic bowel abnormalities; and underlying gastrointestinal or systemic diseases. Cases of intussusception where the onset was within 14 days after an infectious disease secondary to non-enteric or enteric adenovirus, other enteric viruses (such as Enterovirus), enteric bacteria (such as *Campylobacter jejuni*), or enteric parasites (such as *Ascaris lumbricoides*) would not qualify as a Table injury. Proof of these alternate causes may be demonstrated by clinical signs and symptoms and need not be confirmed by culture or serologic testing.

Cases of intussusception in a person with a pre-existing condition identified as the lead point for intussusception, such as intestinal masses and cystic structures (e.g., polyps; tumors; Meckel’s diverticulum; lymphoma; or duplication cysts), would not qualify as a Table injury. Additionally, cases of intussusception in a person with abnormalities of the bowel, including

congenital anatomic abnormalities, anatomic changes after abdominal surgery, and other anatomic bowel abnormalities caused by mucosal hemorrhage, trauma, or abnormal intestinal blood vessels (such as Henoch Schölein purpura, hematoma, or hemangioma); or in a person with underlying conditions or systemic diseases associated with intussusception (such as cystic fibrosis, celiac disease, or Kawasaki disease) would not qualify as a Table injury.

Petitioners may be eligible for compensation for vaccine-related cases of intussusception in which the onset is before 1 day or beyond 21 days, or where the condition does not satisfy the criteria under the Qualifications and Aids to Interpretation for intussusception (an “off-Table” claim), however the petitioners will be required to prove causation-in-fact. Regardless of whether the claim satisfies the criteria in the Table, all petitioners must demonstrate sufficient severity of the injury by proving that the injured person: 1) suffered the residual effects or complications of the alleged vaccine-related injury for more than 6 months after vaccine’s administration; 2) died from administration of the vaccine; or 3) sustained inpatient hospitalization and surgery as a result of the alleged vaccine-related injury. Section 2111(c)(1)(D), PHS Act (42 U.S.C. §300aa-11(c)(1)(D)). In the case of rotavirus vaccine administration and subsequent intussusception, the Secretary does not consider a reduction of intussusception with an enema to be “surgical intervention.”

Petitions must also be filed within the applicable statute of limitations. The general statute of limitations applicable to petitions filed with the VICP, set forth in section 2116(a) of the PHS Act (42 U.S.C. §300aa-16(a)), continues to apply. In addition, section 2116(b) of the PHS Act identifies a specific exception to this statute of limitations that applies when the effect of a revision to the Table makes a previously ineligible person eligible to receive compensation or when an eligible person's likelihood of obtaining compensation significantly increases. Under

this section, individuals who may be eligible to file petitions based on the revised Table may file a petition for compensation not later than 2 years after the effective date of the revision if the injury or death occurred not more than 8 years before the effective date of the revision of the Table (42 U.S.C. §300aa-16(b)).

The Advisory Commission on Childhood Vaccines (ACCV) voted unanimously to approve this proposal at its December 9, 2011, meeting. The Secretary, while moving forward with this proposal, understands that additional science is still forthcoming and recognizes the importance of keeping the Vaccine Injury Table in conformance with science. In addition, the Secretary recognizes that one goal of the VICP is to provide generous compensation to petitioners harmed by vaccines through a less adversarial system. Although post-marketing studies in the U.S. have not identified an increased risk of intussusception associated with rotavirus vaccine, a small risk cannot be ruled out. Therefore, the Secretary feels that the balance between science and policy is best met by acting now, on the basis of the studies outside the U.S. that have detected an increased risk of intussusception following Rotarix and RotaTeq vaccines, rather than waiting to see if the PRISM, VSD, and other studies further bolsters the already published findings.

Economic and Regulatory Impact

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

options that could lessen the impact of the rule.

Executive Order 12866 requires that all regulations reflect consideration of alternatives, 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.

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

The Secretary has also determined that this proposed rule does not meet the criteria for a major rule as defined by Executive Order 12866, and it would not have a major effect on the economy or federal expenditures. The Department has determined that the proposed rule is not a “major rule” within the meaning of the statute providing for Congressional Review of Agency Rulemaking, 5 U.S.C. §801. Similarly, it will not have effects on state, local, and tribal governments, or on the private sector such as to require consultation under the Unfunded Mandates Reform Act of 1995.

The Secretary finds that the provisions of this rule will not have an adverse affect on family well-being, because this rule does not affect the following family elements: family safety; family stability; marital commitment; parental rights in the education, nurture, and supervision of their children; family functioning; disposable income or poverty; or the behavior

and personal responsibility of youth, as determined under section 654(c) of the Treasury and General Government Appropriations Act of 1999.

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

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

Impact of the New Rule

To date, 17 petitions have been filed alleging a vaccine-related injury of intussusception caused or aggravated by a rotavirus vaccine, not including the currently unavailable Rotashield vaccine. This proposed rule will have the effect of decreasing the burden of proof for future petitioners. Under this proposed rule, future petitioners alleging the injury of intussusception as the result of a rotavirus vaccine that meets the criteria in the Vaccine Injury Table will be afforded a presumption of causation. This proposed rule will not change the burden of proof applicable to petitioners alleging other injuries related to a rotavirus vaccine who must rely on a causation-in-fact analysis.

Paperwork Reduction Act of 1980

This proposed rule has no information collection requirements.

List of Subjects in 42 CFR Part 100

Biologics, Health Insurance, and Immunization.

Dated: June 26, 2013

Mary Wakefield,

Administrator,

Health Resources and Services Administration.

Approved: July 17, 2013

Kathleen Sebelius,

Secretary.

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

PART 100—VACCINE INJURY COMPENSATION.

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

Authority: Sec. 215 of the Public Health Service Act (42 U.S.C. 216); sec. 2115 of the PHS Act; 100 Stat. 3767, as revised (42 U.S.C. 300aa-15); §100.3 Vaccine Injury Table, issued under secs. 312 and 313 of Pub. L. 99-660, 100 Stat. 3779-3782 (42 U.S.C. 300aa-1 note); and sec.

2114(c) and (3) of the PHS Act, 100 Stat. 3766 and 107 Stat. 645 (42 U.S.C. 300aa-14(c) and (e)); sec. 904(b) of Pub. L. 105-34, 111 Stat. 873; and sec. 523(a) of Pub. L. 106-170, 113 Stat. 1860.

2. Amend § 100.3 in the paragraph (a) table by revising Item XI and by adding paragraph (b)(3) to read as follows:

§ 100.3 Vaccine injury table.

(a) * * *

Vaccine Injury Table

Vaccine	Illness, disability, injury, or condition covered	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration
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* * * * *

XI. Rotavirus vaccines	A. Intussusception B. Any acute complication or <i>sequela</i> (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed.	1 – 21 days Not applicable
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* * * * *

(b) * * *

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

irritability, vomiting, abdominal swelling, and/or passing of stools mixed with blood and mucus.

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

Table intussusception:

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

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

(C) Onset in a person with a pre-existing condition identified as the lead point for intussusception such as intestinal masses and cystic structures (such as polyps, tumors, Meckel's diverticulum, lymphoma, or duplication cysts);

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

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

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