Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance when appropriate.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Table of Contents

Contains Nonbinding Recommendations

Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are notifying you, blood establishments that collect Whole Blood and blood components, that we have determined Zika virus (ZIKV) to be a relevant transfusion-transmitted infection (RTTI) under Title 21 of the Code of Federal Regulations (CFR) 630.3(h)(2) and we are providing you with FDA's assessment. We are also providing you with recommendations to reduce the risk of transmission of ZIKV by Whole Blood and blood components. The recommendations contained in this guidance apply to the collection of Whole Blood and blood components. This guidance does not apply to the collection of Source Plasma.[1]

This guidance document supersedes the guidance document entitled, "Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus; Guidance for Industry," (dated February 2016) and the guidance document entitled, "Questions and Answers Regarding "Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus; Guidance for Industry," (dated March 2016) no later than 12 weeks after the date of the issuance of this guidance. Implementation of the guidance will be immediate for blood establishments that collect Whole Blood and blood components in states and territories with local transmission of Zika virus by mosquitos, and will be phased in over 4 to12 weeks in other states and territories using a tiered, risk-based approach. Blood establishments should follow the recommendations in the February 2016 guidance until the recommendations in this guidance document have been fully implemented.[2] See section V. of this guidance for further recommendations on implementation.

[1] Source Plasma is used for further manufacture of plasma-derived products. Viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of ZIKV.

[2] Except that blood establishments that collect Whole Blood and blood components in states and territories with locally acquired mosquito-borne cases of ZIKV should implement the recommendations in this guidance immediately or cease blood collection until they implement the recommendations in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

ZIKV is an arbovirus in the *Flaviviridae* family, genus *Flavivirus*. It is transmitted to humans primarily by the *Aedes aegypti* mosquito, but it may also be transmitted by the *Aedes albopictus* mosquito (Ref. 1). In addition, cases of intrauterine, perinatal, sexual, laboratory-acquired and transfusion-associated transmission of ZIKV have been reported (Refs. 2, 3, 4, 5, 6, 7).

The virus was first isolated in 1947 from a sentinel rhesus monkey in the Zika Forest of Uganda (Ref. 2). Human illness due to ZIKV infection was first confirmed in Nigeria in 1953, and epidemiological studies conducted between 1951 and 1981 showed that the virus has circulated in humans in African and Asian countries (Ref. 8). ZIKV illness was first recognized outside of Africa and Asia in 2007 during an outbreak on Yap Island, Micronesia (Refs. 9, 10). An outbreak of ZIKV was next reported in French Polynesia from October 2013 to February 2014, when about 11% of the population had symptomatic infection (Refs. 11, 12).

The global ZIKV epidemic expanded in the region of the Americas by early 2015 when the first local transmission was reported in Brazil (Refs. 13, 14, 15). Local transmission of ZIKV has also been reported in areas outside of the Americas, including the Pacific Islands of Samoa, American Samoa, Marshall Islands and Tonga, and Cape Verde in Africa, and there are now at least 50 countries and territories worldwide with active local transmission of the virus (Refs. 16, 17).

The first local transmission of ZIKV in the United States (U.S.) was reported from Puerto Rico in December 2015, and soon thereafter local transmission was also reported in American Samoa and the U.S. Virgin Islands (Refs. 16, 17). In July 2016, the first cases of local transmission of ZIKV occurring in the continental United States were reported from Miami-Dade County in Florida (Ref. 18). The possibility of further geographic spread of ZIKV exists in regions where the *Aedes aegypti*, and possibly the *Aedes albopictus*, mosquito is present. In January 2016, Zika virus disease was added to the list of nationally notifiable conditions in the U.S. as a subtype of Arboviral diseases (Ref. 18).

ZIKV disease symptoms include fever, arthralgia, maculopapular rash, and conjunctivitis. Less frequently observed symptoms include digestive problems (abdominal pain, diarrhea and constipation), mucous membrane ulcerations (aphthae), and pruritus (Refs. 19, 20). In addition, neurological manifestations have been temporally and spatially associated with ZIKV disease outbreaks (Refs. 1, 2, 20). ZIKV infection has been associated with an increased incidence of Guillain-Barré syndrome (Ref. 21). Zika virus infection during pregnancy is a cause of microcephaly and other serious fetal brain anomalies. Other problems have been detected in pregnancies and among fetuses and infants infected with ZIKV before birth, such as miscarriage,

stillbirth, absent or poorly developed brain structures, defects of the eye, hearing deficits, and impaired growth; however, the full clinical spectrum of the effects of Zika virus infection during pregnancy is not yet known (Refs. 22, 23, 24, 25 26, 27).

Sexual transmission of ZIKV has been reported, including through male to female, male to male, and female to male routes (Refs. 4, 5). ZIKV RNA has been detected for up to 6 months in semen, although the maximum duration of transmissibility remains unknown at this time (Refs. 28, 29, 30). ZIKV has also been detected for up to 11 days in vaginal fluid; however data are currently unavailable on the maximum duration of its persistence in such fluid (Ref. 31). Prolonged circulation of ZIKV RNA in serum has also been demonstrated in pregnant women (Ref. 32).

ZIKV may be spread through blood transfusion. In French Polynesia, 2.8% of samples from asymptomatic blood donors contained detectable ZIKV RNA during the 2013-2014 outbreak, indicating the potential for transmission by blood transfusion (Refs. 11, 33). Confirmation of this finding came in 2016, as close to 1% of blood collected from asymptomatic donors in Puerto Rico tested positive when screened for ZIKV (Ref. 34). Probable transfusion-transmission of ZIKV also has been reported from Brazil (Refs. 6, 7).

Regarding measures to help prevent ZIKV transmission through the transfusion of blood products, ZIKV is likely cleared by the existing viral inactivation and removal methods that are currently used to clear viruses in the manufacturing processes for plasma-derived products. For example, viral clearance steps for various products may include heat, solvent/detergent (S/D) treatment and incubation at low pH (Refs. 35, 36, 37). These methods are highly effective in clearing lipid-enveloped viruses in plasma-derived products, but are not generally applicable for use in blood and blood components intended for transfusion. However, an S/D treated pooled plasma product has been FDA-licensed and is commercially available.

A pathogen reduction device (amotosalen combined with UV illumination) for plasma and platelets has recently been approved by the FDA (Ref. 38) and demonstrated effective reduction of a panel of viruses, including flaviviruses, such as dengue and West Nile virus. The same pathogen reduction technology (PRT) can effectively reduce ZIKV in plasma (Ref. 39). These devices have been used to reduce the risk of ZIKV infection by plasma or apheresis platelet components that are collected in areas experiencing ZIKV outbreaks (Ref. 10).

Risk of ZIKV Transmission by Blood Transfusion

In summary, the risk of transmission of ZIKV by blood transfusion is considered likely based on the following evidence:

1. ZIKV infection is asymptomatic in approximately 80% of individuals, and may be transmitted sexually for an unknown duration of time, potentially for up to 6 months (Refs. 1, 2, 28, 29, 30).
2. When symptoms of ZIKV do develop in individuals, the pre-symptomatic period for ZIKV infection varies from 3 to 12 days, during which viremia may occur (Refs. 1, 2, 40).

3. The viremia with ZIKV infection in non-pregnant individuals may produce up to 8.1 million copies per milliliter in serum, which typically lasts about 1-2 weeks, though duration of viremia may be longer. Whole Blood appears to have longer periods of detectable viremia when compared to serum. ZIKV RNA has been detected in Whole Blood as late as 58 days after symptom onset (Refs. 1, 2, 32, 40, 41).
4. ZIKV RNA has been found in asymptomatic blood donors during the French Polynesia outbreak in 2013-2014 and has been detected in 2016 in asymptompatic blood donors in Puerto Rico (Refs. 11, 33, 34).
5. There has been documented transfusion-transmissions of other flaviviruses such as West Nile virus, dengue virus and yellow fever vaccine virus, all of which have been shown to produce detectable viremia (the presence of virus in the blood) during asymptomatic and symptomatic infections (Refs. 42, 43, 44).
6. Probable transmission of ZIKV by blood transfusion has been reported (Refs. 6, 7).

The totality of the evidence presented above indicates that ZIKV can be transmitted through blood transfusion.

III. DISCUSSION

FDA has identified ZIKV as a transfusion-transmitted infection (TTI) under 21 CFR 630.3(l) and a relevant transfusion-transmitted infection (RTTI) under 21 CFR 630.3(h)(2). This determination is based on the severity of the disease, risk of transfusion-transmission by blood and blood components, the availability of appropriate screening measures and significant incidence and prevalence affecting the potential donor population.[3]

Transfusion-Transmitted Infection

A transfusion-transmitted infection (21 CFR 630.3(l)) means a disease or disease agent:

> (1) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and
>
> (2) For which there may be a risk of transmission by blood or blood components, or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component, or blood derivative product.

[3] Although a licensed screening test is not currently available, investigational screening tests are available at this time for use under investigational new drug applications, and these tests may be approved in the future. The Director of the Center for Biologics Evaluation and Research at FDA, taking into account the available scientific evidence, has issued a variance under 21 CFR 640.120(b), to provide for appropriate blood testing for ZIKV using investigational screening tests. This determination is based upon: 1) the potential severity of outcomes related to ZIKV, 2) the widespread nature of the global spread of ZIKV, 3) the risk of transmission of ZIKV by blood and blood components, and 4) the availability of investigational testing under IND to help reduce the risk of transmission of ZIKV through the blood supply.

Severity of Disease: ZIKV disease symptoms typically include fever, arthralgia, maculopapular rash, conjunctivitis and other less frequent symptoms include digestive problems, mucous membrane ulcerations, and pruritus. Zika virus infection during pregnancy is a cause of microcephaly and other serious fetal brain anomalies. Other problems have been detected in pregnancies and among fetuses and infants infected with ZIKV before birth, such as miscarriage, stillbirth, absent or poorly developed brain structures, defects of the eye, hearing deficits, and impaired growth; however, the full clinical spectrum of the effects of Zika virus infection during pregnancy is not yet known. ZIKV infection has also been associated with Guillain-Barré syndrome. Therefore, infection with ZIKV could be fatal or life threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure.

Risk of Transmission: The risk of transmission of ZIKV is considered likely based on demonstrated viremia in symptomatic and asymptomatic infections, documented perinatal transmission of ZIKV, the identification of ZIKV RNA in blood donations, documented transfusion-associated transmission of other flaviviruses; and reports of probable transfusion-transmission in Brazil.

Therefore, FDA has established that ZIKV is a TTI because it is a disease agent that can be fatal or life threatening and can cause permanent damage to a body structure and it is potentially transmissible by blood or blood components.

Relevant Transfusion-Transmitted Infection

Having determined that ZIKV is a TTI, below we provide FDA's assessment that ZIKV meets the conditions for an RTTI as described in 21 CFR 630.3(h)(2).

Under 21 CFR 630.3(h)(2), relevant transfusion-transmitted infection means: a transfusion-transmitted infection not listed in 21 CFR 630.3(h)(1) when the following conditions are met:

> (i) Appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by the FDA and is available; and
>
> (ii) The disease or disease agent: (A) May have significant incidence and/or prevalence to affect the potential donor population; or (B) May have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

Availability of Appropriate Screening Measures or Screening Test: Although an FDA-licensed donor screening test for ZIKV is not currently available, investigational nucleic acid testing under IND has been developed and testing under IND has been implemented in Puerto Rico and in regions of the United States at risk for local mosquito-acquired transmission of ZIKV.[4]

Sufficient incidence and prevalence: The recent outbreak of ZIKV represents a rapid expansion of the virus in the Americas and the Pacific Islands. Currently 50 countries and territories are experiencing active transmission of ZIKV. As of August 17, 2016, 8,000 locally-acquired cases of ZIKV have been reported in U.S. territories; 2,245 travel-associated cases have been reported in U.S. states; and, 14 locally acquired mosquito-borne cases have been reported in Florida (Ref. 18). Epidemiological investigations of additional non-travel related cases of ZIKV are ongoing in Florida. We conclude that there is sufficient incidence and prevalence of ZIKV to affect the potential donor population.

Therefore, FDA has determined that ZIKV meets the criteria in 21 CFR 630.3(h)(2) for an RTTI because of the sufficient incidence and prevalence of ZIKV to affect the potential donor population in the United States and because of the availability of appropriate screening tests for ZIKV.

Donor Eligibility

Consistent with existing regulations, under 21 CFR 630.10(a), a blood establishment must not collect blood from a donor before determining that the donor is eligible to donate, or before determining that an exception to 21 CFR 630.10 applies. Under 21 CFR 630.10(a), "to be eligible, the donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes in this subchapter. A donor is not eligible if the donor is not in good health or if you identify any factor(s) that may cause the donation to adversely affect: . . . (2) the safety, purity, or potency of the blood or blood component." The provision at 21 CFR 630.10(e) requires blood collection establishments to assess a donor's medical history to identify risk factors closely associated with exposure to, or clinical evidence of, an RTTI. Under 21 CFR 630.10(e)(1), "a donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection if that risk of exposure is still applicable at the time of donation." Furthermore, under 21 CFR 630.10(e)(2), a donor is ineligible to donate when donating could adversely affect the safety, purity, or potency of the blood or blood component. Under this provision, a donor must be assessed for "travel to, or residence in, an area endemic for a transfusion-transmitted infection, when such screening is necessary to assure the safety, purity, and potency of blood and blood components due to the risks presented by donor travel and the risk of transmission of that transfusion-transmitted infection by such donors." (21 CFR 630.10(e)(2)(iii)).

[4] The Director of the Center for Biologics Evaluation and Research at FDA, taking into account the available scientific evidence, has issued alternative procedures under 21 CFR 640.120(b), to provide for appropriate blood testing for ZIKV using investigational screening tests. This determination is based upon: 1) the potential severity of outcomes related to ZIKV, 2) the widespread nature of the global spread of ZIKV, 3) the risk of transmission of ZIKV by blood and blood components, and 4) the availability of investigational testing under IND to help reduce the risk of transmission of ZIKV through the blood supply.

Pursuant to these provisions, FDA considered appropriate measures to assess a donor for risk factors closely associated with ZIKV. Screening donors residing in an area with local mosquito-borne transmission of ZIKV based on a medical history suggestive of ZIKV is inherently inadequate to protect the blood supply because ZIKV infection is asymptomatic in approximately 80% of individuals. Consequently, the majority of infected persons and their sexual partners in such areas could be unaware of their risk. Although history of prior residence in or travel to an area with local ZIKV transmission, or recent sexual exposure to a person who resided in or traveled to an areas with local ZIKV transmission (with or without a diagnosis of ZIKV infection or suggestive symptoms) conveys increased risk of ZIKV, use of these risk factors to select safe donors becomes ineffective as new areas of local transmission emerge.

As we learn more about the changing epidemiology of ZIKV, we recognize that there may be a significant delay between the time that the first case of locally acquired mosquito-borne transmission is first reported in an area and when the risk of transmission is present and could have been more widespread. Therefore, as the affected areas and number of cases of locally acquired mosquito-borne transmission of ZIKV in the continental U.S. increases, screening donors for risk factors will become increasingly logistically complex and decreasingly effective while also resulting in significant donor deferrals potentially compromising adequacy of the blood supply.

Additionally, the possibility exists that sexual transmission of ZIKV may evolve as a significant mode of spread of ZIKV independent of mosquito borne transmissions, rendering determination of locally affected areas by mosquito-borne transmission an inadequate safeguard. In contrast, testing blood donations for evidence of ZIKV or pathogen reduction by an approved device represents a more effective safeguard against ZIKV, rendering donor screening of de minimus value because general use of these alternate measures would: a) obviate determination of affected geographic areas; b) provide highly sensitive detection of virus-contaminated blood donations independent of a donor's medical or travel history; c) provide a safeguard against transfusion risk related to sexual transmissions; and d) assure continued availability of an adequate blood supply. Based on these considerations, FDA has concluded that it is necessary for blood establishments to implement nucleic acid testing of all donations or pathogen reduction technology using an FDA-approved device to reduce the risk of ZIKV transmission by blood and blood components.

Therefore, to provide for appropriate donor screening and testing, the Director of the Center for Biologics Evaluation and Research is providing an alternative procedure under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10 to assess donors for specific risk factors for ZIKV before collecting blood or blood components. The Director of the Center of Biologics Evaluation and Research at FDA, taking into account the available scientific evidence, has issued alternative procedures to this provision under 21 CFR 640.120(b), to provide for appropriate donor testing for ZIKV with an investigational screening test available for use under investigational new drug applications. Alternatively, you may implement pathogen reduction technology using an FDA-approved device as specified in the instructions for use of the device to reduce the risk of ZIKV transmission.

IV. RECOMMENDATIONS

The following recommendations are intended to reduce the risk of ZIKV transmission by blood and blood components. The recommendations apply to the collection of all Whole Blood and blood components[5] in the United States and its territories. If, based upon the available scientific evidence, the risk of ZIKV transmission by blood and blood components significantly changes, FDA may update these recommendations as warranted. In making this determination, FDA will consider available epidemiologic and other scientific evidence.

A. Testing and Pathogen Reduction

We recommend the following:

1. Test all donations collected in the U.S. and its territories with an investigational individual donor nucleic acid test (ID-NAT) for ZIKV under an investigational new drug application (IND), or when available, a licensed test, *or*

2. Implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device as specified in the Instructions for Use of the device. If an FDA-approved pathogen reduction device becomes available for Whole Blood or red blood cells, you may implement pathogen reduction technology for such products rather than testing the donations as described in section IV.A.1.

   Note: Use of investigational pathogen reduction under an investigational device exemption (IDE) may be permitted in situations where approved technologies are unavailable.

Because all donations will be tested using an investigational ID-NAT for ZIKV under an IND or when available, a licensed test, or pathogen-reduced using an FDA-approved pathogen reduction device, you may discontinue providing donor educational material with respect to ZIKV and screening donors for ZIKV risk factors, such as travel history, and deferring them as previously recommended in the February 2016 guidance. Under 21 CFR 630.10(a), if a donor volunteers a recent history of ZIKV infection, you must not collect blood or blood components from that individual. We recommend that you defer such a donor for 120 days after a positive viral test or the resolution of symptoms, whichever timeframe is longer.

[5] The recommendations do not apply to the collection of Source Plasma. Viral inactivation and removal methods that are currently used to clear viruses in the manufacturing process for plasma-derived products are sufficient to reduce the risk of the transmission of ZIKV.

B. Donor and Product Management

1. You may release ID-NAT non-reactive donations provided all other donation suitability requirements are met (21 CFR 630.30).

2. If a donation tests ID-NAT reactive for ZIKV, you must not distribute or use the donation unless an exception exists (21 CFR 610.40(h))[6].

3. You must defer a donor who tests ID-NAT reactive for ZIKV and notify the donor of the deferral (21 CFR 610.41 and 630.30). We recommend that you defer the donor for 120 days[7] from the date of the reactive test or after the resolution of ZIKV symptoms, whichever timeframe is longer. We recommend you counsel the donor regarding a possible ZIKV infection.

4. We recommend that you quarantine and retrieve in-date blood and blood components collected from a donor in the 120 days prior to the donation that is ID-NAT reactive. Additionally, if such blood components were transfused, we recommend that you advise the transfusion service to inform the transfusion recipient's physician of record regarding the potential need for monitoring and counseling the recipient for a possible ZIKV infection.

C. Labeling of Whole Blood and Blood Components Intended for Transfusion

Under 21 CFR 606.122(h), the circular of information must include the names and results of all tests performed when necessary for safe and effective use. When testing is performed, we recommend that you update your circular of information to include the non-reactive ID-NAT results for ZIKV. You should indicate whether the testing has been performed using an investigational or licensed test.

V. IMPLEMENTATION

We recommend that blood establishments implement the recommendations in this guidance as follows:

1. Blood establishments that collect Whole Blood and blood components in U.S. states and territories with one or more reported locally acquired mosquito-borne cases of ZIKV should implement the recommendations immediately. You should cease blood collection until testing or the use of pathogen reduction technology is implemented, consistent with the recommendations in this guidance.

[6] This requirement applies to all donations that test ID-NAT reactive for ZIKV, including those that have been pathogen-reduced.

[7] We recommend a deferral period of 120 days until more data become available on the duration of the viremic period and virus transmissibility.

As of the date of issuance of this guidance, this recommendation applies to blood establishments that collect Whole Blood and blood components in Florida and Puerto Rico.[8]

2. Because of their proximity to areas with locally acquired mosquito-borne cases of ZIKV or because of other epidemiological linkage to ZIKV, such as the number of travel-associated cases reported in a state, blood establishments that collect Whole Blood and blood components in Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina and Texas should implement the recommendations as soon as feasible, but not later than 4 weeks after the guidance issue date.

3. Blood establishments that collect Whole Blood and blood components in all other states and territories should implement the recommendations as soon as feasible, but not later than 12 weeks after the guidance issue date.

Consistent with 21 CFR 601.12, licensed establishments implementing these recommendations should update their annual reports indicating the date that the establishment revised and implemented their standard operating procedures consistent with these recommendations. See 21 CFR 601.12(a)(3). These changes do not require our prior approval.

[8] At this time blood is not being collected on a routine basis in American Samoa and the U.S. Virgin Islands.

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