OPQ staff participating in this program will benefit by gaining a better understanding of current industry practices, processes, and procedures. Participating sites will have an opportunity to showcase their technologies and their actual manufacturing and testing facilities.

Although observation of all aspects of drug development and production would be beneficial to OPQ staff, OPQ has identified a number of areas of particular interest to its staff. The following list identifies some examples of these areas but is not intended to be exhaustive, mutually exclusive, or to limit industry response:

- Drug products
  - Solutions, suspensions, emulsions, and semisolids
  - Modified- and immediate-release formulations
  - Drug-device combination products (*e.g.,* inhalation products, transdermal systems, implants intended for drug delivery, and prefilled syringes)
- Active pharmaceutical ingredients manufactured by
  - Chemical synthesis
  - Fermentation
  - Biotechnology
- Design, development, manufacturing and controls
  - Engineering controls for aseptic processes
  - Novel delivery technologies
  - Hot melt extrusion
  - Soft-gel encapsulation
  - Lyophilization
  - Blow-Fill-Seal and isolators
  - Spray-drying
  - Process analytical technology, measurement systems, and real-time release testing
- Emerging technologies
  - Continuous manufacturing
  - 3-dimensional printing
  - Nanotechnology

III. Site Selection

Selection of potential facilities will be based on the priorities developed for OPQ staff training, the facility's current compliance status with FDA, and in consultation with the appropriate FDA district office. All travel expenses associated with this program will be the responsibility of OPQ; therefore, selection will be based on the availability of funds and resources for the fiscal year. OPQ will not provide financial compensation to the pharmaceutical site as part of this program.

IV. Proposals for Participation

Companies interested in offering a site visit or learning more about this site visit program should respond by submitting a proposal directly to Janet Wilson (see **DATES** and **FOR FURTHER INFORMATION CONTACT** sections of this document for more information). To aid in OPQ's site selection and planning, your proposal should include the information below:

- A contact person,
- Site visit location(s),
- Facility Establishment Identifier and Data Universal Numbering System numbers, as applicable,
- Maximum number of FDA staff that can be accommodated during a site visit (maximum of 20),
- A proposed agenda outlining the learning objectives and associated activities for the site visit,
- Maximum number of site visits (no more than 2) that your site would be willing to host by the close of the government fiscal year, September 30, 2019, and
- Proposed dates for each site visit (*i.e.* month and week).

Please note that the requested proposed agenda will be reviewed to determine the educational benefit to OPQ in conducting the visit, and selected sites may be asked to refine the agenda to maximize the educational benefit. After a site is selected, OPQ will communicate with the contact person for the site to determine the actual dates for the visit.

Proposals submitted without this minimum information will not be considered. Based on response rate and type of responses, OPQ may or may not consider alternative pathways to meeting our training goals.

Dated: August 21, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–18305 Filed 8–23–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0567]

Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes the Food and Drug Administration (FDA or Agency) to award priority review vouchers (PRVs) to tropical disease product applicants when the applications meet certain criteria. The FD&C Act lists the diseases that are considered tropical diseases for purposes of obtaining PRVs and provides for Agency expansion of that list to include other diseases that satisfy the definition of ''tropical diseases'' as set forth in the FD&C Act. The Agency has determined that chikungunya virus disease, Lassa fever, rabies, and cryptococcal meningitis satisfy this definition and is therefore adding them to the list of designated tropical diseases whose product applications may result in the award of PRVs. Sponsors submitting certain drug or biological product applications for the prevention or treatment of chikungunya virus disease, Lassa fever, rabies, and cryptococcal meningitis may be eligible to receive a PRV if such applications are approved by FDA.

DATES: This order is effective August 24, 2018.

ADDRESSES: Submit electronic comments on additional diseases suggested for designation to *https://www.regulations.gov.* Submit written comments on additional diseases suggested for designation to the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Katherine Schumann, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6242, Silver Spring, MD 20993–0002, 301–796–1300, *Katherine.Schumann@fda.hhs.gov;* or Office of Communication, Outreach and Development (OCOD), Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 1–800–835–4709 or 240–402–8010, *ocod@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Background: Priority Review Voucher Program

Section 524 of the FD&C Act (21 U.S.C. 360n), which was added by section 1102 of the Food and Drug Administration Amendments Act of 2007, uses a PRV incentive to encourage the development of new drugs for prevention and treatment of certain diseases that, in the aggregate, affect millions of people throughout the world. Further information about the tropical disease PRV program can be found in guidance for industry ''Tropical Disease Priority Review Vouchers'' (81 FR 69537, October 6, 2016, available at *https://www.federalregister.gov/documents/2015/08/20/2015-20554/designating-additions-to-the-current-list-of-tropical-diseases-in-the-federal-food-drug-and-cosmetic*). Additions to the statutory list of tropical diseases published in the **Federal Register** can be accessed at *https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm.*

On August 20, 2015, FDA published a final order (80 FR 50559) (final order) designating Chagas disease and neurocysticercosis as tropical diseases. That final order also sets forth FDA's interpretation of the statutory criteria for tropical disease designation and expands the list of tropical diseases under section 524(a)(3)(S) of the FD&C Act, which authorizes FDA to designate by order ''[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations'' as a tropical disease.

In this document, FDA has applied its August 2015 criteria as set forth in the final order to analyze whether Chikungunya virus disease, Lassa fever, rabies, and cryptococcal meningitis meet the statutory criteria for addition to the tropical disease list.

II. Diseases Being Designated

FDA has considered all diseases submitted to the public docket (FDA–2008–N–0567) between August 20, 2015, and June 20, 2018, as potential additions to the list of tropical diseases under section 524 of the FD&C Act, pursuant to the docket review process explained on the Agency's website (see *https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm*). Based on an assessment using the criteria from its August 20, 2015, final order, FDA has determined that the following additional diseases will be designated as ''tropical diseases'' under section 524 of the FD&C Act:

- Chikungunya virus disease
- Lassa fever
- Rabies
- Cryptococcal meningitis

FDA's rationale for adding these diseases to the list is discussed in the analyses that follow.

A. Chikungunya Virus Disease

Chikungunya virus (CHIKV) is an arbovirus transmitted by *Aedes* mosquitoes in tropical climates in Africa, Asia, islands in the Indian and Pacific Oceans, Europe, and, since 2013, the Americas (Ref. 1). Although CHIKV mortality is relatively low (0.01 to 0.1 percent), attack rates are very high (33 to 66 percent) and most infections are symptomatic (Refs. 2 and 3). Many infected individuals experience painful arthralgia, which can persist for months and even years (Ref. 4). Life-threatening manifestations of CHIKV, including organ failure, meningoencephalitis, hemorrhagic symptoms, and myocardial disease, and death occur in neonates, the elderly, and individuals with chronic comorbidities (Ref. 3).

There is no approved antiviral treatment for CHIKV in the United States or anywhere else in the world (Refs. 5 and 6). Therapeutic management largely aims to relieve pain and inflammation and limit the loss of mobility and physical fitness through the use of analgesic and non-steroidal anti-inflammatory drugs. There is no approved CHIKV vaccine (Ref. 6).

1. No Significant Market in Developed Nations

CHIKV disease occurs rarely in developed nations (Ref. 1). Outbreaks of CHIKV primarily occur in poor tropical regions where uncontrolled breeding of *Aedes aegypti* and *Aedes albopictus* mosquitoes occurs in close proximity to humans due to inadequate sanitation and poor living conditions (Ref. 7). For example, in 2015, more than 700,000 suspected or confirmed cases of CHIKV were reported in the Americas; however, only 1,185 of those cases occurred in the United States (excluding territories) and Canada, all of which were imported (Refs. 8 and 9). The U.S. territories of Puerto Rico and the U.S. Virgin Islands reported 202 cases, all of which were transmitted locally (Ref. 8). There were no locally transmitted cases of CHIKV reported in Europe, Japan, Australia, or New Zealand in 2015 (Ref. 10). Even among U.S. military and military dependents, who are sometimes deployed to outbreak areas, CHIKV infection is rare; there were only 121 CHIKV cases among U.S. Department of Defense healthcare beneficiaries between January 2014 and February 2015 (Ref. 11).

Based on the epidemiology of reported CHIKV cases, the market for vaccines in developed nations such as the United States would largely comprise travelers at risk of CHIKV infection and military populations. These markets are unlikely to provide sufficient incentive to encourage development of products to treat or prevent CHIKV infection. Although a limited number of locally transmitted cases have recently been reported in U.S. territories, the disease is not currently considered endemic in those areas. Whether those populations could broaden the market for products to treat or prevent CHIKV infection in the future is unknown. CHIKV drug development is not significantly funded by U.S. Government sources, and CHIKV is not among the Centers for Disease Control and Prevention's (CDC) list of potential bioterrorism agents.

2. Disproportionately Affects Poor and Marginalized Populations

Poor populations in tropical environments experience the primary burden of CHIKV disease because they are disproportionally exposed to its mosquito vectors (Ref. 7). Arboviral diseases disproportionally affect low-income urban and rural populations through increased mosquito exposure due to poor housing, lack of sanitation infrastructure, and outdoor occupations such as animal husbandry (Refs. 7 and 12). Large-scale and systematic insecticide mosquito control programs, once considered a public health priority throughout the world due to yellow fever virus, were largely dismantled due to diminishing resources and are therefore not available in most developing nations (Ref. 13).

Although CHIKV infection is rarely fatal, CHIKV sequelae have a major impact on productivity and economics in developing nations (Ref. 7). CHIKV outbreaks are often explosively large, with high attack rates and high rates of symptomatic disease (Refs. 1 and 3). An outbreak in India in 2006 involved more than 1.3 million suspected cases and was associated with more than 25,000 Disability Adjusted Life Years (DALYs) lost (Ref. 14). A meta-analysis of 38 published studies confined to cases occurring in 2005 estimated that CHIKV led to up to 1 million years of healthy life lost and 1.5 million DALYs lost (Ref. 15).

Neonates are particularly vulnerable to serious complications of CHIKV infection. Among neonates born 1 day

before or within 5 days following the onset of their infected mothers' symptoms, 50 percent are born with CHIKV infection (Ref. 3). Neonates are also highly vulnerable to direct inoculation of CHIKV through mosquito bites. Infected neonates present with fever, breastfeeding difficulties, thrombocytopenia, lymphopenia, and moderate hepatic cytolysis. One in four develops one or more serious complications, such as encephalopathy with progressive cerebral edema, sepsis, coagulopathy with hemorrhage, and cardiomyopathy (Ref. 3).

The elderly and individuals with chronic comorbid conditions are also susceptible to life-threatening CHIKV disease (Refs. 3 and 16). A case series of 65 patients admitted to intensive care units with confirmed CHIKV in Martinique and Guadeloupe found that most patients were older than 50, and 83 percent of patients had preexisting comorbidities such as hypertension, diabetes, heart failure, and chronic kidney disease (Ref. 16). Upon admission, 57 percent required mechanical ventilation, 46 percent had shock requiring vasoactive drugs, 31 percent required renal replacement therapy, and 27 percent died (Ref. 16).

The World Health Organization (WHO) has designated Chikungunya as a Neglected Tropical Disease (Ref. 17).

Given the factors described above, FDA has determined that CHIKV disease meets both statutory criteria of ''no significant market in developed nations'' and ''disproportionately affects poor and marginalized populations.'' Therefore, FDA is designating CHIKV disease as a tropical disease under section 524 of the FD&C Act.

B. Lassa Fever

Lassa fever (LF) is an acute viral infection caused by Lassa virus, a single-stranded ribonucleic acid virus belonging to the arenavirus family. LF is endemic in parts of West Africa (Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Nigeria), but probably exists in other West African countries where the animal vector for Lassa virus is distributed. Most Lassa virus infections (~80 percent) are mild or asymptomatic. In the remaining 20 percent of Lassa virus infections, the disease may progress to more severe symptoms that include respiratory distress, bleeding, shock, multiorgan system failure, and death. Involvement of the central nervous system may also occur with tremors, encephalitis, or hearing loss (Ref. 18).

The overall mortality rate of all Lassa virus infections is approximately 1 percent. However, the mortality rate in hospitalized patients is about 15 to 20 percent (Ref. 19). The most common complication of Lassa virus infection is sensorineural hearing loss. About one-third of hospitalized patients develop hearing loss; in most of these patients, hearing loss is permanent. Sensorineural hearing loss may also occur in patients with mild or asymptomatic disease (Ref. 20).

Currently, there are no FDA-approved drugs for prophylaxis or treatment of LF. In the absence of vaccine that protects against LF, disease prevention relies on good community hygiene to avert rodents from entering homes.

1. No Significant Market in Developed Nations

LF does not occur in developed countries, except for a few imported cases. Characteristically, since 1969, only six cases of LF have been documented in travelers returning to the United States (not including convalescent patients) (Ref. 21). Thus, LF appears to meet the criteria of not having a significant direct market in developed countries.

FDA is also unaware of evidence of a significant indirect market for LF products. Lassa virus, like other hemorrhagic viruses, has been categorized as a Category A pathogen by CDC (Refs. 22 to 24). Category A pathogens are considered a threat to public health and are viewed as potential biological weapons threat agents. Therefore, if a drug against a Category A pathogen is developed, it could have an indirect market if stockpiled as a medical countermeasure for the U.S. Government. At present, however, FDA is unaware of any significant funding by the military, the Biomedical Advanced Research and Development Authority, or any other U.S. Government sources for drug development targeting treatment or prophylaxis against LF. Further, Lassa virus is not listed as a high-priority threat in the 2017 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan (Ref. 25).

2. Disproportionately Affects Poor and Marginalized Populations

LF is exclusively endemic in some West African countries. LF cases identified in areas where LF is not endemic have occurred rarely and are usually imported by persons returning from West Africa. Every year, Lassa virus is estimated to cause 100,000 to 300,000 infections in West Africa, with approximately 5,000 deaths (Refs. 19 and 21). All countries where LF is known to be endemic (Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Nigeria) are classified by the World Bank as either low income (gross national income per capita of $1,045 or less) or lower-middle income (gross national income per capita of $1,046-$4,125). Further, the incidence of LF in endemic countries is much higher among the poorest rural populations (Ref. 26). The characteristics of the disease (high morbidity and mortality) indicate a potentially significant DALY impact, although a comprehensive literature search failed to identify any DALY data.

LF causes serious disease and death in both sexes and in all age groups, including children. The mortality rate is much higher for women in their third trimester of pregnancy. Spontaneous abortion is also a serious complication of Lassa virus infection, with a 95 percent mortality in fetuses of pregnant women (Refs. 21 and 26).

LF has not been designated by WHO as a neglected tropical disease. However, a panel of scientists and public health experts convened by WHO met in Geneva on December 8 and 9, 2015, to prioritize the top 5 to 10 emerging pathogens likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist. LF was one out of the nine diseases included in the initial list that need research and development preparedness to help control future outbreaks (Refs. 26 and 27).

Given the factors described above, FDA has determined that LF meets both statutory criteria of ''no significant market in developed nations'' and ''disproportionately affects poor and marginalized populations.'' Therefore, FDA is designating Lassa fever as a tropical disease under section 524 of the FD&C Act.

C. Rabies

Human rabies infection is caused by the rabies virus, which typically enters the body through animal bite wounds or by direct contact of the virus with the body's mucosal or respiratory surfaces. Virtually all patients with human rabies infection ultimately progress to coma followed by death, although rare recoveries have been reported (Ref. 28).

As rabies is almost always fatal, post-exposure prophylaxis is recommended after suspected or proven exposure to rabies virus. Post-exposure rabies prophylaxis (PEP) should include wound cleansing, infiltration of rabies immunoglobulin into and around the wound, and vaccination with cell culture rabies vaccines (Ref. 29). Pre-exposure prophylaxis, consisting of

administration of a rabies vaccine course, is recommended for anyone who is at continual, frequent, or increased risk for exposure to the rabies virus (Ref. 30). Rabies vaccines licensed for human use in the United States include human diploid cell vaccine (IMOVAX) and purified chick embryo cell vaccine (RabAvert). WHO has recommended discontinuation of nerve tissue vaccines, which are associated with more severe adverse reactions and are less immunogenic than cell-culture and embryonated egg-based rabies vaccines, since 1984; however, these vaccines remain in use in some developing nations (Ref. 31). Two rabies immunoglobulin products are licensed in the United States: IMOGAM and HyperRab. There are no approved treatments for symptomatic human rabies infection.

1. No Significant Market in Developed Nations

In developed nations, wild animals (*e.g.,* raccoons, bats, skunks, foxes), rather than domesticated animals, account for the vast majority of reported rabies cases. Successful rabies vaccination programs have eliminated canine rabies in developed nations (including the United States), except for cases contracted while living in or travelling to rabies-endemic areas (Ref. 31). WHO categorizes Europe and North America as low-risk areas for humans contracting rabies (Ref. 32). Specific rabies prevalence information in the U.S. animal population was not identified in review of CDC rabies surveillance data; however, in 2014, a total of 6,033 animals were reported to be rabid in the United States, over 90 percent occurring in wild animals (Ref. 33).

Using pre-exposure or post-exposure prophylaxis can prevent human rabies infection. Christian, et al. reported an estimated 6,000 to 7,000 vaccine doses used annually in the United States for pre-exposure vaccination of critical personnel engaged in occupational activities with a risk for rabies exposure, and a separate survey estimated 6,600 vaccine doses required each year to vaccinate approximately 2,200 veterinary students (Ref. 34).

The United States does not have a national reporting system for use of rabies PEP; therefore, the accurate usage information is unknown. The CDC states an estimated 40,000 to 50,000 PEP treatments are administered annually in the United States, yielding an incidence of 0.01 to 0.02 percent using 2015 U.S. Census Bureau population estimate data (Refs. 35 and 36). Christian, et al. reported that between 2006 and 2008, the annual U.S. national average PEP use was estimated at 23,415 courses (range: 10,645–35,845), with an average annual rate of PEP administration for 16 states and NYC of 8.46/100,000 persons (range: 1.14–18.89/100,000 persons) (Ref. 34). The available data regarding pre-exposure and post-exposure rabies prophylaxis in the United States suggests that the population for whom rabies vaccines and human rabies immunoglobulin products are used is below 0.1 percent of the population, supporting the conclusion that there is no significant market for preventing human rabies infection in developed nations.

Between 2006 and 2011, there were 12 human rabies cases reported in Europe, of which 6 were imported (Refs. 37 and 38). In the United States and Puerto Rico, 37 persons have been diagnosed with human rabies since 2003, including 11 cases (30 percent) with exposure occurring outside of the United States and its territories and 5 cases (14 percent) acquired from organ or tissue transplantation (Ref. 33). Although a specific prevalence is not reported, the rarity of human rabies infection in the United States is well below 0.1 percent of the population. A direct market for products to treat symptomatic rabies would therefore be small.

The Joint Regulation on Immunizations and Chemoprophylaxis for the Prevention of Infectious Diseases Army Regulation 40–562 provides general guidance on rabies prevention recommendations for military personnel (Army, Navy, Air Force, Marine Corps, Coast Guard) (Ref. 39). Nevertheless, FDA is unaware of evidence suggesting any sizable government or other indirect market for rabies virus products.

2. Disproportionately Affects Poor and Marginalized Populations

Although rabies is present in all continents except Antarctica, more than 95 percent of human deaths occur in Asia and Africa. WHO has designated rabies virus as a Neglected Tropical Disease (Ref. 17). It considers rabies a neglected disease of poor and vulnerable populations and reports the majority of deaths (84 percent) occur in rural areas (Ref. 31). In contrast to rabies epidemiology in developed nations, domestic dogs account for 99 percent of human rabies cases globally. Children in particular are at risk for human rabies infection: 40 percent of people bitten by suspected rabid animals are less than 15 years of age (Ref. 40).

Human rabies infection is a preventable disease, and the overwhelming majority of rabies deaths result from the lack of recommended PEP administration following suspected rabies exposure (Ref. 39). The annual number of human rabies deaths worldwide estimated in 2010 ranged from 26,400 (95 percent confidence interval 15,200–45,200) to 61,000 (95 percent CI 37,000–86,000) using different statistical approaches (Ref. 31). Using these data, DALYs for human rabies are estimated at 1.9 million (95 percent CI, 1.3–2.6 million) (id.). In developing countries, licensed purified cell culture and embryonated egg-based rabies vaccines and immunoglobulin for rabies PEP are neither readily available (due to shortages) nor accessible (distance to medical centers, affordability) (Refs. 39 and 40). The average cost of rabies PEP is reported to be US $40 in Africa and US $49 in Asia, which greatly exceeds the average daily income estimated at US $1–$2 per person (Ref. 40).

Given the factors described above, FDA has determined that rabies meets both the statutory criteria of ''no significant market in developed nations'' and ''disproportionately affects poor and marginalized populations.'' Therefore, FDA is designating rabies as a tropical disease under section 524 of the FD&C Act.

D. Cryptococcal Meningitis

Cryptococcus species are encapsulated fungi found in the environment throughout the world. The two most prominent species that cause human disease are *C. neoformans* and *C. gattii* (Ref. 41). The majority of cryptococcal meningitis (CM) is caused by *C. neoformans* infection in immunocompromised individuals. The incidence of CM increased substantially with the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) epidemic in the late 20th century and remains high in developing countries that lack access to effective antiretroviral therapy (Ref. 42).

Cryptococcal infection typically occurs by inhalation of the fungi into the lungs. In immunocompromised individuals, the resulting pulmonary infection frequently spreads to the central nervous system, causing meningitis (Ref. 43). The primary recommended treatment of CM in developed countries includes a 2-week induction phase with amphotericin B and oral flucytosine, followed by long-term maintenance therapy with oral fluconazole (Ref. 44). In resource-limited nations, oral fluconazole is often the only therapeutic option available. Poor access to care and limited availability of standard antifungal therapy for patients with CM result in

significantly higher mortality and treatment failure rates in developing countries (Ref. 45). Park, et al. (2009) estimated that, excluding HIV/AIDS, CM is the fourth leading cause of death in sub-Saharan Africa, causing more deaths than tuberculosis (Ref. 46).

1. No Significant Market in Developed Nations

Immunocompromised patients are typically the most vulnerable population to develop serious manifestations from infection with *Cryptococcus,* and the prevalence of CM is closely linked to the prevalence of untreated and poorly managed HIV/AIDS. There has been a reduction in the incidence of CM in the United States and other developed nations due to the availability of antiretroviral therapy and lower rates of individuals with advanced HIV/AIDS (Ref. 42). Per the CDC, national estimates of the incidence of cryptococcosis are difficult to establish because it is only reportable in a few states (id.). In 2000, a population-based surveillance study in two U.S. metropolitan areas estimated that the annual incidence of cryptococcosis among persons with AIDS was between 2 and 7 cases per 1,000, and the overall incidence was 0.4 to 1.3 cases per 100,000 (Ref. 47). As of 2009, Pyrgos, et al. estimated that approximately 3,400 annual hospitalizations were associated with CM in the United States (Ref. 48). Given that the overwhelming majority of patients diagnosed with CM in the United States will initiate therapy in the hospital, FDA considers 3,400 annually a rough estimate of the number of cases of CM in the United States. Based on the CDC treatment guidelines for CM, FDA estimates that most CM patients will receive at least 1 year of therapy. Therefore, even if the proportion of CM patients on therapy at any given time is 50 times the annual incidence of CM, the prevalence of CM in the United States remains below 0.1 percent of the population.

Clinical practice guidelines for the management of cryptococcal disease do not routinely recommend primary antifungal prophylaxis for cryptococcosis in HIV-infected patients in the United States and Europe. This recommendation is based on the relative infrequency of cryptococcal disease, lack of survival benefits, potential for drug-drug interactions, creation of direct antifungal drug resistance, medication compliance, and costs. Routine primary prophylaxis for cryptococcosis is also not currently recommended in transplant recipients (Ref. 44).

The emergence of *C. gattii* in the Pacific Northwest in 2004, primarily among immunocompetent individuals, raised concerns about a new serious infectious disease risk for people residing in or traveling to the Pacific Northwest states. However, there have been only 60 cases reported to CDC between 2004 and 2010 (Ref. 49). U.S. cases continue to be reported at a relatively low rate, 20–23 cases per year each in 2012 and 2013 (Ref. 50). The emergence of *C. gattii* in the United States has not resulted in a large number of cases that could potentially warrant a significant market for treatment or prevention.

Therefore, in the United States and other developed countries, there does not appear to be a significant market for developing new drugs or vaccines for the treatment or prevention of CM. Additionally, given the low incidence of CM and the low risk of infection to immunocompetent individuals, it is unlikely that antifungal therapies specifically directed against CM will become a national stockpiling priority in the foreseeable future.

2. Disproportionately Affects Poor and Marginalized Populations

CM is not currently designated by WHO as a Neglected Tropical Disease (Ref. 17). Additionally, no DALY data were found to distinguish the disease burden of CM in developing versus developed countries. However, the incidence of CM is high in developing countries due to limited access to antiretroviral therapy to treat HIV infection (Ref. 42). Annually, there are approximately 1 million cases of CM worldwide in patients with HIV/AIDS and 625,000 deaths (Ref. 46). Approximately 75 percent of these infections are in sub-Saharan Africa (id.). The case fatality rate for CM patients living in sub-Saharan Africa is 35 to 65 percent, compared to a 10- to 20-percent case fatality rate in most developed nations (Ref. 51).

The HIV epidemic imposes a particular burden on women and children, specifically in sub-Saharan Africa where women account for approximately 57 percent of all people living with HIV (Ref. 52). In 2012, there were an estimated 260,000 newly infected children in low- and middle-income countries (id.). Children with HIV are more likely to face gaps in access to HIV treatment. For example, in 2012, approximately 34 percent of children had access to HIV treatment versus approximately 64 percent for adults (id.). As CM is most prevalent in persons infected with HIV and HIV disproportionately impacts women and children, it is reasonable to conclude that CM also disproportionately affects these populations.

Given the factors described above, FDA has determined that CM meets both statutory criteria of ''no significant market in developed nations'' and ''disproportionately affects poor and marginalized populations.'' Therefore, FDA is designating cryptococcal meningitis as a tropical disease under section 524 of the FD&C Act.

III. Process for Requesting Additional Diseases To Be Added to the List

The purpose of this order is to add diseases to the list of tropical diseases that FDA has found to meet the criteria in section 524(a)(3)(S) of the FD&C Act. By expanding the list with this order, FDA does not mean to preclude the addition of other diseases to this list in the future. Interested persons may submit requests for additional diseases to be added to the list to the public docket established by FDA for this purpose (see *https://www.regulations.gov,* Docket No. FDA–2008–N–0567). Such requests should be accompanied by information to document that the disease meets the criteria set forth in section 524(a)(3)(S) of the FD&C Act. FDA will periodically review these requests, and, when appropriate, expand the list. For further information, see *https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm.*

IV. Paperwork Reduction Act

This final order reiterates the ''open'' status of the previously established public docket through which interested persons may submit requests for additional diseases to be added to the list of tropical diseases that FDA has found to meet the criteria in section 524(a)(3)(S) of the FD&C Act. Such a request for information is exempt from Office of Management and Budget review under 5 CFR 1320.3(h)(4) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Specifically, ''[f]acts or opinions submitted in response to general solicitations of comments from the public, published in the **Federal Register** or other publications, regardless of the form or format thereof'' are exempt, ''provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the agency's full consideration of the comment.''

V. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for

viewing by interested persons between 9 a.m. and 4 p.m. Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

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Dated: August 21, 2018.

Leslie Kux, Associate Commissioner for Policy.

[FR Doc. 2018–18314 Filed 8–23–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities: Submission to OMB for Review and Approval; Public Comment Request; The Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children's Public Health System Assessment Surveys OMB No. 0906–0014—Revised

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

ACTION: Notice.

SUMMARY: In compliance with of the Paperwork Reduction Act of 1995, HRSA has submitted an Information Collection Request (ICR) to the Office of Management and Budget (OMB) for review and approval. Comments submitted during the first public review of this ICR will be provided to OMB. OMB will accept further comments from the public during the review and approval period.

DATES: Comments on this ICR should be received no later than September 24, 2018.

ADDRESSES: Submit your comments to *paperwork@hrsa.gov* or mail the HRSA Information Collection Clearance Officer, Room 14N136B, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: To request a copy of the clearance requests submitted to OMB for review, email Lisa Wright-Solomon, the HRSA Information Collection Clearance Officer at *paperwork@hrsa.gov* or call (301) 443–1984.

SUPPLEMENTARY INFORMATION:

Information Collection Request Title: The Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children's Public Health System Assessment Surveys OMB No. 0906–0014—Revised.

Abstract: The purpose of the public health system assessment surveys is to inform the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee) on the ability to add newborn screening for particular conditions within a state, including the feasibility, readiness and overall capacity to screen for a new condition.

The Committee was established under Section 1111 of the Public Health Service Act, 42 U.S.C. 300b–10, as amended in the Newborn Screening Saves Lives Reauthorization Act of 2014. The Committee is governed by the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), which sets forth standards for the formation and use of advisory committees. The purpose of the Committee is to provide the Secretary with recommendations, advice, and technical information regarding the most appropriate application of technologies, policies, guidelines, and standards for: (a) Effectively reducing morbidity and mortality in newborns and children having, or at risk for, heritable disorders; and (b) enhancing the ability of state and local health agencies to provide for newborn and child screening, counseling, and health care services for newborns and children having, or at risk for, heritable disorders. Specifically, the Committee makes systematic evidence-based recommendations on newborn screening for conditions that have the potential to change the health outcomes for newborns.

The Committee tasks an external workgroup to conduct systematic evidence-based reviews for conditions being considered for addition to the Recommended Uniform Screening Panel, and their corresponding newborn screening test(s), confirmatory test(s), and treatment(s). Reviews also include an analysis of the benefits and harms of newborn screening for a selected condition at a population level and an assessment of state public health newborn screening programs' ability to implement the screening of a new condition.

Need and Proposed Use of the Information: HRSA proposes that the data collection surveys be administered by the Committee's external Evidence Review Group to all state newborn screening programs in the United States up to twice a year for two conditions. The surveys were developed to capture the following: (1) The readiness of state public health newborn screening programs to expand newborn screening to include the target condition; (2) specific requirements of screening for