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" eligible for PRVs as set forth in the FD&C Act. The Agency has determined that two foodborne trematode infections, opisthorchiasis and paragonimiasis, 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 opisthorchiasis or paragonimiasis infections may be eligible to receive a PRV if such applications are approved by FDA.

DATES: This order is issued on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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 Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

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 (Pub. L. 110-85), uses a PRV incentive to encourage the development of new drugs, including biological products, for prevention and treatment of certain diseases that, in the aggregate, affect millions of people throughout the

world. To be eligible to receive a tropical disease PRV, a drug must be for prevention or treatment of a "tropical disease" as listed under section 524(a)(3) of the FD&C Act. This list can be expanded by the Agency 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 an addition to the list of tropical diseases, approved drug applications for which may be eligible to receive a PRV. Further information about the tropical disease PRV program can be found in the October 6, 2016 (81 FR 69537), guidance for industry "Tropical Disease Priority Review Vouchers," available at https://www.fda.gov/media/72569/download.

On August 20, 2015, FDA published a final order (80 FR 50559) (August 2015 final order) designating Chagas disease and neurocysticercosis as additions to the list of tropical diseases under section 524 of the FD&C Act. The August 2015 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)(R) of the FD&C Act (redesignated as section 524(a)(3)(S) of the FD&C Act). Additions by order to the statutory list of PRV-eligible tropical diseases published in the *Federal Register* can be accessed at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm.

In this document, FDA has applied its August 2015 final order criteria to analyze whether the foodborne trematode infections opisthorchiasis and paragonimiasis meet the statutory criteria for addition to the tropical diseases list under section 524 of the FD&C Act.

II. Diseases Being Designated

FDA has considered all diseases submitted to the public docket (FDA-2008-N-0567) between June 20, 2018, and November 21, 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 web page at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm534162.htm. Based on an assessment using the criteria from its August 2015 final order, FDA has determined that the following additional diseases will be designated as additions to the list of tropical diseases for purposes of the tropical disease PRV program under section 524 of the FD&C Act:

- Opisthorchiasis
- Paragonimiasis

The four primary foodborne trematode infections identified by the World Health Organization (WHO) include these two infections, as well as fascioliasis, which was included in the original statutory list of tropical diseases under section 524(a)(3) of the FD&C Act, and clonorchiasis, which FDA has determined does not at this time meet the requirements to be designated as an addition to the list of tropical diseases, approved drug applications for which may be eligible for a PRV under section 524 of the FD&C Act (see FDA's "Notice of Decision Not to Designate Clonorchiasis as an Addition to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act," published elsewhere in this issue of the *Federal Register*).

Foodborne trematode infections are caused by parasitic trematodes, commonly known as *flukes*. Trematode infections are naturally transmissible from vertebrate animals to people and

back. People become infected through the consumption of raw or undercooked food (e.g., fish, crustaceans, and vegetables), which harbor the minute larval stages of the parasites.

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

A. Opisthorchiasis

Opisthorchiasis is caused by the trematodes *Opisthorchis viverrini* or *O. felineus*, acquired by the consumption of raw or undercooked fish (Ref. 1). The natural final hosts of these *O. viverrini* or *O. felineus* flukes are cats and other fish-eating carnivores (Ref. 1). *O. viverrini* flukes are reported in Thailand, Laos, Cambodia, and Vietnam while *O. felineus* flukes are reported in Italy, Germany, Belarus, Russia, Kazakhstan, and Ukraine (Ref. 2).

The final location of adult *O. viverrini* and *O. felineus* is the smaller bile ducts of the liver (Ref. 3). The symptoms caused by opisthorchiasis are related to inflammation and fibrosis of the tissues adjacent to bile ducts. While the majority of infected individuals are asymptomatic, patients may develop cholangitis, intrahepatic calculi, or cholangiohepatitis. Chronic infection is also associated with the development of cholangiocarcinoma, a severe and fatal form of bile duct cancer, and *O. viverrini* are recognized by the International Agency for Research on Cancer as Group 1, which means that the agent is classified as carcinogenic to humans (Refs. 4 and 5).

There is one FDA-approved treatment for opisthorchiasis, praziquantel, approved in 1982 and indicated for the treatment of infections due to all species of schistosoma and infections due to the liver flukes *Clonorchis sinensis* and *O. viverrini* (Ref. 6).

1. No Significant Market in Developed Nations

No significant market exists for the treatment or prevention of opisthorchiasis in developed nations. As stated above, opisthorchiasis occurs as a result of *O. viverrini* and *O.*

felineus (Ref. 7). *O. viverrini* have been reported in Thailand, Laos, Cambodia, and Vietnam. *O. felineus* have been reported in Italy, Germany, Belarus, Russia, Kazakhstan, and Ukraine (Ref. 7). Since *O. viverrini* and *O. felineus* have a limited geographic range, infections in other countries only occur from movement of infected persons. *O. viverrini* and *O. felineus* flukes have a life span of 25 to 30 years, meaning that opisthorchiasis may persist long after a patient is initially infected, however, as described below, these numbers are low in developed countries.

Thailand, Laos, Cambodia, Vietnam, Belarus, Russia, Kazakhstan, and Ukraine are not on the World Bank list of high-income economies, which, as described in FDA's August 2015 final order, will be used as evidence that the country should be considered a "developed nation" for determination of additions to the PRV-eligible tropical diseases list under section 524 of the FD&C Act (Ref. 8). Germany, Greece, and Italy, however, are on the World Bank list of high-income economies, and therefore are considered to be developed nations for the purposes of this order (Ref. 8).

In developed countries where *O. viverrini* and *O. felineus* are found, the prevalence of opisthorchiasis is very low. There have only been approximately five cases of human infections of *O. felineus* reported in Germany since the 1980s, and two in Greece in the late 1990s and early 2000s (though one of those infections may have originated elsewhere) (Ref. 9). Italy has seen an increase in reported human infections due to the increased consumption of marinated fillets of raw tench (*Tinca tinca*), infected with *O. felineus* (Ref. 9). However, even with this rise in infection rates, the total number of reported opisthorchiasis cases in Italy was only 211 from 2003 to 2011 (Ref. 9). As described in the August 2015 final order, FDA uses a disease prevalence rate of 0.1 percent of the population of developed countries for aiding in the determination of whether a "significant market" may exist for a disease's treatment. In these

three high-income countries where *O. viverrini* and *O. felineus* have been reported, the prevalence rates are significantly lower than that which FDA would consider could offer a sufficient market incentive to drive the development of new drug products to prevent or treat opisthorchiasis. Therefore, in developed nations where opisthorchiasis occurs, the prevalence rates of infection are not large enough to create a significant market for treatment.

There is currently no estimate of the number of individuals infected with opisthorchiasis in the United States. The available information concerning opisthorchiasis in the United States suggests that the prevalence of opisthorchiasis is much lower than 0.1 percent of the population. Of the infections that do occur in the United States, foodborne trematode infections occur predominantly in immigrants and travelers to and from endemic regions (Refs. 10 and 11). For example, in a retrospective study in one U.S. travel medicine clinic over 6 years, only 17 cases of *Opisthorchis spp.* and *Clonorchis spp.* were identified through the review of medical records (Ref. 12). All patients with identified cases were migrants from Laos, Cambodia, Thailand, Vietnam, the former Soviet Union, and Ecuador (Ref. 12).

There is evidence that U.S. military personnel were exposed to *Opisthorchis spp.* and *Clonorchis spp.* during their service in the Vietnam War (Ref. 13). In one study, there was evidence that veterans were likely previously infected, but patients in the study did not have evidence of ongoing infection, given negative stool exams and negative imaging studies, and therefore would not have ongoing infections requiring treatment at present (Ref. 13).

As illustrated above, opisthorchiasis occurs rarely in developed nations. The market for drugs for opisthorchiasis in developed nations such as the United States would largely be comprised of immigrants and travelers to and from endemic regions and military populations serving in endemic regions. These markets are unlikely to provide sufficient incentive to

encourage development of products to treat or prevent opisthorchiasis. At present, FDA is unaware of any significant funding for opisthorchiasis drug development by the U.S government sources, and opisthorchiasis is not among the Centers for Disease Control and Prevention's (CDC) list of potential bioterrorism agents.

2. Opisthorchiasis Disproportionately Affects Poor and Marginalized Populations

Opisthorchiasis disproportionately affects poor and marginalized populations around the world. Within countries where *O. viverrini* or *O. felineus* are reported, opisthorchiasis predominantly occurs in populations living in impoverished settings. For example, in rural northeast Thailand, where the per capita gross domestic product (GDP) is less than $4,000, reported opisthorchiasis prevalence typically exceeds 30 percent of the population (Ref. 14). In contrast, in urban Bangkok, where the per capita GDP is around $15,000, opisthorchiasis prevalence is reported to be less than 5 percent of the population (Refs. 14 and 15). Likewise, in Laos, in the poorer rural southern provinces (poverty rates of 30 to 50 percent), reported opisthorchiasis prevalence is the highest at 20 to 30 percent, whereas in the relatively wealthier urban Vientiane region of Laos (poverty rate less than 20 percent), opisthorchiasis prevalence is reportedly less than 5 percent (Refs. 15 and 16). In Cambodia, a similar trend is noted, where the highest reported prevalence of opisthorchiasis (24 percent) can be found in the rural Kampong Cham and Takéo provinces, where poverty rates exceed 50 percent (Refs. 15 and 17).

Opisthorchiasis is also included in the WHO List of Neglected Tropical Diseases (Ref. 18). The WHO Foodborne Disease Burden Epidemiology Reference Group identified opisthorchiasis as an important cause of disability, with an estimated annual incidence of over 16,315 infections and 1,498 deaths, resulting in a global disability-adjusted life years (DALYs),

which is calculated by adding the number of years of life lost to mortality and the number of years lived with disability due to morbidity due to the illness, of 188,346 (Refs. 19 and 20).

Given the above information, FDA concludes that opisthorchiasis disproportionately affects poor and marginalized populations.

3. FDA Determination

Given the factors described above, FDA has determined that opisthorchiasis meets both the statutory criteria of "no significant market in developed nations" and "disproportionately affects poor and marginalized populations." Therefore, FDA is designating opisthorchiasis as an addition to the tropical diseases list under section 524 of the FD&C Act.

B. Paragonimiasis

Paragonimiasis is caused by *Paragonimus spp.*, which are trematodes acquired through the consumption of raw or undercooked crustaceans (crabs and crayfish) (Ref. 1). The natural final hosts of *Paragonimus spp.* are cats, dogs, and other crustacean eating carnivores (Ref. 1). *Paragonimus spp.* are reported in China, the Philippines, Japan, Vietnam, the Republic of Korea (South Korea), Taiwan, Thailand, Central and South America, Africa, and there have been rare reports of these flukes being found in the midwestern United States (Ref. 21). The final location in humans of adult *Paragonimus spp.* is in lung tissue (Ref. 1). The symptoms caused by paragonimiasis are chronic cough with blood-stained sputum, chest pain, dyspnea, and fever (Ref. 1). *Paragonimus spp.* can migrate to other parts of the body, e.g., to the brain, where they can cause severe cerebral manifestations (Ref. 1). There are no FDA-approved treatments for paragonimiasis.

1. No Significant Market in Developed Nations

FDA is unaware of any significant market for the treatment or prevention of paragonimiasis in the United States or other developed nations. As stated above, paragonimiasis is caused by *Paragonimus spp.* flukes that have been reported in China, the Philippines, Japan, Vietnam, South Korea, Taiwan, Thailand, Central and South America, Africa, and there have been rare reports of these flukes being found in the midwestern United States. The limited range of *Paragonimus spp.* means infections outside of these endemic countries only occur from the movement of infected persons. From the countries and regions listed above, South Korea, Taiwan, Uruguay, Chile, and Panama all are on the World Bank's list of high-income economies (Ref. 8).

In developed nations where *Paragonimus spp.* are found, the prevalence of paragonimiasis is low, according to the published data obtained by the Agency. For example, in Japan, there were 443 patients who were referred to one academic institution and diagnosed as having paragonimiasis from 2001 to 2012 (Ref. 22). The majority of native Japanese patients with paragonimiasis were residents of one island; while one quarter of the cases occurred in immigrants mostly from China, Thailand, and Korea (Ref. 22). In South Korea, the prevalence of paragonimiasis has precipitously dropped as the country has developed; in the 1960s, at least 2 million people were estimated to be infected with paragonimiasis based on intradermal testing; by the 1990s, the prevalence was reduced to 1 percent of the previous estimate (Ref. 23). In a relatively recent review of medical records at another large referral medical center in Seoul, South Korea, only 36 patients were diagnosed with pulmonary paragonimiasis over a 10-year period (1994 to 2004). FDA was unable to find published information about the prevalence of paragonimiasis in humans in Uruguay, Chile, Argentina, or Panama (there are rare reports in the

midwestern United States). One study reported 16 cases of paragonimiasis acquired in Missouri from 2008 to 2014, which were associated with consumption of raw crayfish (Ref. 24).

The market for drugs for paragonimiasis in most developed nations would largely be comprised of immigrants and travelers from endemic regions. These low prevalence rates in developed countries are unlikely to provide sufficient incentive to encourage development of products to treat or prevent paragonimiasis in developed countries.

2. Paragonimiasis Disproportionately Affects Poor and Marginalized Populations

Paragonimiasis disproportionately affects poor and marginalized populations around the world. The true burden of paragonimiasis is unclear given the population it impacts; under-reporting is likely, particularly in African regions (Refs. 25 and 26). While epidemiologic data for paragonimiasis are scant, transmission of foodborne trematodes within countries is typically restricted to limited areas and reflects behavioral and ecological patterns which are related to socioeconomic status. This includes people's food habits, methods of food production and preparation, and the distribution of intermediate hosts. For example, food can be contaminated through unhygienic preparation and storage. Furthermore, the consumption of raw fish and crustaceans is a main risk factor for contracting these parasites. The life cycle of the parasites is closely linked with water and sanitation. In populations without access to toilets, or without sewage system infrastructure, unprocessed human and animal fecal waste may be found near water or used as manure or fish feed. This can contaminate drinking water and aquatic vegetables, leading to a continuous cycle of infections.

Paragonimiasis is included in the WHO List of Neglected Tropical Diseases (Ref. 18). The WHO Foodborne Disease Burden Epidemiology Reference Group identified paragonimiasis as an important cause of disability, with an estimated annual incidence rate of 139,238 infections

and 250 deaths, resulting in global disability-adjusted life years of 1,048,937 (Ref. 27). Given the above information, FDA has concluded that paragonimiasis disproportionately affects poor and marginalized populations.

3. FDA Determination

Given the factors described above, FDA has determined that paragonimiasis meets both the statutory criteria of "no significant market in developed nations," and "disproportionately affects poor and marginalized populations." Therefore, FDA is designating paragonimiasis as an addition to the tropical diseases list 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, visit the Agency's web page at 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. 3501-3521). Specifically, facts 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 marked with an asterisk (*) 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 also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. 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: July 8, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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