4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 317

[Docket No. FDA-2008-N-0567]

RIN 0910-AG37

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 (the 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 to be tropical diseases for purposes of obtaining PRVs, and also 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. FDA has determined that Chagas disease and neurocysticercosis satisfy this definition, and therefore is adding them to the list of designated tropical diseases whose product applications may result in the award of PRVs. Sponsors submitting certain applications for the treatment of Chagas disease and neurocysticercosis may be eligible to receive a PRV if such applications are approved by FDA.

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

ADDRESSES: Submit electronic comments on additional diseases suggested for designation to www.regulations.gov. Submit written comments on additional diseases suggested for designation to the Division of Dockets Management (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: Kristiana Brugger, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6262, Silver Spring, MD 20993-0002, 301-796-3601; 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

Much of the global burden of disease falls on populations who lack the resources to develop, encourage development of, or purchase disease preventions or treatments. For this reason, many of the diseases afflicting these populations do not receive the same level of innovation investment as diseases afflicting wealthier or more empowered populations.

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 (FDAAA), is designed to address the lack of treatment development incentives for such tropical diseases. It 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. Specifically, section 524 of the FD&C Act defines the term "tropical disease product application" and sets forth criteria which, if met, enable those who submit an application for a tropical disease product to be eligible to receive a PRV upon approval of that tropical disease product application. To be eligible for a PRV, the tropical disease product application must meet all of the following criteria:

- The application must be a "human drug application," as defined in section 735(1) of the FD&C Act (21 U.S.C. 379g(1)).
- The application must be for the "prevention or treatment of a tropical disease," as defined by statute.
- The application must be deemed eligible for priority review by the Secretary of HHS.
- The application must be approved after the date of enactment of FDAAA (i.e., September 27, 2007) for use in the prevention, detection, or treatment of a tropical disease.

- The application must be for "a human drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under section 505(b)(1) [21 U.S.C. 355(b)(1)] or section 351 of the [PHS Act]."

Section 524(a)(4) of the FD&C Act. In particular, the requirement that an application must be eligible for priority review demonstrates the PRV program's intent to reward tropical disease product applications that have the potential to demonstrate significant improvements in safety or effectiveness in the treatment or prevention of tropical diseases (Ref. 1).

FDA will award a PRV to the application holder upon the approval of a qualifying tropical disease product application that meets the criteria previously listed. The voucher entitles the holder to a priority review of a human drug application, submitted under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act, of the voucher holder's choosing. Once awarded to the application holder, the PRV may be transferred to another entity, and the original holder may receive consideration (including payment) for the transfer. To redeem the voucher, a PRV holder must notify FDA of its intent to use the PRV at least 90 days prior to the submission of the application for which the PRV will be used. This notification constitutes a legally binding agreement to pay the user fee that must be applied to applications using a PRV.

Section 524(a)(3) of the FD&C Act lists the following diseases as tropical diseases qualifying for a PRV:

- Tuberculosis
- Malaria
- Blinding trachoma
- Buruli ulcer
- Cholera

- Dengue/Dengue haemorrhagic fever
- Dracunculiasis (guinea-worm disease)
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Yaws
- Filoviruses

In addition, section 524(a)(3)(R) of the FD&C Act authorizes the Secretary to expand by order the list of tropical diseases to include "[a]ny other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations[,]" and that is the purpose of this order.

II. Criteria for Expansion of the List of Tropical Diseases

On December 12, 2008, FDA convened a public hearing, at which the public provided suggestions regarding the following topics: (1) Criteria that should be used to determine the eligibility of an infectious disease for designation as a tropical disease, (2) the process that should be used to make tropical disease designations, and (3) recommendations for specific diseases that should be designated as tropical diseases. A number of participants in the public meeting commented that, given the lack of definitive data for some diseases, as well as the lack

of consensus on how these criteria should be defined, FDA should use a flexible approach in determining whether specific diseases meet the criteria.

FDA agrees with the use of a flexible approach to tropical disease designation and is proposing that a scientifically informed, qualitative assessment of disease candidates is appropriate. FDA also is establishing a public docket that will continuously remain open to receive future suggestions for tropical disease designations under section 524 of the FD&C Act. The Agency proposes to review the contents of this public docket periodically and to take action to designate additional diseases when appropriate.

As stated previously, section 524(a)(3)(R) of the FD&C Act authorizes the Secretary 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 the following paragraphs, FDA sets forth its interpretation of this provision and the criteria we propose to use in determining which diseases may be designated by order of the Secretary as "tropical diseases" under section 524.

A. No Significant Market in Developed Nations

1. "Developed Nations"

In interpreting the term "developed nations," FDA acknowledges at the outset that the standards for determining a nation's level of development, as well as the threshold for a "developed" country, are the subject of debate. Some nations may score well in some markers of development (e.g., gross domestic product) and poorly in others (e.g., sanitation), leading to disagreements regarding which measures of development should serve as dominant indicators. After also examining the International Monetary Fund (IMF)'s list of advanced economies (Ref. 2) and the United Nations (U.N.)'s human development index (Ref. 3), the Agency is proposing

to use a country's presence on the World Bank's[1] list of "high income economies" (Ref. 4) as evidence that the country should be considered a "developed nation" for "tropical disease" determination purposes. Similarly, FDA will use a country's presence on the World Bank's list of "low income economies" (id.) as evidence that the country should not be considered a "developed nation" for purposes of "tropical disease" determination.

FDA recognizes that there is a correlation between economic strength (particularly purchasing power) and the market incentive for drug creation: People in high-income economies are more likely to be able to afford disease treatments and, thus, drug companies have an incentive to create products that will be in demand in those countries. The World Bank list of high-income economies is calculated based on gross national income per capita, and, importantly, it thus reflects wealth as a primary basis for categorization. FDA's recognition of the role of wealth is why we deemed the U.N. development index less helpful: It measures development across a broad array of categories (e.g., mean years of schooling) that, while informative, are less directly correlated with the drug development incentives reflected in the statutory scheme. Indeed, the U.N. itself has acknowledged that "[t]he [human development index] was created to emphasize that people and their capabilities should be the ultimate criteria for assessing the development of a country, not economic growth alone" (Ref. 5). And although the IMF's list of "advanced economies" reflects purchasing power to some degree, the World Bank calculus is more transparent and predictable than the IMF's calculus, and the U.S. government routinely uses the World Bank lists when determining a country's eligibility for Generalized System of Preferences benefits for trade in goods (Ref. 6).

[1] The "World Bank" is a term used to refer collectively to the International Development Association and the International Bank for Reconstruction and Development, which are two of the five organizations that comprise the World Bank Group.

2. "No Significant Market"

The list of tropical diseases in section 524(a)(3) of the FD&C includes "[a]ny other infectious disease for which there is no significant market in developed nations…designated by order of the Secretary." As an initial matter, the Agency notes that "infectious diseases," as such do not have markets--but drugs for the treatment or prevention of infectious diseases do. Because the statute offers vouchers for applications for drugs for either the treatment or prevention of infectious diseases, it is reasonable to assume that "no significant market" can refer to drugs for the treatment or prevention of infectious diseases. Thus, FDA will analyze the market for drugs for both the treatment and prevention of infectious diseases for a particular infectious disease.

The threshold for what constitutes a "significant market" for drugs for the treatment or prevention of infectious diseases is difficult to quantify. Because of the challenges in providing a rigid definition of this term, FDA proposes that the following factors be considered in determining whether a "significant market" exists in developed countries.

a. Occurrence of the disease in developed nations.

As discussed previously, market forces are important drivers of drug development. The purpose of section 524 of the FD&C Act is to provide an incentive (through a PRV) for innovation where there otherwise would be an insufficient financial or market incentive to invest in developing drugs for tropical diseases. The market for many FDA-approved products includes situations in which individuals (often reimbursed by their insurers) purchase the products for use by a specific patient. This reflects what we will refer to as the "direct" market, and the direct

market for a drug in a developed country can often be estimated by assessing the occurrence of a particular disease in that country.[2]

If the prevalence of a disease in developed countries is less than 0.1 percent of the population of those countries, it is unlikely that ordinary market forces will offer a sufficient incentive to drive the development of new preventions or treatments. Thus, it is unlikely that there will be a "significant market" for the disease's treatment in those countries. Accordingly, FDA has decided to use a disease prevalence rate of 0.1 percent of the population as a factor for aiding in the determination of whether a "significant market" may exist for a disease's treatment.

b. The existence of a sizeable indirect market for the tropical disease drug (e.g., government, including the military) that would constitute a financial incentive for drug development.

As discussed previously, the market for many FDA-approved products is the "direct" market, involving patients purchasing drugs for their own use. However, some drugs may have a sizeable "indirect" market composed of, for example, government entities or nongovernmental organizations that wish to purchase and distribute a drug for the treatment or prevention of an infectious disease, often for public health reasons, to a particular group of people. Indeed, for some diseases identified as high priorities for public health preparedness, governmental entities have initiated programs to provide support for product development and/or stockpiling (Ref. 7).[3]

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[2] Exceptions may occur for diseases that have a low incidence in developed countries through use of preventive drugs or biologics. Thus, although the disease incidence is lower in developed countries these are less likely to be the types of diseases for which section 524 of the FD&C Act is intended to spur innovation.

[3] For example, certain diseases have been prioritized for medical countermeasure development and investment (see Ref. 7) or are listed as priority pathogens by government entities such as the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), Center for Disease Control or Prevention, and military programs (Refs. 8, 9, and 10). These and other indications of potential priority designation that could affect governmental resource allocation may be taken into account in assessment of whether a market exists in developed countries.

In such cases, FDA would consider that market as a factor in determining whether a significant market for a drug for the treatment or prevention of an infectious diseases disease exists in developed nations.

B. Disproportionately Affects Poor and Marginalized Populations

As with the term "no significant market in developed nations," FDA has elected to analyze multiple factors--none of which, alone, invariably will be outcome-determinative--in assessing whether a given disease meets the requirement of "disproportionately affects poor and marginalized populations" for classification as a "tropical disease" under section 524 of the FD&C Act. Those factors are the following:

1. The Proportion of Global Disability-Adjusted Life Years for the Disease That Is Attributable to Developing Countries

A disability-adjusted life year (DALY) measurement is not a direct measure of the prevalence of the disease; rather, it is a measure of the impact of that disease on a given population. "One DALY can be thought of as one lost year of 'healthy' life" (Ref. 11). An estimate of disease-related morbidity (a term which, as used in this order, refers to the state of being diseased (see Ref. 12)) and mortality in affected countries thus can be made by assessing available information about the DALY burden of a particular disease. "DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost…due to premature mortality in the population and the Years Lost due to Disability…for people living with the health condition or its consequences" (Ref. 11). DALYs are an important measurement, enabling FDA to weigh "tropical disease" eligibility for those diseases that, although they may be present to some degree in developed countries (e.g., because of travel or immigration), cause much more harm to the public health of developing countries.

2. The Relative Burden of the Disease in the Most Impoverished Populations Within the Countries in Which It Is Found

If a disease's prevalence is high in populations who cannot afford treatment and low in populations that can, there likely will be little market incentive for drug companies to create new treatments. In light of section 524 of the FD&C Act's intent to create treatment development incentives, as well as its clear goal of improving the health of impoverished populations, FDA will consider the demographic distribution of a disease in determining whether it should be designated as a "tropical disease" for the purposes of section 524 of the FD&C Act.

3. The Relative Burden of the Disease in Infants, Children, or Other Marginalized Segments of the Population (e.g., Women, the Elderly) Within the Countries in Which It Is Found

One of the clear goals of section 524 of the FD&C Act is improving the health of marginalized populations, who generally suffer poorer health outcomes than their non-marginalized neighbors, even within the same country. To "marginalize" is to place (or keep) a person or population in a powerless or unimportant position (see, e.g., Ref. 13). Individuals or groups may be marginalized for any number of reasons, including, for example, gender, age, or extreme poverty. Marginalized populations generally lack a meaningful voice in societal decisionmaking, including decisions relating to the acquisition, distribution, and use of health resources. These populations, therefore, are less likely to have their health needs met and less likely to have the resources or political power needed to effect change in those aspects of health policy that most affect them--including incentivizing governments or private industry to offer disease treatments. Understanding the relative prevalence of a disease in these populations will help FDA determine whether treatment development for that disease would be spurred by the provision of section 524 of the FD&C Act's PRV incentive.

4. Designation by the World Health Organization as a Neglected Tropical Disease

The World Health Organization (WHO), in its role as the directing and coordinating authority on international health within the U.N. system, has identified a list of diseases that it refers to as "neglected tropical diseases" (Ref. 14). According to the WHO, these diseases "are strongly associated with poverty" and tend to affect those with "little political voice"; rarely receive the attention of disease treatment innovators or the broader international community; and often flourish in tropical climates (id.). The WHO's list includes 12 of the 17 enumerated diseases in section 524(a)(3) of the FD&C Act (see Ref. 15). Because the WHO's list of "neglected tropical diseases" includes many of the types of diseases for which section 524 was designed to incentivize treatment development, FDA believes it is reasonable to consider WHO's "neglected tropical disease" designations in determining whether a disease should be designated as a "tropical disease" for purposes of section 524 of the FD&C Act.

III. Diseases Being Designated

FDA has considered a number of diseases recommended in response to the Federal Register document announcing the December 12, 2008, public meeting (see 73 FR 66050, November 6, 2008), by meeting participants or others directing communications to FDA on the same topic. Based on an assessment using the criteria proposed previously, FDA has determined that the following diseases will be designated as "tropical diseases" under section 524 of the FD&C Act:

- Chagas disease.
- Neurocysticercosis.

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

A. Chagas Disease

Chagas disease, also known as American trypanosomiasis, is a vector-borne parasitic disease caused by the protozoan Trypanosoma cruzi (Ref. 16). After the initial infection, a 2-month "acute" phase occurs, during which there are some antiparasitic drugs that can be used for treatment in some patients (id.). Treatment efficacy generally decreases with length of infection, and if the disease is not cured during the initial "acute" infection phase, the chronic infection lingers over the next several years or decades, often causing organ and tissue damage (id.). For example, some Chagas disease sufferers who contract the disease during childhood die in early adulthood due to heart arrhythmias or other effects of organ damage. Efforts to reduce Chagas disease center around controlling the spread of the vector insects (e.g., through insecticide and roof repair) and protecting people from insect bites (e.g., through bed net use) (id.).

Chagas disease has a disproportionate effect on poor and marginalized populations. Developing countries in Central and South America suffer most of the global DALYs lost because of the disease (id.). Estimates vary, but approximately 8 million people are believed to be infected in Mexico, Central America, and South America (Ref. 17). Within Chagas-endemic countries, the disease often affects rural and/or poor populations who live in the mud huts that also are inhabited by the vector insects (Ref. 16). WHO has designated Chagas as a neglected tropical disease (Ref. 15).

There also is no significant market for Chagas disease treatment in developed nations. Based on estimates derived by applying published seroprevalence data to immigrant population estimates in the United States, it is estimated that there are just over 300,000 persons infected with T. cruzi in the United States (Refs. 17, 18, and 19). The number of persons with chronic cases for whom definitive recommendations for treatment would apply is likely less than

300,000. Transmission and acute cases of Chagas disease would be considered unlikely either in the United States or in other developed countries. The most common insect vector that transmits the parasite, the triatomine bug, is found mostly in Central and South America. The main risk of Chagas transmission to uninfected persons in developed countries is due to mother-to-child transmission, or blood transfusions or organ donations where the donor has lived in or visited Chagas-endemic countries--although there have been a few reports of vector-borne Chagas infecting people in the United States (Refs. 16 and 17).

There are no approved vaccines or other preventative therapies for the disease, either in the United States or elsewhere. The only drugs used to treat Chagas are benznidazole and nifurtimox, which are not approved in the United States for this use. In addition to the lack of a commercial market in developed countries (presumably because of the low prevalence of disease), there does not seem to be a sizeable indirect (e.g., government) market for Chagas treatments either--presumably because of the geographical limitations of the disease. As a general matter, Chagas-endemic countries are developing countries in Central and South America, and thus neither persons with Chagas disease nor their governments are likely to be in a position to provide a financial incentive for treatment development. Given the disease's geographical limitations and its prevalence in non-touristed rural areas, it is unlikely that the travelers' market would be a sufficient incentive to encourage treatment development for Chagas.

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

B. Neurocysticercosis

Cysticercosis is a disease caused by infection with Taenia solium, a tapeworm of the phylum Platyhelminthes, and is contracted when a person ingests the tapeworm eggs. After a person ingests the eggs, the tapeworm enters the larval stage and begins to infect the host's tissues. The most severe form of the disease, called neurocysticercosis, occurs when larvae enter the central nervous system and establish cysts that can cause epilepsy (see, e.g., Ref. 20). Treatment guidelines from the American Academy of Neurology recommend treatment with anti-helminthic drugs like albendazole, with consideration for adjunctive corticosteroid therapy (Ref. 20).

Neurocysticercosis disproportionately affects poor and marginalized populations. Indeed, patients who have infection with T. solium generally have similar socioeconomic and demographic characteristics to those patients with soil transmitted helminthiasis, a disease already on the statutory list of "tropical diseases" in section 524 of the FD&C Act. As of the late 1990s, approximately 50 million people worldwide were estimated to harbor the tapeworm T. solium (Ref. 21), most of them living in poverty in the world's poorest countries that lack effective systems for meat inspection and adequate sanitation (Refs. 22 and 23). Estimates of the number of people who have epilepsy caused by neurocysticercosis ranges from 450,000 to 1,350,000 in Central and South America and from 300,000 to 4,600,000 in sub-saharan Africa (Ref. 23). Neurocysticercosis is believed to contribute to high levels of human morbidity, notably epilepsy, though efforts are underway to adequately characterize an estimate of DALY for neurocysticercosis (Ref. 24). Notably, cysticercosis is included on WHO's list of neglected tropical diseases (Ref. 15).

FDA also has determined that neurocysticercosis products have no significant market in developed nations. Although the disease does occur in the United States, estimates of annual incidence rates in the general U.S. population are low, at approximately 0.2 cases per 100,000 population. Incidence rates are much higher among Hispanics living in the United States, who most likely acquired the tapeworm in cysticercosis-endemic areas of Central and South America (Ref. 25), with estimates ranging between 3.1 and 5.8 cases per 100,000 Hispanic population (Ref. 26). FDA also is unaware of evidence suggesting any sizeable military, government, or other indirect market for neurocysticercosis products.

In view of the disease characteristics discussed previously, FDA considers the statutory criteria for addition of neurocysticercosis to the list of tropical diseases in section 524 of the FD&C Act to be satisfied. This addition is effective upon the publication of this order.

IV. 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)(R) of the FD&C Act. By expanding the list with this order, FDA does not mean to preclude the future addition of other diseases to this list. To facilitate the consideration of future additions to the list, FDA is establishing a public docket (see http://www.regulations.gov, Docket No. FDA-2008-N-0567) through which interested persons may submit requests for additional diseases to be added to the list. Such requests should be accompanied by information to document that the disease meets the criteria set forth in section 524(a)(3)(R) of the FD&C Act. FDA will periodically review these requests, and, when appropriate, expand the list.

V. Paperwork Reduction Act

This final order establishes a 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)(R) of the FD&C Act. This 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."

VI. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday, and are available electronically at http://www.regulations.gov. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

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Dated: August 14, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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