Worldwide Regulatory Affairs
Pfizer Inc.
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Global Research & Development

December 15, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry: Tropical Disease Priority Review Vouchers
Federal Register, October 13, 2008 (Docket No. FDA-2008-D-0530).

Dear Sir or Madam,

Thank you for the opportunity to comment on the Draft Guidance for Industry: Tropical Disease Priority Review Vouchers, which was announced in the *Federal Register* on October 13, 2008 (Docket No. FDA-2008-D-0530). Pfizer's response is enclosed.

We are extremely appreciative of the effort that the FDA has undertaken toward establishing this new program at a time when there are such enormous demands on its limited resources to oversee the safety of medicines approved and sold in the U.S. Pfizer shares the goal of increasing the availability of medicines for tropical diseases and toward this end, applauds FDA for working to implement FDAAA section 1102, the Tropical Disease Priority Review Voucher program (the "Program"). With a long history of research to treat infectious diseases and a large portfolio of antibacterial, antifungal and antiviral medicines that have received FDA approval, we are encouraged by this new incentive and the recognition it provides to the urgent needs as well as to the challenges of drug development for neglected diseases. As a large pharma company that continues to invest in medical innovation for infectious diseases, we hope to benefit from opportunities to both earn and use priority review vouchers through the Program.

Pfizer believes that the Draft Guidance is helpful in providing much needed guidance to companies looking to use the new FDAAA provisions. While the disease scope of the Program has statutory limits, its value could be enhanced by reinforcing the criteria for voucher eligibility as fulfilling practical requirements for new drugs that will likely be used in resource-limited environments, thereby providing added assurance that the approved drugs will actually benefit developing world patients who need them. In addition, a number of details of the Program remain unclear and should be clarified in order to enable sponsors to invest resources in developing new tropical disease

products. By articulating specific guidance in anticipation of predictable scenarios that may occur when a sponsor attempts to use a voucher, the work of the both the sponsor and FDA could be made more efficient while at the same time providing for the most appropriate use of vouchers.

We hope that the FDA will find our comments helpful in further developing and refining the Guidance. Please do not hesitate to contact the undersigned if there are any questions regarding the attached comments, or if further clarification or information is desired.

Sincerely,

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Pfizer submits the following comments to the Agency for consideration:

General:

The focus of the voucher program on NME's may benefit sponsors who already have ongoing programs and late-stage candidates for tropical diseases, but the value of accelerated review for another product is unlikely to defray the entire cost of a tropical disease drug development program. Therefore, the value of this incentive to stimulate new R&D for tropical diseases appears uncertain. Since drug availability, effectiveness and affordability are important considerations for utility in developing countries, we hope the FDA would extend this incentive to study marketed products, including novel combinations and formulations for tropical disease indications, as this research could more rapidly benefit developing world patients.

In any case, complicated methods of treatment, inconvenient mode or route of administration, expensive manufacturing and delivery/storage costs are all barriers to the use of medicines in developing countries, so we hope that FDA will include these considerations as part of the eligibility criteria for a tropical disease application to qualify for priority review and the potential to earn a voucher.

As currently written, the draft guidance does not offer much insight regarding the process of voucher utilization. The obligatory 365-day waiting period for use of a voucher is fraught with a great deal of uncertainty for sponsors. Therefore, we are hopeful that FDA will show some flexibility around the use of vouchers and provide additional details as to how it may handle certain scenarios that will better enable sponsors to plan for voucher utilization.

SPECIFIC COMMENTS ON TEXT

Line number	Comment and Rationale	Proposal (if applicable) (proposed changes in verbiage in italics)
Section II: BACKGROUND		
line 40	Section 524 is designed to encourage development of new medicines to prevent or treat specified tropical diseases prevalent in developing countries. If the Program leads to the approval of drugs that have limited utility in developing countries due to complicated or inconvenient modes of administration or expensive storage requirements, these products are unlikely to meet the medical needs of poor countries. We suggest that it would be helpful for the FDA to clarify this point and explicitly acknowledge these desirable characteristics for qualifying drugs.	Recommended change: Insert text in italics. …innovative drug therapies. *These diseases require new therapies that are suited to resource-poor environments, recognizing cost constraints, ease of delivery, convenience and simplicity of administration as important features.* Although these tropical diseases are rare in the United States,…
line 43	Stimulate new drug development: New drugs that are expensive or difficult to administer are not practical in treating the tropical disease for millions of patients in the developing countries and would not likely have much health impact	Recommended change: Insert text in italics. …to stimulate new drug development *to control, manage and cure neglected diseases at an affordable cost for patients in the developing countries* by offering additional incentives…

Section III: PROVISIONS OF SECTION 524 – AN OVERVIEW		
line 62	It is not clear what standard FDA will use to ascertain whether the application for approval of a qualified tropical disease drug qualifies for priority review. In general, the standard for priority review requires that a product, if approved, would provide safe and effective therapy *where no satisfactory alternative therapy exists* or would be a significant improvement compared to marketed products, including non-drug products and/or therapies, in the treatment, diagnosis, or prevention of a disease. (CDER MAPP 6020.3) See also comment in response to **Q4**, below.	Recommended change: We suggest that FDA should interpret the "where no satisfactory alternative therapy exists" component of this standard as referring to a global context, particularly with reference to developing countries with limited healthcare infrastructure and resources.
line 60	The application must be submitted after the enactment of FDAAA (September 27, 2007)	Statute indicates the date law is enacted. However, it seems unnecessarily inflexible with respect to applications for tropical diseases already submitted. Indeed, there is no reason to block prior submitters out of the priority review voucher program (before a reasonably recent date). Otherwise, there is an incentive for those filers to withdraw those applications in order to trigger the program. Instead of this additional administrative burden and in order to forward the goal of adding treatments for tropical diseases, we suggest that FDA move back the deadline to 2005.
line 70	We would like greater clarity on the issue of the use of a voucher. In this section, it is stated that notifying FDA one year in advance of the intent to use the voucher on a submission, the sponsor using the voucher is legally committed to payment of an extra fee for the review of the intended submission. This is restated in **Q10** of the Questions and Answers section of the guidance. If the sponsor does not ultimately submit a product for review using the voucher, in addition to yielding up the fee, does the sponsor also commit to yield up the voucher? In other words, does the voucher expire in this case?	Recommended change: See recommended change in response to **Q10**, below.

Section IV: POLICIES AND PROCEDURES – QUESTIONS AND ANSWERS		
Q2 (line 103)	Around 18 million people suffer Chagas disease in the world, most of them poor. Although the disease is concentrated in Latin America, the number of cases in the US and the EU is increasing due to migration patterns. Chagas disease patients have been reported in France, Spain, Italy and Switzerland.	Recommended change: FDA should include Chagas disease as one of the tropical diseases that may qualify for a priority review.
Q4 (line 146)	FDA has not stated whether it will interpret the "where no satisfactory alternative therapy exists" component of this standard as referring only to the United States, or globally. With respect to tropical diseases this consideration might be different depending on geographical context. For example, there may be satisfactory treatments for malaria in the U.S. but not globally. Would FDA thereby deem an application for a new malaria treatment as qualifying for a priority review? For many of the other listed tropical diseases, the incidence is so low in the U.S. that, depending on interpretation, it is possible that FDA could deem any given product as failing to meet an unmet medical need, since there is effectively none.	Recommended change: In the spirit of encouraging drug innovation for the developing world, the criteria, FDA should interpret the "where no satisfactory alternative therapy exists" component of the priority review standard in a global context, where the major medical need is in the developing world. This would lead to more consistent review of tropical disease applications. Since most drugs for neglected diseases also undergo prequalification by the WHO for drug quality, safety and efficacy before procurement by UN agencies and other international organizations, it would also be valuable for FDA to indicate that its criteria will be consistent with WHO prequalification standards.
Q10 (line 214)	We request more clarification on timing and FDA position on what could happen during the 365-day waiting period. It appears that in FDA's current interpretation, the voucher date and usage would continue to be legally binding, despite any of these changes. We take exception to FDA's plan – outlined in the Draft Guidance – statement in response to Q10 that "FDA will consider this notification as a legally binding commitment to pay the priority review user fee for the fiscal year in which the application is submitted." We do not believe that the notice to use the priority review voucher should be binding. There are many contingencies in the drug development process that could delay submission of an application on a promised day. For example, a product may not meet clinical trial endpoints; additional safety questions may arise that need to be	Recommended change: FDA should allow some flexibility so that the notice of use of the priority review voucher could be withdrawn if there were a "material" and documented change in the development process (e.g., a product may not meet clinical trial endpoints; additional safety questions may arise that need to be investigated before submission; there may be delays in completing required data analyses; FDA may require additional information before an application is submitted; and/or possibility of generating a priority review without the use of a voucher.)

	investigated before submission; there may be delays in completing required data analyses; and/or FDA may require additional information before an application is submitted. Moreover, the data may be more positive than expected and therefore could trigger a priority review without the use of the voucher. The only alternative to that risk would be waiting a prolonged time between completion of clinical trials and submission of the application—and this would defeat the whole point of using the voucher in the first place.	
Q13 (lines 247-8)	If FDA cannot guarantee that review of a drug submission using the priority review voucher will be completed in 6 months, the value of the voucher is necessarily diminished. Since many FDA action dates have recently been delayed due to resource limitations, there may be skepticism that the voucher will provide a true incentive.	Recommended change: FDA should guarantee that a priority review will be completed within 6 months. If it is unable to keep to its promised timetable, the voucher should be returned to the sponsor.
Q14 (lines 250-8)	Question 14 appears to signal that FDA has no intention of indicating prior to approval (not even submission) whether an application will qualify for the voucher program. This timing is unacceptable to sponsors, who will have invested resources based on some assessment of the probability of being awarded a voucher. There are numerous decision points during the development cycle of any drug, including a tropical disease drug. In order to allocate the necessary resources to build internal investment and expectations, a sponsor would need to know if any given project is voucher-eligible.	Recommended change: FDA should indicate at time of submission whether an application is eligible for a voucher. Eligibility should not be compromised by independent submission of the same NCE for a different indication. It is understood that the actual award of a voucher would be contingent upon approval of the new tropical disease product.
Q15 (lines 260-5)	We disagree that combination drugs including previously approved active components should not be eligible. Research and development for combination products on new indications, effectiveness, and safety for tropical products are long and expensive development projects that should be included, especially to prevent drug resistance, to ease administration and improve compliance. This type of drug development should be encouraged with the provision that, after the new indication for	Recommended change: We encourage FDA to give consideration for voucher eligibility to novel combination products that are essential for managing drug resistance. Development of new drug combinations should be encouraged with the provision that, for voucher eligibility, approval of the new tropical disease indication will require post-marketing commitment to outcomes research and assessment of pharmaco-economic benefits.

	tropical disease is approved, research on outcomes and pharmaco-economic benefits should be conducted.	
Q17 (lines 273-8)	We disagree that drugs already approved for other indications should not be eligible. The time and cost for the development of a new indication can be as extensive as development of a new drug. If a drug is developed for an entirely different indication that represents a breakthrough in the treatment of tropical disease, and particularly if it requires a different formulation, it should not be excluded. This should be further encouraged with the provision that, after the new indication for tropical disease is approved, research on outcomes and pharmaco-economic benefits should be conducted.	Recommended change: We encourage FDA to allow a drug previously approved for other indications to be eligible for a voucher if its clinical utility to prevent or treat a neglected tropical disease represents a novel use unrelated to the indication(s) of its prior approval. New development programs should be encouraged with the provision that, for voucher eligibility, approval of the new tropical disease indication will require post-marketing commitment to outcomes research and assessment of pharmaco-economic benefits.
Q22 (line 319)	In addition to the role of determining whether an application meets the eligibility criteria, CDER and CBER will develop expertise in the review and approval of tropical disease treatments	Recommended change (Add the following text): *In addition, CDER and CBER will develop expertise in the review and approval of tropical disease treatments.*