Bridging the Gaps:
FDA's Role in Improving the Development Pathway for Neglected Disease Therapies

Testimony for the U.S. Senate Appropriations Subcommittee on Agriculture, Rural Development, the Food and Drug Administration, and Related Agencies

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Chairman Kohl, Ranking Member Brownback, and other distinguished members of the Subcommittee: Thank you for recognizing the importance of neglected diseases to global health and U.S. interests. I am grateful for this opportunity to testify about ways in which the U.S. Food and Drug Administration (FDA) may expand its leadership role in supporting the development of products (drugs, vaccines, and diagnostics) for diseases that afflict the world's poorest.

The essence of the problem is this: while philanthropists and private companies have increasingly seen the value in devising products for heretofore neglected diseases, the regulatory infrastructure necessary to develop and introduce these therapies to the developing world is sadly inadequate. Regulatory inefficiencies and gaps add costs to product development, deter private investment, and delay patients' access to potentially life-saving treatments. Building the needed regulatory infrastructure is a substantial challenge and unprecedented opportunity to improve the lives of millions around the globe and promote the well-being of Americans at home and abroad. The United States government and FDA in particular should take a leadership role in improving the clinical development and regulatory pathways for neglected disease products.

My testimony will proceed in four parts. First, I will summarize the burden that neglected diseases impose on affected people and their communities. Second, I will discuss the tremendous promise of the current pipeline of candidate products to address neglected diseases. Third, I will give an overview of how novel therapies are developed and approved for use in the developing world and the persistent regulatory gaps that undermine this process. Last, I will offer recommendations on how FDA can help bridge those gaps.

My testimony today reflects the work I have the honor of leading at the Center for Global Development with the support of the Bill & Melinda Gates Foundation and the substantial input of the public private development partnerships (PDPs) and nongovernmental organizations that comprise the Global Health Technologies Coalition.

The burden of neglected diseases

Neglected diseases are a heterogeneous collection of predominantly infectious conditions for which few, if any, effective therapies exist. An estimated one billion people, including 400 million children, suffer from one or more of these diseases. As defined under U.S. law, "neglected diseases of the developing world" include malaria, tuberculosis (TB), and a dozen other parasitic, soil transmitted, bacterial, and tropical infections endemic to Africa, Asia, tropical regions of Latin America, and parts of the Middle East.[1]

Neglected diseases have a staggering impact on the individuals and communities which they afflict. Many of these diseases exact a large and lethal toll, with tuberculosis and malaria alone killing an estimated 2.6 million people annually.[2] Other neglected diseases are less deadly, but disable, deform, and increase their sufferers' vulnerability to other infectious diseases like HIV/AIDS. Children and pregnant women suffer disproportionately. In 2008, an estimated 8.8 million children worldwide under the age of five died from largely preventable causes, many of which are related to neglected diseases.[3] Neglected diseases cause adverse pregnancy outcomes and impair children's cognitive development, school attendance, and earning potential for the decades that follow.[4] In sum, neglected diseases rob the world's poorest communities of their hope for a better future. They sap current and future worker productivity, undermine economic development, and perpetuate the cycle of poverty, insecurity, and infirmity in the communities in which these diseases are endemic.

Neglected diseases also threaten the well-being of Americans at home and abroad. These diseases cross borders with trade and travel; the health and economic consequences of outbreaks are significant.[5] Americans travel to neglected disease-endemic countries and the women and men of the U.S. military serve there. Neglected diseases undermine the security of our allies and the economic development of our potential trading partners.

Given that approximately one out of six people worldwide suffer from one or more neglected diseases, it may seem surprising that there are few, if any, effective therapies for them. The extreme poverty of those afflicted, however, greatly limits the potential market return on the substantial investment needed to develop therapies for neglected diseases.

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[1] Section 524(a)(3) of the U.S. Food, Drug, and Cosmetic Act (21 U.S.C. 360n(a)(3)).

[2] WHO, *Global tuberculosis control: A short update to the 2009 report* (2009) and WHO, *World malaria report 2009* (2009).

[3] UNICEF, Table of Basic Indicators, accessed at http://www.unicef.org/rightsite/sowc/pdfs/statistics/SOWC_Spec_Ed_CRC_TABLE%201.%20BASIC%20INDICATORS_EN_111309.pdf (last visited June 16, 2010).

[4] Hotez PJ, Ferris MT. *The antipoverty vaccines*. VACCINE 2006; 24: 5787-99.

[5] Ruth Levine, *Healthy Foreign Policy: Bring Coherence to the Global Health Agenda* in WHITE HOUSE AND THE WORLD, Center for Global Development 43-45 (Birdsall ed. 2008).

Accordingly, of the nearly 1400 new chemical entities approved worldwide between 1975 and 1999, fewer than 40 were for neglected diseases.[6]

The promise of the current pipeline of candidate therapies

A confluence of private philanthropy and enlightened government intervention has dramatically changed the landscape for neglected diseases over the last decade. Led by the efforts of PDPs and fueled by the support of the Gates Foundation and U.S. government actors (including members of this Subcommittee, National Institutes of Health, USAID, FDA, and Department of Defense), dozens of such products are now in development.

The therapies, diagnostics, and preventative tools in the product pipeline will be, for many neglected diseases, the first new tools in a generation and, for others, they will be simply the first. Promising examples include:

- A malaria vaccine candidate in late-stage clinical testing which, if approved, will be the first vaccine against malaria (a disease that kills 900,000 annually) and the first vaccine against a parasite approved for use in humans.

- Nine new TB vaccine candidates in clinical trials worldwide, including the first late-stage infant study of a TB vaccine in over 80 years. There are also eight new TB drug candidates in testing, which, if approved, would become the first new TB drugs in over 40 years. These therapies could help reduce the 8 million new TB infections and 1.7 million TB-related deaths that happen each year.

- New vaccines for Rotavirus (the most common cause of childhood diarrhea) and pneumoccus pneumonia, which together kill millions of children under five each year.

The persistent gaps in the development pathway for neglected disease therapies

Discovery of a novel therapeutic which may be effective against a target disease is only the first step in bringing that therapy to patients. Developers must demonstrate the safety and efficacy of the candidate therapy in a series of clinical trials and register that therapy for use in disease endemic settings. In the case of neglected diseases, substantial gaps and inefficiencies in the development and regulatory pathway for these products threaten to delay or derail their introduction to patients.

Late-stage clinical trials must be conducted in settings where individuals suffer from the target disease and under the circumstances in which the product will be ultimately used. For neglected diseases, those settings are generally developing countries, with, in many cases, limited clinical research capacity and under-developed regulatory systems. It is difficult to conduct ethical, sufficiently regulated trials in such environments. Lack of regulatory

[6] Tufts Center for the Study of Drug Development, *Drug Approvals for neglected diseases increase along with more R&D Funding*, 11 IMPACT REPORT (2009).

capacity and clear rules hinders trial planning, initiation, and patient recruitment, and may lead to regulatory non-compliance. That risk of non-compliance and harm to subjects deters private investment. The shortcomings of these regulatory environments are further exacerbated by the complexity of the diseases and products involved and highly vulnerable, often pediatric subjects.

Upon completion of the necessary trials, sponsors must usually advance through multiple regulatory processes in order to register their product for use in the target neglected disease-endemic countries.

1. *FDA Approval*

In practice, most sponsors first submit their novel therapy for marketing approval by a developed country regulator, like FDA, in order to minimize the risk of liability and to take advantage of that regulator's experience in assessment, resources, and clear protocols and rules. The challenge is that FDA may be unfamiliar with the neglected disease (since it is not endemic in the U.S.) and the conditions and patient populations in which the product will be used. This may delay FDA's assessment of the safety and efficacy of the product and reduce the value of that assessment for the national regulatory authority (NRA) in the disease endemic country where the product will be used.

2. *WHO Prequalification*

Upon receiving marketing approval, the sponsor will next submit its product to the WHO prequalification program, which ensures that drugs, vaccines, and diagnostics meet prescribed standards of quality, safety, and efficacy and are appropriate for procurement by UN agencies. WHO is not a regulatory authority. A novel therapy must first be approved by an NRA which the WHO deems to be "fully functional" (such as FDA) in order to be eligible for prequalification. Many developing country regulators, however, rely heavily on WHO prequalification and will not approve a novel therapy without it.

Unfortunately, WHO prequalification can be a slow process. The average time to prequalify is 18 and 24 months for drugs and vaccines, respectively.[7] These delays often result from the inexperience of nontraditional product developers in preparing dossiers and the time required for WHO to assemble each assessment team *ad hoc*.

3. *Approval by the local regulatory authority*

Once WHO prequalifies a novel drug or vaccine, the sponsor can finally submit it to the NRA in the target neglected disease-endemic country for its approval. Even with WHO prequalification, substantial delays may occur at this step. Many NRAs, particularly in Africa and Southeast Asia, have limited experience, resources, and mandates for assessing, approving, and registering innovative products. Assessment of novel products can be complicated even for well-resourced and experienced developed country regulators; the historical mission of many developing country NRAs has been to provide their population with affordable generic medicines, rather than assuring timely access to innovative products.

[7] THE GEORGE INSTITUTE, REGISTERING NEW DRUGS: THE AFRICAN CONTEXT 13, 18 (2010).

The average time required for a novel drug or vaccine to advance through this multistep regulatory pathway is approximately three years.[8] These delays and the uncoordinated and sequential nature of these processes defer patients' access to potentially life-saving treatments, deter private investment, and add significant expense. Realizing the promise of the current product pipeline for neglected diseases will require not only increased funding for clinical trials and developing country NRA capacity building, but also greater attention to how clinical development and regulatory pathways for these products may be improved to reduce unnecessary costs and delays.

How FDA can improve the development pathway for neglected disease therapies

FDA already plays a central role in the development of safe, effective, and high quality therapies for neglected diseases. FDA administers the Orphan Drug Act and priority review voucher program to provide useful incentives for developing novel therapies for neglected diseases. FDA pathways for priority review and accelerated and fast track approval offer important opportunities for consultation on clinical development plans and submissions, and expedited product assessment. In 2008, the FDA Center for Biologics Evaluation and Research (CBER) issued guidance confirming the scope and availability of the FDA approval process for developers of vaccines against infectious diseases or conditions not endemic in the U.S.[9]

While FDA has performed admirably in its role, there remain significant organizational and logistical challenges particular to reviewing therapies intended for foreign use. The challenges are twofold.

First, resource limitations and FDA reviewers' unfamiliarity with neglected diseases and the conditions and patient populations in which the product will be used often delay and reduce the utility of FDA's product assessment. Put simply, FDA is performing a job it is not fully empowered, resourced, or designed to do.

Second, FDA regulatory pathways and programs are not well coordinated with or sufficiently supportive of the other entities involved in developing and approving these products. FDA approval is important, but it is a component of a larger, multistep process that also involves WHO and developing country NRAs. Accordingly, while it is important that the resources and pathway for FDA approval of products for neglected diseases be improved, it will not be sufficient if those improvements do not address the gaps and inefficiencies in the larger process for approving therapies for use by the patients who need them.

Pursuant to the efforts of this subcommittee and the requirement in the FY 2010 Department of Agriculture appropriations bill, FDA recently established a new review group to prepare recommendations for the FDA Commissioner and Congress on "appropriate

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[8] *Id.* at 18.

[9] Food and Drug Administration, U.S. Dep't of Health and Human Services, *General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases* (2008).

preclinical, trial design, and regulatory paradigms and optimal solutions for the prevention, diagnosis, and treatment of neglected diseases of the developing world."[10] This review group provides an excellent opportunity for FDA to develop new mechanisms and strategies for bridging the persistent gaps in the development pathway for neglected disease therapies.

As part of that effort, I respectfully recommend that FDA consider adopting the following measures:

1. *An Integrated, Sufficiently Supported Neglected Disease Product Approval Process*

Simultaneous, coordinated reviews by all the regulatory entities – FDA, WHO, and the developing country NRA – involved in the approval of a potential therapy would minimize duplication of scarce regulatory resources and reduce delays in product approval and introduction. It would combine FDA's resources and expertise in assessing novel and complex therapies with WHO and developing country NRAs' understanding of neglected disease presentation and local conditions, patient populations, and health care delivery platforms.

FDA should consult with WHO to develop a formal collaborative process, akin to that which exists between the European Medicines Agency (EMA) and WHO, in which FDA would commit to address the requirements for prequalification as part of its approval process and WHO would commit to an expedited decision on prequalification post-FDA approval. This collaborative process should be formal and the details of its operation made public in order to improve its predictability for prospective product developers. The process should also include:

- WHO and developing country expert observers. FDA reviews of neglected disease products should include, with the consent of the sponsor, WHO and developing country experts as formal observers.

- Confidential information sharing arrangements. There should be arrangements in place between all FDA Centers, WHO, and priority developing country NRAs to share confidential data and inspections reports on neglect disease product submissions.

- Developing country experts on advisory committees. The budgets of advisory committees should be sufficient to enable the active participation of developing country experts.

- More FDA reviewers with relevant expertise. FDA should hire more full-time reviewers with tropical disease expertise and experience.

[10] FY 2010 Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, § 740 (2009).

There is precedent for such an approach. In conjunction with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), FDA has a program to review the safety, efficacy, and quality of HIV/AIDS medications manufactured in countries where they are off-patent, prior to the expiry of those patents in the U.S. FDA works with eligible sponsors to help prepare applications for this program and for inspections. It prioritizes review of submissions and, as part of its assessment process, engages with the WHO prequalification program and developing country NRAs to facilitate the products' assessment and adoption.

2. *Strengthen FDA's ability to support its WHO and Developing Country NRA partners*

The efficiency and productivity of the development pathway for neglected disease therapies depends on the capacity of the WHO prequalification program and priority developing country NRAs. FDA should support that capacity with:

- More resources for WHO prequalification. FDA should commit additional experienced and qualified FDA reviewers to conduct prequalification assessments on behalf of WHO in priority neglected disease areas (similar to FDA's role in prequalifying PEPFAR products) or a fixed number of neglected disease product dossiers per year.

- Regional platforms for clinical trial regulation and product registration. Regional approaches can pool scarce regulatory resources and provide a more efficient vehicle for FDA technical assistance. WHO has used *ad hoc* regional, joint reviews to support African countries' regulation of vaccine clinical trials; working with partner U.S. government agencies such as NIH and USAID, FDA could help foster the improvement, expansion, and formalization of those programs.[11]

- Employee exchanges with WHO and developing country NRAs. Initiating a pilot project for one to two-year rotations of mid-career FDA reviewers into developing country NRAs and WHO prequalification programs would help build the capacity of regulatory counterparts and improve mutual understanding. If successful, this program could be expanded to other areas such as food and drug safety and serve as the foundation of a FDA version of the successful Epidemic Intelligence Service (EIS) at the Centers for Disease Control.

3. *Enhance FDA support and guidance for nontraditional developers (i.e., PDPs).*

Intermediary nonprofit organizations and PDPs manage a significant portion of global neglected disease product development, but may not have experience with late stage clinical development, dossier preparation, or product registration. FDA should support these PDPs and intermediaries and attract more interest in neglected disease product development with:

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[11] *See* Thomas J. Bollyky, *Bridging the Gap: Improving the Clinical Development and Regulatory Pathway for Health Products for Neglected Diseases,* Center for Global Development, forthcoming June 2010.

- Guidance for prospective developers of neglected disease therapies. FDA should issue clear and detailed public guidance on the full menu of support services that FDA offers for neglected disease drug, vaccine, and diagnostic candidate development and registration, including incentives, fee waivers, and accelerated reviews.

- More support for neglected disease product submissions. FDA should institute a program to work with PDPs and other nontraditional product developers on their submissions to ensure clinical development plans are both scientifically sound and cost-effective, and that those developers take full advantage of the tools, incentives, and expedited pathways available to them under the IND and BLA processes.

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By adopting these measures and assuming a leadership role in improving the development and regulatory pathways for neglected disease therapies, FDA can do much to further the interests of all Americans in controlling these diseases and improve the lives of millions around the globe.