Written Statement of Jay Siegel, MD
Chief Biotechnology Officer and
Head of Scientific Strategy and Policy
Johnson & Johnson

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"Addressing the Neglected Diseases Treatment Gap"
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Chairman Smith, Ranking Member Bass, members of this esteemed committee: Thank you for inviting me to testify today. It is an honor to be here. My name is Jay Siegel, and I am Chief Biotechnology Officer and Head of Scientific Strategy and Policy at Johnson & Johnson.

On behalf of the Johnson & Johnson family of companies, I applaud you for organizing this hearing today on the important subject of neglected diseases of the developing world.

It is my privilege to be able to view this topic through many different lenses of experience. Early in my career, I was trained in Infectious Diseases Medicine at the Stanford University School of Medicine. That training instilled in me a lasting awareness of the devastating impact of many infectious diseases in the developing world.

During two decades in the U. S. Public Health Service and at the FDA, I gained a deep appreciation for the complexities of drug development. Also, I witnessed the rise of the AIDS epidemic and its crushing impact, and experienced first-hand the importance of building broad-based collaborations across the public and private sectors in accelerating the development of and patient access to life-saving therapies.

Ten years ago, I became president of what was then Centocor Research & Development, a biotechnology company within Johnson & Johnson. There, and in subsequent posts, I came to know firsthand the staggering costs, risks, and challenges of global drug development.

Additionally, as an FDA negotiator and signatory for 16 international harmonized guidances on drug development, and in my current role overseeing Global Regulatory Affairs operations in more than 100 countries, I have gained many insights into how differences in the practice of medicine, the regulation of drugs, culture, and economic circumstances can have major impact for global drug development.

Together, all of these experiences have deepened my personal commitment to addressing unmet medical needs, particularly needs most pronounced in developing countries. That same depth of commitment is reflected on a broad scale at Johnson & Johnson.

Last year, Johnson & Johnson was a proud signatory to the London Declaration on Neglected Tropical Diseases, or "NTDs." Standing alongside the U.S. and UK governments, the Bill and Melinda Gates Foundation, our counterparts in industry and leading NGOs, we pledged a "new level of collaboration" in the global effort to conquer NTDs. Since that signing, we have followed through on our pledge, building collaborations and expanding our efforts to address NTDs.

As part of our NTD efforts, Johnson & Johnson is collaborating with the Drugs for Neglected Diseases Initiative, with funding from the Gates Foundation, on pre-clinical development of flubendazole, a potential new treatment against parasites that cause lymphatic filariasis (elephantiasis) and onchocerciasis (river blindness), two debilitating diseases affecting millions of people in Southeast Asia, sub-Saharan Africa, Central and South American and other tropical countries. Currently available treatments are unable to kill the adult worms associated with these diseases—worms that live in the body and lay millions of larvae in the lymphatic system, blood and tissues, perpetuating a cycle of infection and suffering. If our pre-clinical efforts are successful, in collaboration with the Gates Foundation, J&J will launch a full clinical development program with the intention to register and distribute flubendazole to all countries where these diseases are endemic.

Our company is also a leader in efforts to expand distribution of existing treatments for intestinal worms. Through Children Without Worms, a partnership between Johnson & Johnson, GlaxoSmithKline and the Task Force for Global Health, our company donates more than 200 million doses of mebendazole every year to almost 40 countries where children are disproportionately afflicted with intestinal worms. Our commitment to innovation in this area continues as we explore the development of a new chewable formulation of mebendazole which, if successful, will one day enable treatment of younger children.

In addition to flubendazole and mebendazole, we have a sizeable and growing portfolio of products with high potential public health impact. This portfolio includes a newly approved medicine known by its trade name as SIRTURO™. SIRTURO™ is an antimycobacterial drug indicated as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis, or MDR-TB. It is the first new medicine for TB with a new mechanism of action to be developed *in more than 40 years*, and is the first new drug specifically indicated to treat a drug-resistant form of tuberculosis. Our experiences with SIRTURO™—today and since its discovery in our labs more than a decade ago—illustrate some of the challenges associated with the development and introduction of a new therapy for a neglected disease.

MDR-TB can be transmitted by a simple cough. As MDR-TB is resistant to the two drugs most effective in the routine therapy of TB, it is associated with a frequent treatment failures and a high mortality rate. The World Health Organization estimates that with existing treatment options, fewer than 50 percent of patients treated for MDR-TB will be cured. And although Margaret Chan, the WHO Director General, aptly described MDR-TB as "a time bomb" in 2009, alarmingly little has been done to control this global public health threat.

Against this backdrop, SIRTURO™ received accelerated approval from FDA in December 2012. Product introduction responsibilities for SIRTURO™ are daunting: they include patient registries aimed at bolstering the safety and efficacy data, global medical education to ensure appropriate use and sustained longevity of this drug, and lending support to strengthen pharmacovigilance efforts in developing countries.

And our work doesn't end there. Our post-marketing commitments for SIRTURO™ are substantial. They include a lengthy Phase 3 research program; a pediatric formulation and first-ever randomized, open label, controlled clinical study in a pediatric MDR-TB population; and a 5-year prospective study to characterize the acquisition of resistance to this new drug.

Our experience with SIRTURO™ highlights the breadth of post-approval responsibilities and the magnitude of sustained investments required to appropriately ensure its safe and effective use worldwide. We estimate that approximately half of all investments required to develop and support Sirturo™ will be realized *after* regulatory approval.

These are investments for which we expert no "return" as the term is traditionally defined. Normal cost recovery and profit-deriving sources for the pharmaceutical industry are well

characterized and continue to rely on advanced-economy markets with more equitable and advanced healthcare systems. However, MDR-TB case numbers in the U.S. and EU amount to fewer than 2,000 patients per year. In the United States, fewer than 150 cases are reported annually. As is the case for most neglected diseases, cost recovery and profits associated with eventual sales of SIRTURO™ will prove to be relatively small, elusive and incomplete.

While efforts such as those described are complex and costly, we are proud of what we have done and are increasing our efforts to address Global Public Health issues. Indeed, this week, we announced the establishment of a new Global Public Health organization within our company – a group dedicated to developing and creating access to medicines that can improve the health of those who live in some of the most economically challenged areas of the world.

We applaud the many other organizations that have undertaken similar goals in this area—including government agencies such as FDA and NIH, WHO, the Gates Foundation, public-private partnerships, other private organizations and alliances, and other companies; they have yielded substantial benefit. Still, however, the challenge remains large and complex, and much more remains to be done. We believe that a re-working of current models—R&D models, regulatory models, incentive models, partnership models and otherwise—could enable greater investments and greater progress. Public policy can play an essential role in bringing these new models to life.

As we approach this exercise in the U.S., we ought to do so with a sense of urgency.

We might wish to be able to comfortably and permanently classify many diseases as "diseases of the developing world" and, at most, "orphan diseases" here in the U.S. However, given the realities of climate change and international travel, it may be most prudent for us to conceive of these not as "orphan diseases," but rather as "*morphing* diseases" —morphing in terms of the size and extent of their reach. Not only are American travelers, military personnel and diplomats potentially exposed, but with climate change and with exposure to returning travelers, Americans at home are also at increased risk. For example, Dengue fever acquired in the U.S. has re-emerged as a public health threat as warmer temperatures enable carrier mosquitos to flourish and expand their range.

Even for those diseases that appear to be more tightly constrained to resource-limited settings, the absence of therapeutic and other means for managing those diseases can have devastating and reverberating impacts. The ravages of Chagas disease, Trachoma, rabies and other afflictions

stretch far beyond the physiological, relegating those affected to the margins of their societies and economies. Such diseases have *root-cause* roles in perpetuating poverty and deprivation. Thus, they take their toll not only in terms of tremendous human suffering but also in social and economic impacts that can ripple across our increasingly interconnected world.

For these diseases, we need new therapies where none exists and better therapies where those that are available are suboptimal. Congress can help to create the conditions that accelerate progress toward these aims.

The complexity and enormity of the challenge demands that we be thoughtful in analyzing what has been done and that we learn as we go. Drawing from our own experiences in neglected-disease R&D and drug delivery, we encourage Congress to reflect upon three considerations in the design of policies to accelerate progress:

1. First, such policies should take into consideration a *holistic view of the costs and risks required to develop, introduce and support these products worldwide*. The development of innovative therapies is recognized for its cost, risk, complexity and lengthy duration. Less than one in every 10 drug candidates entering Phase I clinical trials ever makes it to market.[i] Extensive and expensive clinical testing is necessary and for those that do succeed to the point of market approval. The list of *post-market* commitments can be extensive. Policies intended to incent R&D investments for neglected diseases should be structured in ways that appreciate innovators' pre- and post-market costs and risks.

2. Second, to spark the types and level of investment needed to close research gaps for neglected diseases, incentives should be ample in number and capable of being accessed in combination. A menu of incentives should include both so-called "push" and "pull" mechanisms: "Push" incentives that encourage research inputs—such as preclinical studies—and "pull" mechanisms that reward successful research outputs, such as a fully developed drug.[ii] Well-designed incentive structures include both these methods.

3. Third, and finally, policies should encourage partnerships including public-sector and non-industry entities as well as industry. Such partnerships can serve both to bring a variety of critical capabilities and perspectives together and also to help to *diffuse the risks* of drug development and delivery across multiple actors. Where funding is sufficient, public-private co-funding models supporting early- to late-stage drug

development can themselves serve as incentives for companies to participate in neglected disease R&D.

On this point, a number of federal agencies and departments, including FDA, NIH, CDC, USAID and DoD, play important roles in addressing neglected diseases and can be valuable partners. We applaud this committee's work to facilitate partnerships between and among these agencies, and also with partners from other sectors.

We also note that through various actions including, for example, the Orphan Drug Act of 1983, Congress has already demonstrated the favorable impact it can have in this area.

Regulatory approaches and requirements can have a major impact on drug development challenges, risks, and costs. Providing access to a new medicine for patients in developing countries generally requires obtaining approval from FDA and/or European regulatory authorities. But approval requirements based upon potential use in the U.S. may be challenging to address for drugs primarily intended to treat diseases in the developing world since factors influencing need and use including, for example, stage and severity of disease, disease prevalence, underlying conditions, supportive or alternative therapies available, distribution channels and availability of cold chain, in the U.S. may differ substantially from those in the developing world.

The Neglected Diseases Priority Review Voucher program at FDA, established by Congress in the Food and Drug Administration Amendments Act of 2007, is a significant step in providing innovator firms with tangible incentives to enter the neglected disease space. Our company received a Priority Review Voucher with the accelerated approval of SIRTURO™ in December of last year. However, the voucher program provides limited incentive to invest in high risk early research into innovative therapies because, in considering such investments, the voucher value is discounted both by the high risk of program failure and the substantial delay (typically over a decade) before the voucher would be received. We believe the Priority Review Voucher would be most effective as an incentive for firms to pursue R&D for neglected diseases if it were part of a more complete, diverse and integrated set of incentives that Congress can help to make available.

Examples of Incentive Models and Complementing Programs to Support Increased R&D for Neglected Diseases of the Developing World (presented in alphabetical order)

There are many different types of incentive models and complementing programs available for policymakers' consideration. With few exceptions, most remain in concept form only, yet to be implemented or tested. Until such testing occurs and programs are assessed and refined, the key questions of *what will work?* and *how, when and where will it work best?* will be difficult or impossible to answer. A multi-tiered or "package" approach to incentives and programs—allowing innovator firms and their partners to access an assortment of incentives—offers potential to address various issues facing different organizations and programs at different stages of development. Such an approach could also allow for efficient testing and refining of incentive models; indeed, finding what "works" within an acceptable period of time will almost certainly require the testing several options simultaneously.

While by no means comprehensive, the list that follows is designed to illustrate for the committee the variety and types of options available for its consideration. While Johnson & Johnson does not endorse any one model at this time, we would welcome the opportunity for further dialogue with Congress on any of these or other options.

Advanced Market Commitments

An Advance Market Commitment (AMC) guarantees a market in return for reduced pricing. This can reduce the market risks, thereby providing incentives for potential providers of needed therapies to make necessary investments, such as expanding manufacturing capacity.
A promising AMC for pneumococcal vaccines was implemented by the GAVI Alliance in 2009 with the support of a number of developed countries. In this program, funders have guaranteed $1.5 billion for a specific annual supply of pneumococcal vaccines. Companies are then compensated with a share of this fund directly proportional to the percentage of the vaccine order which they fulfill. By the end of this year, 43 developing countries are expected to be participating in this program.[iii]

An AMC program structured to encourage the development and distribution of therapies for neglected diseases could function in a similar fashion.

Cures Acceleration Network

Often, insufficient funding and support leads to stagnation in development of new cures and therapies. The NIH is attempting to break that stagnation with its Cures Acceleration Network (CAN). This new model provides direct R&D funding for promising medical advances that

might otherwise not be carried through the more expensive and difficult stages of clinical development.

Interestingly, the structure of the CAN program is based on the research and development branch of the Department of Defense—DARPA—whose innovative format for R&D has yielded substantial returns since its implementation over 50 years ago.[iv] CAN involves a vetting process and grant structure very similar to this Department of Defense program.[v]

If CAN is able to emulate the success of DARPA, it could open a pathway to the successful and expeditious manufacture of new treatments and cures for a wide variety of diseases, including neglected diseases. A specific focus within the CAN program on NTDs could drive considerable progress in the future.

Export-Import Bank Model for Market Creation and Strengthening

Experts in global health have long maintained that when it comes to explaining the historical dearth of drug-development for neglected diseases, "The heart of the problem is the lack of market demand sufficient to induce the private sector to commit resources to R&D…the people who suffer from neglected diseases do not have substantive purchasing power, and cannot constitute a profitable market."[vi] As we consider sustainable solutions to advance the development and delivery of needed treatments, it behooves us to examine options for addressing this market challenge in particular.

Thankfully, there are models in place that have helped to address similar challenges for other industries in the U.S. Several federal agencies use financing programs to help provide important products to developing countries. Loan guarantee, loan subsidy, and grant programs help to promote the sale of U.S.-made products to developing countries. Title I of the Department of Agriculture's "Food for Peace" program, for example, allows for the provision of government-to-government sales of agricultural commodities to developing countries under long-term credit arrangements.

Likewise, the Export-Import Bank of the United States (or "Ex-Im Bank") is one of the most prominent models for market creation and bolstering. As this committee is well aware, the Ex-Im Bank was founded to sustain and maintain American jobs by supporting the export of U.S. goods and services to foreign buyers. The Ex-Im Bank is dedicated to creating trade finance programs that help both American exporters and emerging countries that otherwise would not be

able to purchase U.S. products. The Bank accomplishes this through a range of Special Initiatives in Agribusiness, Aircraft, Renewable Energy, and Construction Equipment, to name a few.

The Ex-Im Bank also has Special Initiatives in the area of Medical Equipment & Services. On this front, the Bank has noted, "It is a priority for good business and international citizenship to support the creation of American jobs and of facilities that deliver humanitarian benefits."[vii] Building on this priority, and in line with shared humanitarian and economic objectives, there may be an opportunity for Congress to facilitate a partnership among the U.S. Department of Health & Human Services, the U.S. State Department, and the Ex-Im Bank to expand the Bank's Special Initiatives in Medical Equipment & Services to include financing for U.S.-made medicines, diagnostics, and other medical technologies capable of countering the incidence and spread of serious diseases of the developing world. The potential for positive synergies via this kind of partnership could be substantial.

The Global Health Investment Fund Model

The Global Health Investment Fund (GHIF) is a novel initiative designed to raise low-cost capital to develop drugs and vaccines for neglected diseases. The GHIF, established by JP Morgan in collaboration with the Bill & Melinda Gates Foundation and Lion's Head Global Partners, is currently in its first phases of implementation. For its initial investments in neglected-disease R&D, the GHIF will leverage at least $100 million USD, provided as seed money from the government of Canada through its "Grand Challenges Canada" program.

Unique to the GHIF's equity model is the Gates Foundation's commitment to bear 60 percent of potential losses—a critical de-risking strategy to gain and secure valuable investors for future health ventures. The project, launched at the end of last year, is expected to have a return on investment of four to six percent in five years.[viii]

The U.S. government can play a role in supporting GHIF and similar social impact investment models, whether through direct funding or through less direct but still meaningful approaches to encouraging the creation and success of such funds.

Milestone Based Prizes (push + pull)

Milestone prizes are simple cash prizes awarded at various stages along a new therapy's development. For example, an innovator of a new neglected disease therapy might receive a prize payment upon presenting a well-developed treatment proposal, another upon completing pre-clinical research for the drug, another upon finishing clinical trials, and another upon the therapy's approval by the FDA, and another for successful conduct of post marketing studies and pharmacovigilance. This approach could be relatively simple to implement, and potentially could encourages all phases of a new drug's development.[ix]

Milestone rewards programs are widely recognized as a straightforward way to goad the sustained development of new medications, and have been endorsed by the WHO as a promising way to "maximize public health returns in the developing world."[x] This simple mechanism may be well suited to a coupling or integration with other incentive models for neglected disease R&D.

Project BioShield Model

The Project BioShield Act of 2004 was designed to incent the pharmaceutical industry to develop medical countermeasures (MCMs) against chemical, biological, radiological and nuclear (CBRN) attacks by providing a large, guaranteed market. The Act mandated a Strategic Reserve Fund for the purchase of MCM agents and authorized purchase of such agents prior to extensive testing in humans. Since its inception nine years ago, eight MCMs against CBRNs are in the government's hands in case of an attack, and eighty more MCMs are undergoing advanced development investments to commercialize countermeasures that are not yet mature enough for a guaranteed market contract.[xi]

Some elements of the Project BioShield model may be suited for adaptation to the context of R&D for neglected diseases.

Public-Private Partnerships Designed to Diffuse Risks in R&D for Neglected Diseases

R&D partnerships between the public and private sectors can be useful models for leveraging the strengths and resources of both. Public-Private Partnerships, or "P3s," are a "push" strategy being tested now in a broad range of R&D contexts around the world. P3s are co-managed and funded by both public and private sector entities. To date, P3 models have been used effectively to raise billions of dollars in both public and private funds to increase access to existing vaccines and accelerate R&D for NTDs.[xii] Current examples of P3 models with co-management and

funding from the U.S. government include USAID's Malaria Vaccine Development Program and the Medicines for Malaria Venture. A significant benefit of the P3 model is its inherent diffusion of R&D costs and risks across a broader pool of actors.

Social Impact Bonds Model

Social Impact Bonds (SIBs) are a relatively new method for financing programs of potential social value, built on a distinct "pay by success" design. The model leverages private investments to cover the upfront costs of an innovative social program, with the promise of public payment, contingent upon demonstrated fulfillment of pre-defined objectives.

While SIBs have yet to be tested in pharmaceutical R&D or healthcare delivery contexts, the model may lend itself to either or both. Under the leadership of the Center for Global Development, a non-profit international development think tank, and Social Finance, a UK-based non-profit and originator of the social impact bonds concept, efforts are currently underway to explore the application and adaptation of the SIBs model to address unmet needs in developing countries.

Transferable Market Exclusivity Periods

One potentially effective "pull" incentives for innovators might be the reward of *transferable* market exclusivity periods (MEPs), granted in exchange for developing and obtaining market approval on a "socially desirable but unprofitable medicine" that can address unmet medical needs in poor countries.[xiii] Transferable MEPs could be an effective way to compensate for and incentivize investment in otherwise low-grossing drugs (like drugs for neglected disease) by increasing the amount of time full revenues can be collected from higher profitability products.[xiv] Transferable MEPs might be quite attractive to drug developers even if relatively brief in duration.

Conclusion

In conclusion, there are many synergies in this area yet to be created or maximized—synergies among stakeholder institutions, and also synergies among the array of incentive models not yet available. The U.S. Congress is well positioned to bring together these key components, to create a new wave of momentum to address current challenges, and to make progress against the devastating set of illnesses for which no sufficient treatments exist today.

Thank you, Chairman Smith, Ranking Member Bass, members of this committee, for your leadership on this issue and many others in global public health.

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