

Tufts Center for the Study of Drug Development (Tufts CSDD) Forum***Neglected Diseases in the Developing World:
Progress, Current Challenges, and Promising Approaches*****Summary Proceedings****Christopher-Paul Milne, christopher.milne@tufts.edu, Program Moderator**

(Please note that the views expressed in this summary are those of the speakers and panelists, and do not necessarily represent those of the Tufts CSDD or PhRMA)

Background

On October 16, 2009, the Tufts Center for the Study of Drug Development (CSDD), with support from PhRMA, held a Capitol Hill forum on *Neglected Diseases in the Developing World: Progress, Current Challenges, and Promising Approaches*. The program commenced with morning keynote presentations on two new studies and a panel discussion with representatives from several federal agencies, academia, and NGOs, followed by a lunch-time presentation on the overarching issue of access, and closed with an afternoon session highlighting perspectives from the international community. The focus of the event was to highlight progress being made to develop effective treatments for neglected diseases (i.e., infectious, tropical diseases without a significant market in the developed world that disproportionately affect the poor in the developing world), and to discuss challenges and opportunities looking forward.

Morning Keynotes

Mary Moran, Director, Health Policy Division, The George Institute – Dr. Moran reviewed findings from the 2008 G-FINDER report (2007 data), which surveys global investment into R&D related to new products for neglected diseases. Although by some accounts, there are well over 100 product areas that could be considered neglected, the report focused on a consensus group of approximately 30 disease areas about which they collected data from approximately 700 groups working in 43 countries. [For more on the 2008 G-FINDER report's basic results, please refer to the keynote summary in the forum brochure on this website]

According to the report, approximately \$2.5 billion was invested in neglected disease R&D in 2007 with the major funders being the National Institutes of Health and the Bill & Melinda Gates Foundation. The Gates Foundation was the source of most of the philanthropic funding flow with the Wellcome Foundation coming up as a creditable second, but all other charitable organizations accounting for 3%. Of particular note, the pharmaceutical industry was the third highest funder of neglected diseases R&D with the contributions of individual pharmaceutical companies being greater than that of some of the G8 countries. In fact, the results of the 2009 report will reveal that two developing countries will be among the top 10 funders (2008 data), even as the current

economic crisis has taken its toll by causing some funders among the developed countries to drop out (e.g., the Irish government).

What the author found troubling was that almost 80% of the funding was directed towards just three disease areas: HIV/AIDS, malaria, and tuberculosis. The next five most important disease areas, including pneumonia and diarrhea (number one and two in terms of mortality), each receive from 1 to 5% of the total funds. Even less is spent on the next twenty or so diseases areas, such as rheumatic fever, the 7th highest cause of death, but which has only two funders and the least amount of funding, or Buruli Ulcer which has no discernible investment, nor even an assessment of the disease burden, and for which the only existing treatment is surgical excision. Recent good news is that the Wellcome Trust and Merck have invested \$170M in R&D of a rheumatic fever vaccine and a stable vaccine platform.

Another troubling finding was that funding was very concentrated on a few funders, a few diseases, and a few product types, resulting in the fact that most diseases don't even get enough funding to develop even one treatment. The good news is that small amounts of money can make a big difference, i.e., \$5-10M can be enough to create a diagnostic, and most Product Development Partnerships (PDPs) are less than 10 years old and still reaching their potential. Similarly, the private sector is playing an increasingly pivotal role in some disease areas, such as meningitis, dengue and diarrhea, because they can be incorporated into the existing R&D portfolio or are considered reasonable commercial prospects.

During the question and answer period, Dr. Moran noted that she was especially surprised by two findings. First, she was taken aback by the randomness of the investment and found it distressing that funders are not coordinated and just pick their own targets, so that if Gates or NIH aren't interested in a disease, then not much gets done. When asked about this lack of rational investment, she opined that it might be due to "policy colonialism," i.e. acting on others' behalf but out of one's own self-interest and convictions about what's best instead of what is best investment for the region or sub-population being impacted. For example, she noted that rheumatic fever was at bottom of the list "because nobody thinks about it." She added that neglected diseases are often low-impact diseases for many developing countries compared to diabetes, cancer, etc. Second, Dr. Moran thought that the magnitude of the investment was impressive (having already noted earlier that it didn't capture all of the resources being dedicated to the R&D of neglected diseases such as in-kind contributions by drug companies because it is hard to quantify and would muddy the waters).

Joshua Cohen, Senior Research Fellow, Tufts CSDD – Dr Cohen presented recent analysis of drug approvals, including approvals for new indications, and adoption of these approvals, e.g., inclusion in the WHO essential drug list (EDL). The purpose of the study was three-fold: 1) reassess the findings by Trouiller et al (study published in the Lancet in 2002 purporting that only 16 of 1393 "new" drugs marketed between 1975-

1999 targeted neglected diseases); 2) mark progress in the number of approved products and indications for neglected diseases as well as inclusion/exclusion criteria for the WHO EDL; 3) discuss the part that R&D of treatments plays in the overall picture. Dr. Cohen acknowledged that there are indeed multiple definitions of what constitutes a neglected disease, and that for practical purposes he adopted the same definition as Dr. Moran. He noted that his analysis found differences in the number of approvals for neglected diseases compared to Trouiller even taking into account the fact that Trouiller was essentially focused on tropical diseases. According to Cohen, 46 new drugs were approved between 1975 and 1999 targeting neglected diseases for a total of 56 indications. Of the 46 new drug approvals, 38 (85%) were placed on the WHO EDL. In addition, Dr. Cohen presented analysis for new drug and indication approvals between 2000 and 2008, finding that 26 drugs for neglected diseases were approved for a total of 26 indications. Cohen also found that the number of drug approvals sponsored by public-private partnerships (PPPs) increased from 9% to 46% between 2000 and 2008. *[For more on Dr. Cohen's study, please refer to the keynote summary in the forum brochure on this website]*

During the question and answer period, Dr. Cohen pointed out that their determination of sponsorship of approvals was based on data collected from multiple sources, not only FDA and EMEA databases, and that one of the differences between R&D during the Trouiller period and the 2000s is the emergence of PDPs/PPPs. He also pointed out in response to a question concerning the proportion of breakthrough products versus incremental innovations that most of the 46 products approved during the 1975-1999 period were breakthrough products, i.e., most formed a unique therapeutic class.

Panel Discussion

Tim Coté, Director, FDA Office of Orphan Products – Dr. Coté posed the question: What is FDA doing? His own answer was: Not enough! Why? He noted that there are several problems. Although the Orphan Drug Act (ODA) has been a highly successful program, it doesn't work that well for neglected diseases because it is not enough of an incentive and ironically, the ODA can't really address these globally significant threats to the public health due to the inherent limits imposed by the prevalence requirement for orphan designation status here in the US. Nonetheless, they have had some successes in recent years – approximately two score approvals and designations for tuberculosis, malaria, leishmaniasis, leprosy, and African sleeping sickness. Dr. Coté also believes that the priority review voucher is an extraordinary incentive and success is an empiric question that will just take a matter of time. In addition, the Brownback amendment to the FDA Appropriations Bill just signed in October 2009 established two internal committees, one on rare diseases, and one on neglected diseases. In sum, he believes that while ODA has been an underperforming incentive for neglected diseases, “there is a new sheriff in town” (presumably a reference to President's Obama's stated interest in global health issues).

Steven Groft, Director, Office of Rare Diseases, NIH – Dr. Groft believes there is a changing landscape that could facilitate R&D for rare and orphan disease with industry

looking for niche products and the increase in virtual drug companies. However, there is a major need for a more rational, coordinated, systematic approach to product development. It requires many partners to get an orphan product through R&D to approval, and in the past, the prioritization of rare disease R&D was spearheaded by patient advocacy, although the major R&D role was still played by industry. It's different now. New players are needed to not only take the lead but play a more active role, such as the Cystic Fibrosis Foundation and the Duchene's Dystrophy Association, and apply what we have learned in rare diseases to neglected diseases. Other needs are: to expand our current activities; develop different and collaborative research teams and partnerships of basic clinical scientists with product development experts to translate research advances into products; to build R&D infrastructure in different countries (the intent of NIH's Fogarty Center); to identify appropriate genetic predictors, biomarkers and surrogate endpoints; to expand utilization of publicly available information, such as Pub Med; to enhance utilization of existing collaborations (e.g., NIH's Rare Disease Clinical Network of 19 consortia addressing 90 diseases, which allows the conduct of clinical trials with smaller numbers of patients at multiple sites); to mobilize the health community to take action in conjunction with philanthropic groups; to improve health literacy of affected populations; and overall, to reduce disparity in global health. In sum, we are moving towards a collaborative, global approach in which the US is no longer alone, as there is increased interest and activity worldwide. Importantly, this initiative fits in with two of Francis Collins stated priorities for his tenure as Head of the NIH: global health and translational research. Where we've been the last few years doesn't really begin to show where we're going in the future.

David Ridley, Assistant Professor of Economics, Duke University – Dr. Ridley wrote a paper with Moe and Grabowski in 2007 entitled “Developing Drugs for Developing Countries,” in which a Priority Review Voucher program was proposed. This approach piqued the interest of Senator Brownback and his staff, who later incorporated it into the 2007 FDA Amendments Act, which subsequently became law. This program allows the developer of a new drug or vaccine for certain neglected diseases to receive a transferable voucher for a priority review from FDA for a drug of its choice. The time-value of money drives the value of the voucher (potentially worth \$200M). The priority review voucher could potentially stimulate new treatments at low cost to taxpayers (i.e., “doing it on the cheap” as Dr. Ridley put it), while benefiting US consumers from earlier access to blockbusters and possibly earlier entry for a generic competing with the blockbuster. Dr. Ridley stated the approach may not be perfect but it's on the books so we ought to try to make it work (and one has already been approved for Novartis' Coartem), even though additional push-pull mechanisms are needed to get us where we need to go.

Melinda Moree, former Director of Malaria Vaccines Initiative & currently Interim CEO of BIO Ventures for Global Health (BVGH) – BVGH is an organization focused on getting biotechs to work on global health. According to Dr. Moree, the product pipeline was dry 10 years ago, now it's pretty full with innovative products as well as sponsors tweaking old products for new uses. She also talked about the good works being done by PDPs,

such as setting up clinical trials infrastructure where it didn't exist before, like in Africa, where clinical trials can now be conducted according to globally accepted standards allowing products to be approved worldwide. PDPs have the advantage of making a number of products targeting one disease, so you get increased learning across a portfolio, both failures and successes, compared to just working on one product. Another advantage of PDPs, according to Dr. Moree, is that some do their own advocacy work, which is why some things make "the list" and others don't. In the future, there is a need for commercially viable strategies for products, because there isn't enough philanthropy in the world to serve the needs of 6.5 billion people. This raises a big question of how to incentivize biopharmaceutical companies. Some companies may engage for public relations purposes while others, such as small companies, will engage in this area for the potential profits. Some of the companies that have the strongest expertise and capabilities relevant to developing products to address neglected diseases do not necessarily need or want to engage in this area. They are not playing in the global health arena, because they need competition, not monopoly, like you have with PDPs. And you need incentives to bring product champions to the table. While some have been critical regarding the use of the priority review voucher in the US, disease advocates need to understand that the voucher has to prove valuable to serve as an incentive. Technology drives change in health systems, not the other way around. You need "controlled chaos" like what you get by bringing people together to create unanticipated synergy – that hasn't happened yet in this field.

Angela Watson, Assistant Director, NTD Control Initiative, USAID – Dr. Watson is involved in the scale-up of drug distribution in developing countries, by learning from good programs and transferring that knowledge to other countries. Some neglected diseases can, in fact, be controlled with existing drugs: Onchocerciasis, Schistosomiasis, Filariasis, Soil-transmitted helminths, and Trachoma. Dr. Watson stated that most of these treatments are donated by drug companies and are worth hundreds of millions of dollars. Congress created a \$15M earmark to facilitate the efficient dissemination of these treatments by ministries of health (MOHs) by eliminating duplication and providing for joint planning, training and logistics. In 2006, USAID launched its Integrated NTD Control Program to support MOHs through NGOs like WHO to develop plans, map regional disease burdens, train the drug distribution chain, and monitor implementation. The program started in five countries that had the following characteristics: high burden of disease, great financial need, and a high level of commitment from the domestic government. These countries were Burkina Faso, Ghana, Niger, Mali, and Uganda (now the program has expanded to eight additional countries in Asia, Africa, and the Caribbean). The program is entering its 4th year and has provided over 160M treatments to 40M people. In one very successful case example, the post-conflict country of Sierra Leone, the program achieved almost 100% coverage for several diseases, which persuaded the indigenous government to involve multiple ministries (i.e., not only the MOH but the Ministry of Education as well) and increase their own resources dedicated to these efforts. With US government support and a commitment by the G8 countries (in particular Japan and UK), as well as the announcement by President Obama of the new global health initiative in May 2008,

USAID plans to scale up program goals to encompass 30 countries over the next five years and provide 1B treatments with a view toward not only control but eradication of these diseases.

Panel Q&A summary – Key points raised by the panel in response to audience questions included the need to develop more commercially viable and sustainable solutions. For example, some speakers indicated that the pipeline long-term is thin compared to the many issues that need to be addressed, such as potential toxicity and resistance problems for existing medicines. Clinical trial projects need more than just a few years of funding up front in order to ethically enroll patients in studies, and research teams need to be able to count on an even longer time horizon. In the meantime, we must use what’s currently available such as the PDPs, the priority review voucher, and the “smart switchboard” program which provides resources to PDPs by acting as a marketplace for the exchange of expertise and technology. One panelist stated that the concern over the potential for overly generous incentive programs is largely misplaced as the needs are significant, the challenges are not insignificant, and potential cost-effectiveness is high (e.g., malaria causes \$12B in productivity loss annually in Africa compared to \$240M in R&D expenditures per year). In any case, the prospect of an occasional blockbuster emerging from a successful incentive program like the ODA is acceptable based on prior history of congressional and public debate.

Lunch Keynote

Michael Reich, Harvard University School of Public Health – Dr. Reich discussed a number of challenges related to improving access. He noted that medicines alone were not sufficient to ensure better health care outcomes. He urged an increased focus on addressing the multiple dimensions of improving access to health technologies in developing countries, and presented a framework for analyzing access based on the dimensions of architecture, affordability, availability, and adoption. He discussed examples of different health technologies and the problems confronted in creating effective access. He concluded by noting that creating access to good health technologies in poor countries is not easy, but can be done through attention to processes of agenda-setting and implementation at global and local levels as well as strategies to manage imperfect markets and imperfect governments. *[For a summary of the findings in Dr. Reich’s book, see the keynote summary in the forum brochure on this website]*

Afternoon Sessions

Valerio Reggi, Senior Adviser, Department of Control of Neglected Tropical Diseases, WHO – Dr. Reggi noted that these diseases cause high morbidity and disability in almost 1 billion people, inflict enormous economic burden on afflicted communities, and impair childhood growth and development. There are four basic approaches being taken to address these diseases: 1) case management, surgery and chronic care; 2) transmission control; 3) promote healthy behavior; and 4) preventive chemotherapy.

Some diseases require large-scale interventions through improved access to well-established medicines, which is provided through donation programs managed directly by some MNCs such as Merck, J&J, and Pfizer, or through WHO, such as Novartis, GSK, Bayer and Sanofi-Aventis. Other diseases need innovative therapeutics and diagnostics, and for them the way forward will take three basic paths: 1) existing PDPs for protozoal infections and dengue; 2) WHO-industry collaboration to convert veterinary drugs to human use for helminthic infections; and 3) piggybacking TB research for mycobacterial infections.

John Kilama, Director, Kilama International Consulting Group – Global health issues are complicated and involve neglected and “not neglected” diseases, such as those for the treatment of chronic diseases such as diabetes, which are as deadly in Africa as they are in other parts of the world. Global health shouldn't focus only on treating diseases once they've been identified, but instead should include a focus on how to prevent the diseases, using vaccines, education, training for health care workers and the public, and strengthening the health care infrastructure.

Kena Mphonda, Deputy Ambassador, Embassy of the Republic of Malawi – Malawi has a population of 13 million, or slightly larger than the state of Illinois, but more than 80% of the population lives in rural areas with limited access to medical facilities and trained medical staff. Despite this and the many serious public health challenges faced by Malawi, progress is being made. For example, in the recent past hundreds of pregnant women would line up each week at the Zingwangwa health center for check-ups, but overworked nurses lacked the time and training to administer malaria prevention treatment and if the pills went home, women often didn't take them due to myths about potential harm to their babies. Now, thanks to improvements in process and education through a collaborative program with the USAID and CDC, the percent of woman taking the recommended doses has increased from 29% to 70%. But neglected diseases such as trachoma and hookworm still take a heavy toll in sub-Saharan Africa, perhaps as much as one-quarter that of AIDS and half that of malaria. As demands for prevention, care and treatment of these diseases increase, public-private partnerships with NGOs and pharmaceutical companies that have provided workforce training, education programs targeting health care providers, and support for local health infrastructure will continue to be relied upon.

For further information, please call 617-636-2170, or contact Peg Hewitt, CSDD Research Librarian, at peg.hewitt@tufts.edu, or visit <http://csdd.tufts.edu/negd> for copies of presentations and additional materials related to the forum.