FOOD AND DRUG ADMINISTRATION

PART 15 PUBLIC HEARING
"ADVANCING THE DEVELOPMENT OF MEDICAL PRODUCTS USED IN THE PREVENTION, DIAGNOSIS, AND TREATMENT OF NEGLECTED TROPICAL DISEASES" (DOCKET NO. FDA-2010-N-0364)

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C O N T E N T S

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P R O C E E D I N G S

(9:00 a.m.)

OPENING REMARKS

MR. SACKS: Good morning. My name is Leonard Sacks. I'm the acting director of the Office of Critical Path Programs at FDA. On behalf of the Commissioner, Dr Margaret Hamburg and I'd like to welcome you to this part 15 hearing on, "Advancing the Development of Medical Products Used in the Prevention, Diagnosis, and Treatment of Neglected Tropical Diseases."

The hearing is intended to address the challenges in developing new treatments and diagnostic tests for neglected diseases. As I'm sure you are all aware, these are generally tropical diseases that affect developing countries, but are rarely seen in affluent developed countries. Many of you in the audience have just spent the past two days listening to extensive presentations on the topic of NTDs at the IOM meeting and we value your perseverance and stamina in attending this meeting.

The identification of neglected diseases is somewhat subjective. The priority review voucher legislation in Section 524 of the Food Drug and Cosmetic Act identifies the following 16 eligible diseases.

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, any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary (section 524(a)(3)).

There are clearly many other neglected tropical diseases which also require the development of new treatments and diagnostics and we believe the list will change with time.

Many of these diseases exact an enormous toll in global morbidity and mortality. An estimated 11 million people worldwide have tuberculosis. 243 million cases of malaria occurred in 2008. Other diseases such as human

African trypanosomiasis are more geographically confined, but result in high fatality rates. We all recognize that treatment is not always effective and often toxic.

Why are these diseases neglected? There is little financial incentive for industry to develop products to deal with these diseases. Most of the victims live in poverty, and affected countries battle with limited health resources. Clinical trials may be challenging in many of these environments. Development of products for these diseases often relies on the altruism of the pharmaceutical industry, recognizing the global responsibilities of wealthy nations.

While FDA approval of products is not required in other countries, many of these countries have limited regulatory capacities and defer to FDA for confirmation of safety, efficacy, and product quality. Congress has articulated its humanitarian concern for these neglected diseases and in addressing this, they have charged FDA with drafting a report. The report should address the preclinical, clinical, and regulatory challenges to developing products for the treatment, diagnosis, and prevention of these diseases. The report should also

include recommendations on possible solutions to these challenges.

We are using this meeting as an opportunity to hear from the public and from the medical community about the perceived challenges and potential solutions to the problem of developing products for tropical diseases.

We are interested in hearing about the perceived challenges in obtaining FDA approval or clearance of products for neglected tropical diseases. We are also interested in your views on incentive programs, the pros and cons of orphan drug designation, the Priority Review Voucher program, the Humanitarian Device Exemption program.

We welcome comment on new approaches to development of products for neglected tropical diseases, and on new strategies for international cooperation, consultation, and collaboration in reviewing these products.

This is a hearing, so this is an unusual opportunity for FDA to remain silent and not to be questioned, so we appeal to you not to question us. We have -- I believe five speakers registered to speak.

Our panel of FDA staff represents the three centers dealing with medical products. And they -- it would be nice to listen to the presentations and to ask questions to the presenters about their statements. Please do not interrupt the presentations. There may be an opportunity for you -- additional comments from the audience or statements from the audience after completion of the presentations. Comments may also be submitted to the docket until October the 20th. And I've also been asked to appeal to you to silence your cell phones.

We're very grateful for your participation in this hearing and for your dedication to this very important public health issue. We look forward to your presentations and to the help you will be providing us in dealing with this challenging issue.

I think -- let me open the meeting by just asking the panelists to go around and introduce themselves. And then we will introduce the first speaker, if you don't mind.

MR. NARDINELLI: I'm Clark Nardinelli, FDA chief economist.

MR. BEERS: I'm Don Beers, and despite what my little placard said, I'm not the chief counsel but I am an

attorney in the Office of Chief Counsel.

MS. GRUBER: My name is Marion Gruber; I'm the deputy director in the Office of Vaccines Research and Review at the Center for Biologics Evaluation.

MS. FINN: I'm Theresa Finn; I am also with the Office of Vaccines Research and Review at the Center for Biologics at FDA.

MR. TOERNER: Good morning, my name is Joe Toernur, I am -- work at the Center for Drugs in the Office of Antimicrobial Products. And I'm the associate director for Medical Affairs.

MR. ROEDER: My name is Dave Roeder; I also work in the Office of Antimicrobial Products. And I'm in CDER and I'm the associate director for Regulatory Affairs in that office.

MR. GITTERMAN: Hi, I'm Steve Gitterman. I am a medical officer in the Division of Microbiology Devices in the Center for Device and Radiological Health.

MS. HOJVAT: Hi, my name is Sally Hojvat. I'm with the Office of In Vitro Diagnostics, CDRH. And I'm director of the Division of Microbiology Devices, so very interested in your comments on diagnostics.

MS. CHARO: Hello, I'm Alta Charo. I'm a senior advisor in the Office of the Commissioner.

MR. SACKS: Thanks very much. So then without further due I'd like to introduce the first two speakers, Kaitlin Christenson, who's Coalition Manager of Global Health Technologies Coalition and Florence Kaltovich, Quality Assurance and Regulatory Affairs advisor for PATH.

PRESENTATIONS

MS. CHRISTENSON: Good morning, I'm Kaitlin Christenson, coalition manager for the Global Health Technologies Coalition. And I present these comments today with my colleague, Florence Kaltovich, on behalf of the Global Health Technologies Coalition members.

Esteemed members of the FDA Neglected Disease group and panel members today, colleagues, thank you all for joining us. And thank you for your recognition of the need to find new solutions to advanced development of medical products to prevent, diagnose and treat neglected tropical diseases.

My colleagues -- my colleague, Florence

Kaltovich, and I are grateful for the opportunity to present the following remarks to you as well as for your efforts to develop recommendations about ways in which the FDA may play a greater role in ensuring that safe and effective medical interventions reach those in need in the developing world.

We're speaking today on behalf of the Global Health Technologies Coalition, a group of more than 30 nonprofit organizations working together to educate U.S. policy makers about the need for U.S. government policies to advance the development of new global health products including new vaccines, drugs, diagnostics and other tools.

The Global Health Technologies Coalition strong -- members strongly believe that an expanded role for the FDA in global health can contribute to accelerated availability of products for NTDs and other diseases of poverty. Our comments today reflect the needs expressed by our member organizations which include product development partnerships, such as the Aeras Global TB Vaccine Foundation, the PATH Malaria Vaccine Initiative, and the Drugs for Neglected Diseases initiative as well as

advocacy organizations and think-tanks.

Though we will present different perspectives on the issue today, all of the groups with planned statements today are members of the Coalition. Our comments today will be organized in four parts. First, I will address the critical need for new global health technologies for neglected diseases. Second, I will explore the promise that lies in the current pipeline of products for neglected diseases. Third, I will share our perspective on the key challenges facing the development of new products. And fourth, Ms. Kaltovich will offer recommendations for your consideration.

New health technologies have the potential to save millions of lives each year. The world urgently needs new vaccines, drugs, microbiocides and diagnostic tests to slow the global threat of diseases including malaria, tuberculosis, and other NTDs. And to tackle many other pressing health needs.

Every day, more than 35,000 people die from AIDS, TB, malaria, and other neglected diseases. NTDs afflict more than 1 billion people each year, roughly one-sixth of the world's population. And kill more than

500,000 people on an annual basis. Those who are most affected live in poverty in the developing world.

The impact of these illnesses extends beyond the health of those infected. Worker productivity suffers, leaving families with lower household incomes and developing countries with weakened economies.

For many of these diseases, tools either do not exist or are grossly inadequate. For example, anti-malarial drug distribution has increased substantially in recent years but drug resistance is now prevalent around the world. Though research efforts have advanced significantly, there is no current vaccine to prevent malaria infection. Also, while millions have been cured from TB, drug resistant TB cases are rising world-wide and 1.8 million people die each year from TB. The current vaccine in use is almost 100 years old and existing TB drugs are 50 years old.

Additionally, global efforts to eliminate river blindness, a historically neglected disease, have delivered more than 100 treatments, but approximately 37.2 million people are still infected world-wide.

Because there are strong reasons for private

industry not to invest in the development of products for NTDs, a host of new organizational models and incentive mechanisms have emerged to address this challenge. Some mechanisms like the Priority Review Voucher, the transferable voucher awarded to a company that receives FDA approval for a new vaccine or drug for an NTD -- which we'll hear more about from another speaker today -- hold great promise.

Industry stakeholders await additional information about the value of the first voucher granted to Novartis for its antimalarial drug, Coartem. Other mechanisms, such as the Orphan Drug program which was anticipated to drive development for both rare and neglected diseases have proven to be less effective for spurring investment in neglected disease.

One organizational model that has proved promising is the Product Development Partnership or PDP. PDPs are a unique form of public-private partnership established to drive greater development of products for neglected diseases. Currently, there are more than 20 such PDPs developing drugs, vaccines, microbiocides and diagnostics that target a range of infectious and

neglected diseases including HIV and AIDS, malaria, TB, chagas disease, dengue fever and, visceral leishmaniasis among others.

While each PDP operates differently depending on the disease area or areas of focus, they typically employ a portfolio approach to research and development to accelerate product development by pursuing multiple strategies for the same disease area. They also work in close partnership with academia, large pharmaceutical companies, the biotechnology industry and with regulatory and other government agencies in the developing world.

PDPs are delivering on their promise to develop life-saving products for use in countries where disease burden are highest and no viable commercial market exists. To date PDPs have developed and licensed 12 products to combat neglected diseases in low and middle-income countries. More can be expected from PDPs in the future with sustained and additional support. In 2009, PDPs had more than 120 biopharmaceutical diagnostic and vector control candidates in various stages of development, including 32 in late-stage clinical trials.

In the next 5 years, it is anticipated that

several new technologies could be ready for use or in final stages of clinical development. For example, the RTSS/ASO1 malaria vaccine candidate manufactured by GlaxoSmithKline Biologicals and co-developed with the PATH Malaria Vaccine Initiative is currently being tested. And if all goes well, it could be available for general implementation for infants in Africa within 5 years or so. Such a vaccine would reduce the burden of sickness and death from malaria.

Nine new TB candidates are in clinical trials world-wide including the first late-stage infant study of a TB vaccine in more than 80 years. There are also eight new TB drug candidates in testing, which if approved would become the first TB drugs in nearly 50 years. These therapies could help reduce the 8 million new infections and 1.7 million TB death related -- TB related deaths that happen each year. Finally, new rapid PCR based diagnostic tests for TB could expedite treatment for patients with TB.

In order to be prepared for these and other products in the pipeline we must act now to strengthen regulatory capacity world-wide to review and approve these

products.

Developers of products intended for the developing world face key challenges in three areas. First, capacity to conduct as well as adequately regulate clinical trials does not exist or is often weak in countries where diseases are endemic. Second, there is a lack of financing for late-stage clinical trials which are necessary for testing the advocacy and safety of new tools. And third, the approval process for new products for neglected diseases is poorly coordinated and involves multiple complex steps.

Global regulatory systems are not sufficiently streamlined and the capacity of regulatory authorities to approve products to the developing world is frequently weak. Therefore, regulatory review as well as introduction of new, safe and effective products takes longer than necessary.

The FDA has demonstrated through a number of recent actions that it can have an impact on the introduction of global health tools. These include FDA's program to review HIV and AIDS drugs delivered in the developing world through the U.S. president's Emergency

Plan for AIDS Relief or PEPFAR, the release of a guidance document that outlined FDA's willingness to review vaccines for diseases not endemic to the United States. The agency's partnership with global bodies such as the World Health Organization to enhance access for medicines in the developing world and assist other countries in bolstering their regulatory capacity.

The FDA's Priority Review Voucher program, which awards a voucher for future expedited product review to the sponsor of a newly approved drug or biologic that targets an NTD. The FDA's efforts in these areas are to be applauded. The agency can and should continue to increasingly leverage its expertise to benefit the millions of people affected by infectious diseases around the world.

We encourage the agency to consider the following recommendations to be presented by my colleague, Ms. Kaltovich, which would help make needed products for global diseases available. Thank you.

Ms. KALTOVICH: Good morning. These are our recommendations for FDA's consideration.

Number one, build stronger partnership with

other regulatory and nominative bodies. First, FDA should strengthen its partnership with global regulatory stakeholders such as the WHO and national regulatory authorities in endemic countries that are working to enhance access to health tools for the developing world.

The WHO, specifically improve interactions between the FDA and the WHO should be pursued to a) decreased delays for prequalification of products approved by FDA and b) expand FDA's role in capacity building and joint review initiatives of the WHO.

Following clinical development, neglected disease product sponsors typically submit a dossier to a fully functional regulatory authority such as FDA or the EMA -- European Medicines Agency -- as a first step. Although approval by a fully functional authority may not always be necessary to license a product for use in the developing country, many multinational companies prefer to pursue this step because of familiarity and the clarity of guidance in regulations. Additionally, many developing world governments do require approval by a fully functional regulatory authority before they will consider a new product.

When licensing a product for use in the developing world WHO prequalification is an important next step, and a signal of product quality, safety and efficacy to developing countries without significant regulatory functions. However, this process can be lengthy, sometimes taking as long as 18 to 24 months although the WHO is undertaking efforts to shorten this timeline to 12 months or less.

FDA's Center for Drug Evaluation and Research, CDER has engaged in joint inspections and information sharing with EMA and the WHO, a collaboration that is governed by a confidentiality agreement that permits sharing of pre and post approval regulatory information about medicinal products subject to evaluation or authorized under the centralized procedure including regulatory issues, scientific advise, orphan drug designation, inspection reports, marketing approvals and post authorization surveillance information.

The agreements aim to streamline the FDA's regulatory activities, the WHO's prequalification actions and the EMA's regulatory duties. They also seek to achieve quicker review and approval of health products as

well as allow for information sharing and exchange.

A harmonized link to WHO is needed across the FDA and the successful model established by CDER should be built upon and extended to other centers within the FDA. We recommend that FDA consider adopting a formal arrangement with WHO to conduct simultaneous review of products for neglected diseases similar to WHO's arrangement with the EMA under the Article 58 process. This step could minimize time delays that exist when FDA review and WHO review occur in stepwise fashion rather than in parallel.

For national regulatory authorities, in 2008, the WHO found that only about 20 percent of countries, all of them industrialized, have fully operational regulatory systems for medicines. Among the remaining 80 percent of countries, approximately one-half have varying regulatory capacities and approximately one-third have very limited or no regulation for medicines.

According to the WHO, more than two-thirds of people, worldwide, live in countries with a marginal or inadequate systems for ensuring drug, quality, safety, and effectiveness. FDA can play a key role in improving this

capacity through increased collaboration with countries and regional networks.

In particular, FDA should consider these mechanisms for direct exchange of information between FDA and the developing countries -- excuse me, developing country national regulatory authorities, or NRAs, and for providing training and other assistance to strengthen the NRAs.

Some potential activities which FDA might explore include; provide training in areas such as Good Manufacturing Practices, GMPs, and assistance on review of manufacturing facilities to NRAs in low-income countries engaged in product manufacturing. Provide training on Good Clinical Practices or GCPs to enable monitoring and acquisition of clinical data at remote sites, evaluation of clinical data and assistance in evaluating post-marketing surveillance systems; encourage memorandums of understanding between the FDA and countries with high incidence of global diseases to promote sharing of information that will harmonize regulatory activities.

FDA currently works closely with several regulatory initiatives including the African Medicines

Registration Harmonization or AMRH initiative and that of the American of -- excuse me -- Association of Southeast Asian Networks or the ASEAN.

The agencies should take a more active role in regulatory networks such as the African Vaccine Regulators Forum or AVAREF and the Developing Countries' Vaccine Regulators Network or DCVRN, to strengthen integration of regulation, registration, ethical approval, and mutual recognition of inspections for clinical trials in developing countries.

Number two, bolster FDA's internal capacity in neglected diseases. A key barrier to FDA's work in the area of global diseases is that FDA staff is not sufficiently resourced nor mandated to address neglected diseases. When FDA is asked to review a new product for a neglected disease, delays may occur if staff are unfamiliar with a disease and the conditions in which the product may be employed.

We recommend the following be considered to build FDA's internal capacity in this area. FDA needs sufficient resources to provide training opportunities to its staff and to hire additional staff with expertise and

entities. This could also serve to strengthen the scientific programs at FDA.

An additional step in improving FDA's capacity to review products intended for the developing world is the agency's consideration of having experts from emerging and developing countries on FDA advisory boards, particularly when products for global diseases are under discussion.

Especially when considering products for diseases that are not endemic to the United States and with -- and with which FDA staff may not be familiar, ensuring that developing country representatives participate is critical. For many of the first generation neglected diseases products currently under development, partial efficacy levels which may or may not meet FDA's typical standards maybe more appropriate and beneficial for a population where the disease is widespread.

Measuring the risk benefit ratios between -- will be a critical component of FDA's evaluation of these products and representatives from areas where diseases are prevalent can provide a crucial perspective. I understand that my colleague Dr. Hotez will speak more regarding

FDA's regulatory science portfolio.

In addition to the recommendations we have outlined here, the GHTC is supportive of broadening FDA's regulatory science program as requested in the president's Fiscal Year 2011 budget request and as suggested in Dr. Goodman's testimony to the Senate Appropriations Committee on Agriculture, Rural Development, FDA, and Regulatory Agencies in June of this year; to the extent that this work is applicable for both global health -- for all global health and diseases.

Number three, strengthen FDA's engagement with NTD product sponsors. FDA should consider mechanisms to increase and improve engagement with groups developing the tools to prevent diagnose and treat diseases of the developing world. Specifically, the agency should -- the agency should establish a new -- establish new review teams or specific points of contact for sponsors that are primarily focused on neglected diseases.

Through these terms or point of contacts, FDA can -- should encourage less formal Pre-Investigational New Drug Application process or the IND discussions with product sponsors to ensure that submissions to FDA are

scientifically accurate and appropriate. Since PDPs and other non-profit organizations facilitating the development of products for global diseases typically do not have the resources of large pharmaceutical companies, assistance from the FDA in an early stage of development would help PDPs develop realistic, targeted product profiles for their products.

Additionally, given the range of entities engaged in regulatory functions for global health products, there is a need for forums that foster increased collaboration and coordination across the globe. We request that FDA establish twice yearly global disease roundtables to include representatives from the FDA, product development partnerships, private foundations, WHO, EMA, and other select entities.

Through gains in these three areas, building stronger partnerships with other regulatory and non-native (phonetic) bodies bolstering FDA's internal capacity in neglecting diseases and strengthen the engagement with product sponsors, FDA can do much to advance the development of new products to combat these diseases.

Thank you very much for the opportunity to share

these remarks. We welcome your comments and questions.

MR. SACKS: I guess I'm turning it over to the panel now for any questions, looking around me -- perhaps I can just start with a question.

I guess a lot of the emphasis of your talks has been on regulatory pathways to get things more efficiently approved. I think we all recognize that one of the other fundamental problems in this area is that products are not being developed *de novo*. And my question is do you have any thoughts on ways that FDA can facilitate that pipeline looking at preclinical development of these products and the clinical development as well?

MS. KALTOVICH: Well, our recommendation to discuss -- early discussions for the IND process essentially, or with IDE process also, would help facilitate, I think, the -- in much early stages, because as you mentioned most of these products are very early in the R&D pipeline. So it would be good, I guess, to discuss where in this pipeline it may be beneficial for all of the PDPs to discuss the development with FDA.

MS. CHRISTENSON: I would add to -- I know our colleague Andrew will speak more about the Priority Review

Voucher mechanism. We see that as a promising mechanism. But still await additional data about the actual value of the first voucher that was granted to Novartis. Other mechanisms like the Orphan Drug program have not been as effective in driving development for neglected diseases.

Broader than FDA's mandate, we encourage the U.S. government as a whole to consider new incentive mechanisms and a portfolio of mechanisms that will help drive greater development of products for neglected diseases even at earlier stages than FDA's engagement. But to the extent in which FDA can play a role in the mechanisms like the priority review voucher, we are certainly supportive of that.

Also I believe, Dr. Hotez will speak about regulatory science program, and I think that's another area where more investment in global health can help with development of new products.

MR. SACKS: Dave Roeder?

MR. ROEDER: In just -- in looking back on the -- that -- how the PEPFAR program evolved. I remember back then, initially there was a great deal of controversy about whether the U.S. should procure drugs that are not

approved in the U.S. and should we recognize WHO prequalification. You know, and people felt very strongly, and you know, differently about that. The approach that we took, though, was encouraging a company to come in with application so that these products would meet -- would be -- meet all of the standards that are -- we would expect for any -- we would require for any drug marketed in U.S.

And with PEPFAR that's worked out really well, but that's very different, different challenges than what we've got here. We had already approved drugs and really largely we're looking at getting generic copies or new formulations, new combinations, and things. When you're looking at some -- more collaborative kinds of approaches such as say, Article 58, are you envisioning anything short -- that we would have -- anything short of an FDA approval or what are you really seeing there?

I mean, is -- because we've already seen that -- you know, our goal has been to get an approval at the FDA. And that -- what are your thoughts about that and how that fits into the Article 58 approach in that?

MS. CHRISTENSON: Well, you know, that it's a

challenging and complex issue and under the Article 58 process, there is not an EMEA -- EMA approval per se but a scientific opinion; that's certainly an interesting program for FDA to explore. What we find the key attractive benefit of that program and of that partnership is that it reduces the time, the delay between when FDA approval happens and then when WHO prequalification happens by having those two join in partnership.

And so as to whether we would be seeking FDA approval versus FDA scientific opinion, other colleagues may have more comments on that, but I think the key component, we think is important is reducing that timeline because of the delay that occurs in getting products out to the developing world. I think PEPFAR was a unique program.

MR. SACKS: Yeah.

MS. CHRISTENSON: You know that we are -- PEPFAR was dealing with -- the partnership under PEPFAR is dealing with products that were already approved.

MR. SACKS: Exactly.

MS. CHRISTENSON: One of the recommendations that we are making is more consultation with

representatives from the developing world because it's very likely we'll be dealing with products that may not meet efficacy levels and standards that FDA might set for U.S. population. And there is a need to understand what the risk benefit ratio of such a product might be. We are not supportive of removing safety and efficacy barriers simply for the purpose of getting products on to market, but there will be instances where it will be important to weigh a risk -- respect that risk benefit ratio and where colleagues from the developing world, where these diseases are endemic can provide greater expertise and perspective on that issue.

MS. KALTOVICH: And just one more thing for consideration is during the Article 58 scientific review process along with the WHO pre-qualification process, there is the opportunity for these NRAs to also collaborate and review and learn how -- what they are doing which is an initiative that WHO -- that the MVI is trying to do now to -- for the RTS,S vaccine.

MR. SACKS: Thank you. Sally?

MS. HOJVAT: Just wanted to add a little bit about diagnostics that -- often left out of this picture,

but we do have something called a pre-IDE process, which is exactly what you are talking about. We encourage sponsors, developers of diagnostics to come and talk to us even early in the game and we have been dealing with small companies who really don't have a lot of regulatory experience. So we are well aware of that need and that is available. And if anyone is interested, they can contact my division.

And on the interaction with WHO, not as defined as with the drugs or vaccines but beginning there have been some contacts made in that direction.

SPEAKER: That's promising to hear and we'll look forward to future developments in that regard.

MR. SACKS: Theresa?

MS. FINN: Hi, I just wanted to follow up on that. You -- Sally just mentioned about the pre-IDE process, and you know, we have a pre-IND process as well. But when you were specifically -- when you were talking, Florence, I think you mentioned less formal arrangements. And so I imagined that you were talking about something that was beyond the usual pre-IND process, which is a -- in which companies come in and present basically what's

going to be their package for their initial IND submission.

So could you a little -- expand upon this -- less formal interactions so that we could get an idea of what type of a discussion you were thinking about?

MS. KALTOVICH: Understanding that you have a defined pathway for meetings and the pre-meetings and things like that, I'm uncertain how you may consider putting it into having it available being that there is something more formal. I suppose one way to look at it would be much more earlier on than just a package.

We are talking about some of the research -- sharing some of the research that's being done, and maybe a timeline towards what we foresee the -- submitting it to FDA for an IND because oftentimes we are working several years ahead and really into early research with only minimal data.

And maybe you would be even learning FDA having -- a time with FDA to share some of that minimal early data to see if they -- we are on the right path and then thinking about, you know, what additional preclinical studies would be needed.

MR. SACKS: Just -- it's been suggested to me that maybe this interference is coming from somebody's BlackBerry or cell phone. So if -- anybody who thinks they may be guilty, please turn it off. Are there anymore questions from the panel here, the speakers?

Well, thank you very much. We'll move on to the next speaker. This is Shing Chang who is the -- from -- who is the research and development director for DNDi.

MR. CHANG: Thank you for giving us the opportunity. I apologize for being late. I went to the wrong building. I got the date right. So I suspect there would be some overlap in terms of the stakeholders' feedback. I would just quickly go over the slides. What I would cover is a few slides just to introduce you what DNDi is and just to help you understand our perspective. Then we will -- I will address the challenges and the actions.

DNDi started in 2003 based on the fact there is no tools, that's adequate tools, to address some very fatal neglected tropical diseases. So the goal was to develop alternative or better treatment for sleeping sickness, chagas, and leishmaniasis, the most -- three

most fatal entities. And at that time also WHO recommended four fixed dose combination for malaria that nobody else stepped forward. So we picked two of those as our immediate target.

And our founders included many disease endemic countries, India, Brazil, Malaysia, and KEMRI in Kenya. As I mentioned, this -- the disease we covered other than malaria, which was an ad hoc effort, the others are more long-term and we are -- we are a virtual R&D organization. So we do every thing through collaboration and mobilize through partnership. Here is the portfolio not to -- just to give you an idea what we do in terms of projects related to development that -- where FDA can potentially make a very big difference.

I think as you can see on the far right side, we've two fixed dose combination already introduced, ASAQ been introduced, approved, originally in Morocco and then subsequently now approved in 26 African countries and pre-qualified and our partner is Sanofi and the next year we anticipate 50 million doses will be distributed.

So we have very long, big clinical studies at multiple sites. ASAQ is in collaboration with FIOCRUZ,

with a Brazilian manufacturer, government manufacture, and a clinical study was done in the Amazon area. It's 28,000 patients and it's approved in Brazil, and we are conducting studies in Asia and Africa.

And that is a combination therapy for sleeping sickness. A phase III study was done in Africa and the -- there is no -- since the two drugs we combined with, one was approved -- listed for chagas, that's nifurtimox, the other has been used and indicated for HAT. So this combination therapy provided a short course simplified treatment and there was no specific regulatory pathway other than we went through essential medicine list and now had nifurtimox specifically recommended in a combination treatment for HAT. So it's the equivalent of approval.

And then we have compounds in clinical study. We have just completed a large -- a fairly large phase III study studying various combinations of existing drugs to treat visceral leishmaniasis in India, and we are starting to -- preparing for the phase IV implementation study in India and expand that into Bangladesh and then Nepal.

So anticipation is that the three drugs would be used in various combinations that will involve probably

15,000 to 20,000 patients in the next few years. This will be done in collaboration with TDR and with Institute for OneWorld Health.

And in Africa we also have done combination treatment. The situation in Africa is different because for visceral leishmaniasis the only drug available is Sodium stibogluconate, SSG, which is a 30-day injection. Drugs available in India are not available in Africa; metafocin (phonetic), not registered; AmBisome, not registered; paromomycin, not registered.

So our short-term goal is to get those drugs registered through clinical study, demonstrate their efficacy, and very interestingly, the dose that worked in India did not work in Africa, with same efficacy. So we have to actually make adjustment. So we are also looking to -- whether that's due to patient difference or whether it's due to parasite differences.

So we are dealing with fairly complex populations, geographic areas therefore -- so also regulatory. We have sleeping sickness drug, top and clinical effects in there as well, that's in phase I. The phase I study is done in France and -- but the phase II

will be conducted in a disease endemic country. So that's basically a quick highlight of our experiences and portfolio.

So a challenge for us, I think at different stages, the preclinical testing, frequently we are dealing with diseases -- there is no good efficacy model, and I think particularly chagas would be a good example. One can develop very sophisticated animal model but how does that correlate into human.

There is no efficacious treatment for human chronic disease. So there is no way to validate a chronic disease model that works -- that one suspects may be relevant. And lack of pharmacodynamics predictor. So when we study visceral leishmaniasis, intercellular parasite, is it CMX (phonetic) driven or is it AOC driven and those informations are not available.

For a trial, we actually prefer use drugs in combination based on the concern about losing effectiveness due to resistance development. So there is certainly some gray area in terms of how to develop combination therapy, what are the best approaches, and of course, right now we are developing a combination of

approved drugs and soon we are going to study combination of drugs that probably not licensed, but still in phase II.

There is a lack of validated gold standards or endpoints, a lack of surrogate markers, and the example on chagas, I think, illustrates that really very well. Difficulty in safety assessment related to the fact that patients we are dealing with, when they present the case, they are probably really no good study. But our guess is they probably come in with at least two or three more other infections, whether its helminth, TB, or worse in Ethiopia, a fair high percent with HIV, and those patients are really in bad shape.

But it also creates problems in terms of doing clinical study and managing patients, to begin with, they are malnourished. And so when you do clinical study, do you feed them, do you nurture them back to better status, health status, before you treat? That will make a lot of difference.

Our regulatory approach; clearly, the lack of regulatory capacity is a serious concern. And I think many stakeholders have discussed this and with various

ideas. The role of FDA to provide advice, guidance and -- in developing new products is crucial, and I think it is probably under-recognized by some of the PDPs. I think FDA certainly has worked -- has actively engaged with WHO, with EMA, but I think there is still a gap between what I will call the users, the developers and the regulatory, and we certainly like to explore and understand better.

And FDA may lack the experience in appropriately making risk benefit ratio, and I think that's -- but I think the previous presenter already discussed that. I think it's a recurring thing. And it's something FDA has recognized. But I don't think it is necessarily a barrier, but it's a challenge in terms of how to combine FDA expertise with the experts who actually has a good appreciation of risk benefit ratio and merge into a single process to make it efficient.

So I will address some of the issues individually. Whether the -- what are the specific areas and diseases where progress is needed? Certainly, from our perspective, kinetoplastid diseases, they are fatal and they affect patients that generally live in rural area or poor condition. And for us, for instance, we did study

in sleeping sickness. And our challenge is really how do we deal with special populations, the pregnant women, children, and how do you -- do you treat anyone 5 years and older just as a young adult based on body weight or other considerations.

Unfortunately, it's very difficult to actually monitor multiple parameters in the field, because where we do clinical study, we just barely have electricity to light up the microscope. And we don't have very sophisticated tools.

Preclinical development for new chemical entities -- I think certainly from our perspective -- have been in our seventh year and we're moving our portfolio -- start moving to new chemical entities, thus start to represent different challenges. Because phase I study is safety and then how does the experience from phase I in France translate into your safety observation in phase II in Democratic Republic of Congo.

What can be done to advance development of products? From DNDi's perspective, we are very much focused on patient needs. So if we advance something, we have a strong sense of urgency. We want to go through the

regulatory process as fast as we can to -- if the product meets the requirement, then we like the patient to benefit from the product as soon as we can.

So we usually do not include FDA or EMA in our consideration as a routine consideration just because we're concerned and might actually add -- might delay. However, we always look for pharma partners to ensure supply and availability access. So we certainly will honor our partners' wish -- wishes if they want to register a drug.

For example, you know, you look at HIV, TB certainly there is a market for developed country. And now you look at Chagas, that's also the case which estimates 300,000 infected individuals in the U.S. So that does start to introduce another variable for us, but we want the highest standard to be applied, but not losing speed.

So for us historically, we focus on pre-qualification, we focus on endemic country. Some require the drug to be listed on their formulary. So if they have the desire, then you can apply for approval. It's a pre-requisite. I think some of the comments, particularly the

African regulatory perspective -- we have worked with Mary Moran, commissioned her to do a study. And that's available on the website. And some of my points of view are actually a reflection from that study.

The perceived benefit or non-benefit of some of the mechanisms -- orphan status I think are a concern as orphan drug usually evaluate in a small patient population whereas where we're talking about neglected diseases, they actually affect huge population. They're neglected, but they're certainly not minority. So we need to ensure some kind of safety information data that's not going to suffer because of the orphan drug kind of status.

Now the priority review voucher, to be honest, so far it's intended as a U.S. government's commitment to provide incentive to develop drugs. And other than Novartis, a simple example which is inappropriate in many ways, we have yet to see the benefit. In fact, for us to form partnership with pharma, it actually -- I'm sorry to say that, but it actually created a barrier for negotiation because now you -- we have a unknown value of asset, and who is going to own what if we form partnership.

And so fortunately, we managed to chart this course and mostly delayed a discussion. And so we haven't really seen a great incentive from pharma's side because of this. I think they're very conservative, they're cautious, they'll wait and see what is this, what does this mean. But I think, you know, we do appreciate the effort. And I think, you know, it's really the reflection of -- from Congress which is really speaking for American citizen's commitment.

Other potential incentive -- potential fast track approval and things like that. So our -- you know, to a larger extent, we're still trying to learn more about how that might impact. How am I doing with time? I don't want to --

SPEAKER: (Off mike).

MR. CHANG: Okay. I have few more slides. What can be done to advance the development? We're looking for -- I mean, it's not the FDA's role to finance, but we're very encouraged to see that FDA actually has also recently offered the opportunity for funding TB and NTD proposals. And I would like to see a long-term drive from all stakeholders to commit more resources to develop

treatments for neglected diseases.

From a regulatory point of view, we'd like to see a far more twined review that is described in Mary Moran's document.

But it's really -- we like to see the regulatory authority from a stringent -- stringent regulatory countries -- like FDA to work with, say for instance, African countries' regulatory agencies, and work together, have a streamlined joint process to -- partly to -- it's like a trimming through actual exercise and partly is to combine the expertise, the risk-benefit ratio, and other local experiences together with more sophisticated regulatory experience.

And what's really important is to speed up the move of drug to license and to pre-qualification because I think a lot of patients do not pay for the drug than the donors. And donor usually will donate only if the drug is pre-qualified. We heard just from previous testimony the fund -- additional funding to support development trending in African countries and create something similar to Article 58.

I think for us, we actually are just

experiencing going through this -- we have a meeting coming up that's taking advantage of the Article 58. So we're going to have -- for the first time, have first-hand experience on how that might benefit us. So I cannot really comment more than what's the general description of the process.

What can be done to advance the development products? That is really our new strategies for international cooperation. I know FDA, EMA -- being based in Europe, we have maybe a little bit more interaction with EMA. So we understand it's really a very frequent interaction between the agencies and with WHO. And I think we certainly love to see more of that with a stronger sense of urgency.

In terms of training, guidance, I think we have more or less touched on that in the previous presentation. And I think the geopolitical complexity in Africa is one of the barriers, but I think our recent experience showed that actually each country has certain expertise. And when you pull them, indeed they really have very high capacity of potentially dealing with regulatory issues in a very competent, efficient way, but then we just have to

facilitate and make it possible.

So in conclusion, we believe that FDA certainly can provide advice to developers like DNDi in terms of guiding us. We've been a virtual company, a virtual organization. We really don't have a dedicated regulatory person. So -- and even if we hire someone from pharma, it has a very different perspective.

So it's really the combined field experience from DNDi and regulatory experience from FDA that we need to have more interaction. And this allows us to receive -- to ask the right question and to get valuable advice.

Recognize the strong role -- I think for PDPs in developing NTDs, I think, is really taking advantage of our understanding being closely linked to the patient, to the field condition. I think most urgent need is really ultimately we like the disease endemic countries to have greater capacity to take care of their own issues.

For us, it's certainly getting approval, a drug approved. But you know, they deal with many other issues like counterfeit drugs that very urgently they need help. Continue to enhance collaboration -- I think as I said it's really a very positive thing and that we need to do

more. We need to engage more stakeholders.

And also I want to congratulate FDA's not only with interest and intent, but a very innovative approach to Critical Path Initiative. I think it's really a very encouraging sign in terms of our future interactions. Thank you.

DR. SACKS: Thank you very much. Questions?

SPEAKER: Yes. Yeah. Well, thank you very much for this very interesting presentation. I have a question, because I realize some of the common themes of what our, you know, partners in the MVI sort of presented and what you just mentioned and that it gets again at the -- in terms of regulatory approaches and the role that FDA can play in terms of providing advice and guidance, especially to non-traditional partners or product developers.

And you referred to what you called a gap between, you know, the FDA experts and these -- and the developers. And in your concluding slide you mentioned that you would wish a facilitation more easy access to FDA experts and also a mechanism of providing more informal advice, again, mentioned by the people at MVI.

Earlier on we heard about the possibility of creating roundtables to discuss some of these issues. Can you elaborate a little bit more in terms of how you would see for FDA to be able to provide you with more informal advice during this maybe early stages of development? Because as you know, we do have the pre-IND process, but it sounds that this is really not sufficient and what you are all thinking of goes way beyond that.

MR. CHANG: Yes. And I have to say our recent -- very recent experience with FDA is actually through our pharma partner, Eisai Pharmaceutical. We just had participated in a meeting to discus developing the drugs for Chagas and it was very helpful.

However, I think -- their being a regulatory agency, I think you have fairly well-established process in terms of what you can say, what you can do, what you cannot do. But I think it would be beneficial to be able to participate in roundtables whether we sponsor or whether you sponsor, as we move with compounds at the preclinical stage ready to -- committed to IND path.

And early on -- and it's less formal, it's not -- it's more like a scientist talking to a scientist rather

than a regulatory agency talking to applicants. And so that would be very useful. So based on the current way things are structured, for instance, we talk to EMA and they talk about possibly join FDA-EMA, discuss with us our sleeping sickness drug development.

And -- but then we need to brief the regulatory about our field experience. And it is very difficult with limited time. So we figured the only alternative is maybe set up a workshop, half-day workshop prior to the formal meeting. So essentially, we are trying hard to work around so many rules.

And so I think a biannual kind of gathering is good, a more specific topic in terms of compound in development to have discussions, more educational, and exchange rather than a regulatory opinion would be very useful. And in those cases, I think we -- for DNDi would be happy to invite disease endemic countries' regulatory agencies for participation.

Because I think for us, you know, for all our clinical studies in Africa, in -- whether it is East Africa for leishmaniasis or west side for sleeping sickness, we have regular meetings in terms of the project

team that we engage regulatory -- local regulatory. So they knew what we're doing, they knew where we are, and so just to allow us to speed up the development. So they seem to have less stringent requirement in terms of what they can or cannot say or cannot do.

SPEAKER: Okay. You mentioned -- you recommended that one of the slides said that following twin reviews, automatic WHO pre-qualification, but -- so you really -- you were recommending twin -- when you say you're -- when you're recommending that we do joint reviews with the disease endemic country regulatory authority, are you thinking in terms of this process and this interaction happening during the drug development stage, or are you thinking more -- I mean, I'm sure you're thinking that, but are you also considering a joint review of the registration package?

MR. CHANG: Yes. What we're thinking is simplification of the process to improve the speed of a good drug reaching patients, all right. So instead of going through stepwise get reviewed by, say, FDA, then some countries will accept it, then goes through WHO essential drug or pre-qualification and they --

SPEAKER: Oh -- yeah.

MR. CHANG: Yeah. So either a single process that triggers multiple gates -- open several gates and -- that would really be the most helpful -- helpful thing.

SPEAKER: Okay. So when you're talking about streamlining, you're actually streamlining the multiple gates rather than the -- just --

MR. CHANG: Right, right.

SPEAKER: Okay -- than just the FDA gate.

MR. CHANG: Yeah, yeah, yeah, yeah. But you know, for us it's really -- we want to work with FDA or EMA or others -- for us it's really -- we'd like to be fast and be good at the same time. So whoever can offer the best advice and also help to strengthen the capacity and get things out of the door fast will be the most desirable for us.

SPEAKER: I just have a brief question which I hope you won't misinterpret. It's a little provocative. But I guess -- what is the advantage to you in having streamlined regulatory activities between, for example, the EMA and FDA if the product that you're going to use is going to be used in some other country and not the EU or

FDA? Wouldn't it be better for you to go for both agencies and see who gets there first, for example?

(Laughter)

MR. CHANG: Or you might end up having to live with the most stringent demand, you know, the combined -- so you know, for us part of it is really the burden of going through a process. And to go through two processes we just -- you know, it's very difficult for us to deal with it.

SPEAKER: I did have one more question if nobody else does. In the earlier talk, you were speaking about strengthening the capacity or building capacity in local areas, in areas of the clinical studies. And seeing you very much sort of in the trenches there, perhaps you can just give us a little bit more insights into how we could do that capacity-building onsite.

MR. CHANG: My understanding is that within African countries there is already discussion in terms of regional kind of yearning to share the capacity. For instance, if you -- if, let's say, Kenya, Uganda and Ethiopian regulatory agency reaches agreement because they all -- economically they share a lot of interest.

And so if we can build on that, have more combined resources for regulatory, so we don't have to train the small regulatory agency to be professional in everything. And that is certainly an idea that has been discussed. And certainly, also removes the barrier for us, because we have to deal with Ethiopian regulatory, Uganda regulatory, Kenya regulatory separately.

So if they can reach agreement and if FDA or EMA provide additional incentive, I think it could actually be one mechanism that will speed up. And of the francophone countries, you know, might be willing to do similar things.

DR. SACKS: Any other questions from the panel?

MR. CHANG: Thank you.

DR. SACKS: Thank you very much. And I'd like to call on the next speaker. This is Andrew Robertson, chief policy officer, BIO Ventures for Global Health.

MR. ROBERTSON: Good morning. Thank you very much for the opportunity to address the committee today. We think it's a very important topic. Our statement today provides a brief account of the response to the priority review voucher program that my company, BIO Ventures for

Global Health, that we've observed since the program's enactment.

I think I've been scheduled for 30 minutes. We've also submitted, however, a written testimony which will go into more detail on some of the points which I'll highlight today. And as such I'll try to highlight the key headlines from there and refer you to the document for more detail.

But before I begin, I definitely want to recognize and thank the FDA for convening this public hearing, and in including input from stakeholders and organizations such as BIO Ventures for Global Health. We believe this is a really exciting time in addressing global health disparities. And it's really encouraging to see the FDA and partner agencies taking a leadership role in this effort.

Next slide, please. So BIO Ventures for Global Health is a non-profit organization. Our mission is to save lives by accelerating the development of novel biotechnology-based drugs, vaccines, and diagnostics to address the unmet medical needs of the developing world.

So most of us here today have a sense of the

profound global health problems caused by neglected tropical diseases. These diseases affect the poorest populations often living in remote rural areas. And further neglected diseases, while they're medically diverse, they share features that allow them to persist in conditions of poverty.

At BIO Ventures for Global Health, we believe that biotech and private industry play an important role in addressing NTDs. Our core focus is promoting innovation in neglected topical disease research. And we feel that we can do this through -- we're going to address this issue through a very unique perspective.

We have -- our staff consists of experts both in private industry, but also in global health. It's through this dual lens that we think we could actually provide unique contributions to this discussion. To break down our work really quickly, it really is in the pursuit of two goals. The first is to reduce the cost of drug research and development for neglected tropical diseases.

Now, to this end, many of our projects -- for example, they help define markets for neglected diseases, they provide information about global health to private

industry stakeholders, and we work to build partnerships between academic and private sector researchers. One project that's gotten a bit of press recently is we also are the administrators for the Pool for Open Innovation against neglected tropical diseases.

This is a program that helps -- that was initiated by GlaxoSmithKline and Alnylam and helps share intellectual property around diseases such as malaria, tuberculosis, and leprosy. These initiatives and others in our portfolio, they serve to lower the costs -- sorry -- lower the cost demands of research and development for neglected tropical disease research.

Now, in addition to lowering the cost, we're also looking to increase the reward incentives. And this -- we've got a few initiatives in this area, but one of our core ones is the priority review voucher program. This is a great example of -- on ways to increase the rewards, and is the focus of this presentation.

Next slide, please. So this is a busy slide, but I just wanted to put it up there to highlight our core assets. One of the strengths of BIO Ventures for Global Health is our extended network that branches into most

fields relevant to global health. This includes law, business, academia.

Also to draw your attention to top left corner, we have a working group that we set up specifically to address the priority review vouchers. We've got a good cross section of stakeholders that are involved in this working group. And it's worth noting as well that Doctors Ridley and Grabowski, who are the original authors of the PRV program, they're also members of this group.

Next slide, please. So our support of the PRV program stems from the organization's core mission in developing market-based incentives for investment in global health. In short, we see it as a very powerful market-based incentive program. And it's run by the FDA. And it's very, very elegant in concept.

And the long and short of it is if a company develops a drug for 1 of 16 neglected tropical diseases, they actually receive a voucher in hand that can be then used to gain priority review for a drug of their choice in the future. Further, and a key part of this is the vouchers are transferable so that if a company that obtains the voucher doesn't have a drug in the pipeline,

they then have the option to sell it to another company that does.

This scheme you can see, it carries a lot of potential benefits. The way we see it, it can shave off between 4 and 12 months from the standard FDA review process by reducing the review time that obviously allows companies to bring a drug to the market faster and earn revenue sooner.

Earlier market entry also means more time -- not only means more time for sales, but it also gives companies a greater advantage over the competition through a first mover advantage. They can really help shape the market as they move forward.

So all in all, depending on how the voucher is ultimately used, the type of drug and the disease for which it's designated, experts believe that it could be somewhere in the range of $50 million to $500 million. But however, as our colleague noted earlier, this is a large range. It's a little bit hard to pin it down, but that's the thing, I think, we are working with.

But in short, it does constitute a concrete -- it has the potential to constitute a concrete, tangible,

and very low-cost incentive designed to attract industry to research and development for neglected tropical diseases. For more details about this I'll definitely refer everybody to our website, www.bvgh.org, and also we brought some one-page fact sheets that are outside in the lobby.

So a quick review of the PRV program, it was passed into law September 27, 2007, under the FDA Amendments Act for that year. FDA released guidance for industry in October 2008. There are some limitations that were introduced through the FDA guidance though. These include that sponsor planning to use the PRV must notify the FDA of its intent, at least 1 year in advance.

A sponsor using the PRV must also pay an additional user fee. It's a standard for priority review. But we just got an announcement from the FDA that this user fee is in the range of $4.6 million. Finally, the PRV sponsor, the holder of the voucher, is limited to only one-time transfer of the voucher to another sponsor. So this cap on sales has some limitations which I'll discuss in little bit more detail in a second.

In April 20, 2009, the FDA issued the first

priority review voucher to Novartis. This is for the antimalarial drug Coartem. It's an ACT, and although the drug was developed in 1996 and has been used for over a decade, it has never been submitted to the FDA for approval within the U.S. before this voucher program. I mean, as such it's, from our understanding, it's the first ACT that was actually approved by the FDA.

Novartis has not yet used, traded, or sold their PRV, but this is something that we're obviously watching very closely. Before I conclude on the background, just to add that there are partner -- or sorry, similar initiatives that are being proposed as well.

Recently, a few weeks ago the original authors of this program introduced something very similar, but for use in Europe. The economics are a little bit different as the regulatory process is a bit different. But their conclusion is that this is also a system that could be used not only within the U.S. FDA process.

Also interestingly, the U.S. PTO, the Patent and Trade Office is actually similar -- looking to a sister initiative. I understand they're in the very early stages of this. What it would do is the voucher in this case

would be used for expedited review, reexamination of the patent. So it's got a lot of potential. We think it's quite elegant and it's one way to actually increase the reward incentive for pursuing neglected tropical disease drug research and development.

Next slide please. So I mean, despite its great potential we have received feedback that there are a few concerns as to how the program is actually implemented. We put three up here. There were a few more. But these are the ones that we've heard the most about. They basically, for the most part, they center around the uncertainty of the program. These concerns are -- the limit on transferability of the voucher, which I just discussed, a need for greater clarity and transparency for how the vouchers can be used and some concerns about establishing a regulatory process for updating the list of diseases that would be eligible to receive the voucher.

So regarding the issue of transferability, as I mentioned, FDA limits the PRV to only one transfer or sale. Now, in contrast, the original authors of this plan as well as the congressional sponsors, Senators Brown and Brownback, they aim for unlimited transferability to

maximize the free market value of this voucher. The greater the market value, the greater the incentive to pursue this line of R&D.

Capping the transferability of PRVs, it kind of frustrates the creation of a secondary market and this is, we feel, it's a critical component towards really monetizing the value of the voucher. You know, as my colleague just before discussed about the PRVs, one of the key barriers to these being a real powerful incentive is that there's not very much accuracy about how much it's worth about how -- and so as such companies have trouble developing business plans, securing investment, and looking towards future reliability of getting a PRV. If we were to actually help build a secondary market, we can create a more accurate estimate of the value of the PRV and which in turn this helps to find the risk and secure investment.

The second one is -- sorry, the companies actually have reacted positively to the PRV program as an incentive to pursue neglected tropical disease research, but we really do feel that the unlimited transferability clause is a strong or actually almost critical for the

establishment of a market and for really developing this as a core incentive mechanism.

Now, the second issue that we've encountered is the need for a greater clarity and transparency. We go into this into more depth in our written testimony. Long and the short of it is that industry stakeholders, they've expressed concern that their, "rules of engagement" for the use of the PRV that they're not quite clear. This uncertainty just like the transferability has caused companies and PDPs difficulty in structuring deals and developing business strategies around the priority review voucher.

For example, it's unclear whether a new drug application will earn a PRV until the time of the FDA approval. Now, FDA has been very generous in encouraging sponsors to initiate contact at an early stage of development to determine the likelihood and eligibility of a new drug to receive a PRV. But early official designation remains an important priority for industry stakeholders. To give you an example, the vaccine community wonders whether a previously approved vaccine that contains a new adjuvant would qualify for a voucher.

Similarly, what if the status of the active ingredient changes during the application review? Would the sponsors still be eligible to receive a PRV for that drug? Likewise, clarification of the conditions for the use of the PRV could be also improved. For example, if a sponsor elects not to use a PRV after declaring his intent to do so by virtue of the 365-day requirement for advance notice, we understand that the user fee is forfeit, but the actual unused voucher, the status of the voucher, stakeholders are unclear as to where the fate of that voucher lies.

So in this vein, definitive FDA guidelines on these and similar issues would help improve clarity about PRV eligibility and use and it would give the biopharmaceutical industry a much needed guarantee regarding these and similar issues. We've listed these and other issues in our written testimonies, and mentioned in greater detail.

The third issue on here concerns the need for the FDA to establish clear criteria for a disease to be included within the list of PRV eligible diseases. The original legislation gave FDA the authority to expand this

list as necessary, but we'd like to encourage FDA to actually develop definitive guidelines as to how this would be done and to be happy to use it to exercise that process. For example, since the enactment of the legislation it has been noted through the Global Health Community that the Chagas disease is not actually included within the list of diseases eligible for the PRV program. And Chagas disease is responsible for more deaths in Central and South America than every other parasitic-borne disease, including malaria. Estimated 8 to 9 million people are currently infected with 750,000 new cases and 14,000 deaths occurring each year. An additional 25 million people are at risk for infection.

Yet despite its profound impact, R&D of new treatments for Chagas is severely under-funded. So including diseases such as Chagas as well as other diseases which exists or arise in which disproportionately affect low- and middle-income countries we feel is essential.

But in the expansion of this list, we definitely encourage FDA to do so with an eye to the preservation of the overall PRV incentive. This is a very elegant

program. We understand that there is a lot of interest in it. While the addition of diseases is definitely within the authority of the FDA, we understand or we believe there may be limits to the number of PRVs to be issued and have this still remain a strong incentive program.

So next slide, please. So right now there's a piece of legislation that's under review in Health Committee. They are considering the Creating Hope Act of 2010 or S.3697 and we think this would actually address many of the points which I just discussed. In short, it does address the limited transfer or sales of the vouchers, improves clarity and transparency of the voucher use around some of the points discussed such as specifying that the withdrawal of the PRV by the sponsor before a full review is allowed and so the sponsor could retain the rights to that voucher. It also, likewise does a good job of explaining notification requirements, timelines, end-user fees and it allows the FDA to make an early designation of PRV eligibility at the request of the sponsor.

Regarding my earlier comments on expansion of disease list it also specifically adds Chagas disease to

the list of PRV eligible diseases. However, as I discussed, a future expansion of the PRV eligible list we feel it must be done with the full awareness of the potential costs associated with an unrestricted expansion of the PRV program. So I mean along this line believes that an evidence-based process is really what's needed here. We've previously made recommendations to the FDA for this evidence-based process and we're definitely happy to resubmit those details in writing.

Finally, the proposed legislation actually has a couple of other key points. These are concerns that have been raised within our stakeholder working group but not as prominently; 3697 closes the loophole to ensure that only truly innovative products are eligible. This is in reflection of some of the criticism of the Coartem decision and it also requires sponsors to submit a statement of good faith to ensure access to products and a plan for production and distribution as well. This is in response to the criticism as we understand that the PRV program, while it may incentivize innovation, it doesn't do much to further access.

Last slide, please. So just to summarize our

recommendations, we do support the Creating Hope Act of 2010 to the extent that it actually develops a very tangible incentive for innovation in neglected tropical disease research. We also -- but until the legislation -- like in the event that the legislation doesn't pass we definitely encourage the FDA to adopt a rulemaking process for expanding the PRV eligible list to continue its efforts in communication and transparency and extend outreach to relevant stakeholders and finally, to convene an internal PRV committee to address the needs for clarification of these guidelines as the incentive goes forward. Thank you.

DR. SACKS: Thanks very much, Andrew there.

Any comments from the panel?

Do you in your more extensive testimony address Dr. Chang's concern that the voucher program has created some unintended consequences that are not helpful?

MR. ROBERTSON: We do not on point, but I think that these go to a core issue which is that there is -- right now, there is some uncertainty regarding the PRV program. To date, there's only been one issued, so we don't really have a good case study as to how it could be

used. Our belief is that as this program matures and this becomes an incentive that companies would be able to comprehend more -- in more accuracy and more detail that we think it will become more of a powerful incentive.

My understanding with Dr. Chang is that part of this is the uncertainty regarding the voucher system and that it actually becomes a bargaining chip that might delay negotiations. Again, I think this is a -- this might be a growing pains issue as this progresses as long as uncertainty regarding the voucher system is increased regarding like what is a voucher worth, how is it used, who has used it successfully? These are points that we think can be overcome in the future.

SPEAKER: But I take it that this incentive is an incentive that would lead a company to go through the FDA regulatory system as opposed to working through perhaps EMA or the regulatory systems of the countries where the drugs would be used. Is that --?

MR. ROBERTSON: Yeah, I mean, until a similar program is introduced through the -- I mean these points are actually also addressed in some detail or not in some detail, to a point in the proposed legislation 3697. But

again, I mean, BVGH, our core mission is to promote innovation to prime the pipeline and to get products developed. Access is definitely an interesting point. It's definitely a critical point but we'll focus more on the upstream part of the equation how do we actually get new drugs developed, how do we get them approved, how do we get them to the point where they can be used in developing real context.

SPEAKER: Have you modeled the how much the lack of transferability might reduce the value or the bids, in percentage terms obviously.

MR. ROBERTSON: Sure. Sure. We've done initial studies but nothing conclusive yet. These reflect more stakeholder concerns. Again, going to the certainty of the voucher there is obvious benefits of developing the secondary market that would help address the certainty issue. But yeah, the short answer is we've haven't done a detailed economic analysis.

SPEAKER: Also the -- you presented your -- the range as an uncertainty range, but it also I would say it's a variability range because the value is obviously, for any given cohort is going to vary dramatically from

year to year. So it's good. I think it's probably going to take more years than you've indicated to --

MR. ROBERTSON: Yeah, no.

SPEAKER: -- really establish what this is worth.

MR. ROBERTSON: We definitely agree. You know depending on who you ask, this is why we have this range is because different people have given different -- taken into consideration different factors which has given different results. But again this is where the secondary market might be valuable because you can actually say what's the market value as opposed to what is the actual internal value to -- of a voucher.

SPEAKER: And finally have you modeled a particular auction mechanism?

MR. ROBERTSON: No. That's interesting. There is some work on secondary markets for intellectual property for patents which would be very interesting but we're dealing with much more of a low volume system. So no, it's not yet but it's something we should look into.

SPEAKER: If I can just chime in with a short question. I guess one of the issues is the extent to

which the PRV program addresses early drug development, pre-clinical drug development, and discovery. Obviously, its accent is on products which are very close to approval and Coartem is a very clear example of that.

MR. ROBERTSON: Yeah.

SPEAKER: Any thoughts about that or other incentives which may encourage development?

MR. ROBERTSON: So if I understand your question, you're saying that what's the effect on early pipeline discovery? You know, that's a really interesting question and it is one that we definitely discussed internally without being definitive on the statement. It does -- it kind of reflects maybe a lack of early metrics for innovation. You know what -- it's -- the process is a 10- to 15-year process to get from very initial drug or sorry -- identification all the way to getting a drug on market.

So while you have, you know, mid term or mid pipeline to late pipeline markers, the early pipeline markers are still, we feel, still kind of lacking. And these are things that, you know, if we can develop those more precisely, would give us a better reflection of how

this PRV is incentivizing very, very early stage drug research and development.

DR. SACKS: Any more questions for Andrew? Thank you very much. I would like to invite the next speaker that's Peter Hotez. I think he probably needs very little introduction to most of us here. He is president-elect, American Society for Tropical Medicine and Hygiene, president of the Sabin Vaccine Institute American Society for Tropical Medicine and Hygiene so --

DR. HOTEZ: Thank you very much for having this session and for inviting us. I think I'm here wearing my new American Society of Tropical Medicine and Hygiene hat so I'm president-elect. I'll be president in November. As my wife says more work for free. And I'm also president of the Sabin Vaccine Institute coincidently which hosts a Sabin vaccine development which is a product development partnership for neglected disease vaccine. So I think I'll be able to speak from both angles.

I deeply appreciate your having this hearing. The level of engagement now for FDA and Global Health is at an all-time high and this is deeply appreciated. We recently had Dr. Hamburg visit our laboratories, so having

you engaged at this very profound level is really very meaningful for the members of our society and we can't thank you enough.

So just very briefly about the society. It's the largest member organization of tropical medicine researchers and clinicians in the world. Many of our members are leaders in developing new vaccines, therapeutistic diagnostics for neglected tropical diseases arguably the most common infections of the world's poorest people. I know there were some comments at the beginning about NTDs. I just want to make a couple of brief remarks that when we talk about the NTDs we are differentiating them from AIDS, tuberculosis, and malaria because we do think there are some differences in regulatory pathways associated with it.

Very briefly, this is a group of major chronic parasitic and related infections. These are the most common infections of poor people in Africa, Asia, and Latin America. They have a non-emerging quality about them having affected human kind for thousands of years. You could find descriptions of these diseases in the Bible, in the Talmud, in the Vedas, in the Quran, and they

clearly disproportionately affect the world's poorest people. These are the diseases of the bottom billion, the subsistence farmers and their families, the European slum dwellers.

An important distinguishing feature about the NTDs versus the big three; AIDS, malaria, and TB is that for the most part they tend to be high morbidity, but low mortality conditions. They cause enormous disability but they're -- they, for the most part, are not killer diseases and that changes some of the risk-benefit equations when we think about developing products including vaccines.

Another interesting feature about them is they not only occur in the setting of poverty but they cause poverty. So here is a laundry list of the major neglected tropical diseases as these have extraordinary numbers, hundreds of millions of people infected with intestinal worms ascaris, trichuris, and hookworm; maybe as many as 600 million with Schistosomiasis, 100 million people have filarial worms in their genitals and lymphatics, dengue, which is now becoming extremely common, Trachoma, 40 million people, very impressive numbers.

And the -- one of the reasons we've had such difficulty despite how common these diseases are getting them on the global health radar screen is that overall their mortality tends to be low. So they -- our estimates are around 400,000 to 500,000 deaths per year, I know that's a lot.

But when you're sitting at the table with the AIDS people and the malaria people and you're talking about millions of deaths, that's not where these diseases have their biggest impact. Rather it's because they are such a cause of disability. We don't -- we do not have a great metric for disability.

The one that we've been using is the DALY, the Disability-Adjusted Life Year. The number of healthy life years lost because of premature death or disability. And that's the reason why when you start comparing with AIDS, malaria, TB, here's where the neglected tropical diseases shape up so that there is a fourth leg to that tripod.

And the other very important feature of these NTDs is their -- in their economic impact because they impair intellectual and physical development of children, particularly hookworm and Schistosomiasis so a child

chronically infected with hookworm loses 40 percent of his or her future wage-earning capacity, they cause adverse pregnancy outcomes, reduce productive capacity, worker productivity.

India loses a billion dollars every year because from lymphatic filariasis, elephantiasis because people are too sick to work out in the fields so this concept that they actually promote poverty. There is also an interesting geopolitical dimension to these diseases. President Obama in his speech last year in Cairo talked about the United States reaching out to the Islamic world. One of our analysis show that about 40 to 50 percent of these neglected tropical diseases occur in the world's Islamic countries places such as Indonesia which has 60 million cases of hookworm, almost a 100 million cases of Ascaris, or Yemen or Pakistan, Sudan, Mali, Chad, Bangladesh. So these are -- there is some relevance there with the geopolitical interest of the current administration.

They also occur in large middle countries including those which have a lot of technological capacity and innovation. This is an analysis we did showing that

20 to 30 percent of the world's NTDs don't occur just in the very poorest low income countries, but middle income countries which are also nuclear weapon states such as India, China, and we're going to come back to that in a little bit when we talk about manufacturing.

Now there is a few trends that I think it's unclear whether FDA is aware of or not and we thought it would be worth sharing an experience with you that we think you need to know about which is that there is now in process being supported, in part, by USDA what is arguably the world's largest drug delivery program ever undertaken. And it has to do when we look at the global distribution of the seven most common neglected tropical diseases which are the three soil-transmitted helminth's infection ascariasis, trichuriasis, and hookworm as well as schistosomiasis, lymphatic filariasis, onchocerciasis.

In Trachoma it turns out these diseases don't occur in isolation, they occur in clusters, so if you look at countries such as the orange or the red that means we have six or seven of those neglected tropical diseases in one place. People are polyparasitized. They don't just have hookworm. They have hookworm and schistosomiasis and

lymphatic filariasis.

And with that in mind a package of drugs has now been developed which include either albendazole or mebendazole for soil-transmitted helminths, diethylcarbamazine, or Ivermectin for the filarial worms, praziquantel primarily for schistosomiasis as well as Zithromax from Pfizer. And with the package of drugs we're knocking off having a big impact on the seven most common neglected tropical diseases and we get some bonuses as well, Strongyloides, food-borne trematode infections, scabies.

Because these drugs are largely being donated by pharmaceutical companies, so GSK is donating the albendazole, J&J the mebendazole. They just announced a scale-up donation. Merck's donating the Ivermectin, and Pfizer donating the Zithromax. This is being done for roughly about $0.50 a person per year. Once yearly administration of those drugs often in the package sometimes done -- being done individually.

So this is now being scaled up. The largest contributor of the scale-up administration of these rapid impact packages is being provided by USAID. So the Obama

administration has put forward $65 million for these packages in 2010 at $0.50 a person per year. We're looking at about 100 million people treated trying to scale to 155 million for neglected tropical diseases. This is the president's request in 2011.

So now you're looking at the prospect of hundreds of millions of people receiving these medicines. There is a monitoring and evaluation program that's put in place by USAID, but in some respects this is in our opinion one of the world's largest pharmacovigilance programs ever undertaken and I think there is a great opportunity, I think, for the expertise of the FDA to be involved in this. I don't have a sense of the level of engagement that FDA has been involved in this massive drug delivery program.

So USAID is currently supporting control. These tend to be national scale control programs where the whole country gets treated in 14 countries including 11 African countries, two Asian, one Latin American country, and through Sabin Vaccine Institute we have an organization known as the Global Network for Neglected Tropical Diseases. That's -- we're using private funding doing

this now in Burundi and Rwanda. We have aspirations for others.

So the other G8 countries have not really stepped up for this. It's primarily the U.S., to some extent the U.K., and now we're in discussions with the Nordic countries some of the other European countries as well as emerging economies.

So that's one important trend that's happening. The other is that the -- one always has to be concerned when you're scaling up at that level with hundreds and millions of treatments the specter of resistance. Fortunately, it doesn't look like resistance has been widespread to those package of drugs, however there is not -- quite honestly, there is not much resistance monitoring going on, and again that might be a very useful role for the FDA to look at some of the -- look at resistance monitoring in more detail.

This is just showing that we have now seen some high rates of drug failure for single dose mebendazole for hookworm infection and meta-analysis showing now only 15 percent cure rates. It's still working well for Ascaris in the pink squares up at the top, but for hookworm, we're

seeing 5 percent cure rates, 10 percent cure rates. We don't even know if this is resistance or not, what the basis for.

We do know that resistance can develop when you use these class of drugs benzimidazol, anthelmintics in cattle. In sheep, it only takes a single point mutation, in a nematode (inaudible) to cause resistance. And now there's widespread resistance when this class of drugs is used in livestock in South Africa, New Zealand, Australia. South Africa, we're concerned about this as a possibility and it's something that's going to be an important trend.

So overall, this is a list of some of the new drugs that are going to be required over the next decade, which we're hoping that will come past -- come through your agencies. So you've already heard from DNDi about the need for specific antiprotozoal agents for Chagas disease, human African trypanosomiasis, and leishmaniasis. We're going to need new drugs for hookworm and strongyloidiasis. Again, these are going to be widely deployed, a macrofilaricide for lymphatic filariasis, and onchocerciasis, anti-viral, bacterial agents for dengue and other flaviviruses, cholera, Buruli Ulcer, leprosy.

We're also going to need new vaccines. So there were -- there's several vaccines under development by several product development partnerships including us for amibiasis. There's Chagas and Leishmaniasis vaccine being looked at. There are several anthelmintic vaccines under development because of the concern about resistance for hookworm, for schistosomiasis which is -- also needs prevention strategy because we now realize that 75 percent of women, young women who have urinary tract schistosomiasis in Africa, one of the most common infections there, also have the same granulomas in their genital tracts, cervix and uterus.

And now there's good evidence from Zimbabwe being reproduced in Tanzania, that that's associated with the three and fourfold increase in horizontal transmission of HIV AIDS. So this is a very -- these entities are important co-factors in the AIDS epidemic in sub-Saharan Africa. There's a liver fluke vaccine being developed, veterinary vaccines for cysticercosis and echinococcosis which would hopefully function as transmission blocking vaccines, anti -- I have "agents" written there, but it should be vaccines, antiviral and antibacterial vaccines,

and I'm sure the dengue vaccine you are familiar with, are the dengue vaccines.

New diagnostics, you heard about Chagas, Leishmaniasis and human African trypanosomiasis. We need new diagnostics for Strongyloidiasis, toxocariasis, filarial infections, Schistosomiasis, as well as the viral bacterial agents. And there's actually a full table of products needed or under development in our written testimony that we provided.

Another very important trend, which you may want to be aware of if you're not already are, is that the United States -- turns out it's not Denmark. We have poor people. And with that level of poverty, there's very high burden of -- unanticipated high burden of parasitic infections and related neglected infections of poverty in the United States. We don't call them NTDs, they're not tropical per se because it is the United States, but for all the world they resemble them.

There is a new piece of legislation that is now being marked up in the House Energy Committee called the Neglected Infections of the most Impoverished Americans Act of 2010, and it has to do with this hidden burden of

neglected infections among people in the United States, primarily living in areas such as the Mississippi Delta, post-Katrina Louisiana, the border with Mexico, the -- our inner cities Appalachia and other regions of poverty. And I think an important point here is that it's not a question just of immigration, there's transmission of these diseases within the United States.

So the other irony about these neglected infections of poverty is several of them, most of them, would not qualify for the Orphan Drug Act because they're not rare. So there are more than 200,000 of these cases. These are common infections, an estimated 3 million African Americans with toxocariasis. This is a parasitic worm infection associated with asthma and developmental delays. What's the relationship between that and the rise of asthma among inner city African Americans and other minority groups? Nobody knows, because they have been so neglected, so understudied.

One million African-American women with trichomoniasis, which is now a neural and it's been shown to be an important cofactor in the AIDS epidemic there. Congenital CMV infection has a 50-fold higher increase in

transmission among young African American women with -- and this is a major reason why you see kids in homes for the mentally disabled from congenital CMV infection. So this is a big burden of disease that we are just kind of getting our arms around. And we hope that this legislation will stimulate greater interest and maybe bring forth new products.

It will be interesting to see because these products are -- only occurring among the poorest Americans predominantly whether there will still be an incentive by the pharmaceutical companies to take on these conditions or whether they are going to be done through product development partnerships.

Let me just switch gears very quickly. And some of the things I'm going to say now are not too different from what my previous colleagues have said including my colleague from DNDi. There's a lot of technical challenges in NTD product development, the difficulty in maintaining causative organisms in the laboratory. Our animal models are often not great. They don't entirely reproduce human disease. They have a complicated pathogen structure. In some cases, there's no completed genomes or

proteomes for these pathogens. And so it's -- it slows down our ability to identify drug and vaccine targets. Reverse vaccinology, reverse drug development is often not possible.

There are lots of difficulties in production and scale-up, absence of serological and other correlates of protective immunity. And the absence of correlates of immunity for vaccine development is a real hindrance in moving forward.

There's -- in addition to the technical hurdles the economic hurdles are obviously very daunting. This is -- and if you haven't seen this document, it's a great one that's put out by an organization, used to be called the George Institute, now it's been separated out from Policy Cures where each other they look at the R&D support for neglected diseases.

And they define them fairly broadly to include the big three, AIDS, TB, and malaria. And what it shows is that globally, meaning the NIH, the Gates Foundation, the Welcome Trust, the -- you know, the British MRC, you name it, spends around $3 billion on all neglected diseases of which three quarters of that is devoted to

AIDS, tuberculosis and malaria, roughly around $2 billion of funding.

But for the non-big three NTDs, it's obviously much less. So there's only about a $146 million spent globally on all the kinetoplastid infections, meaning Leishmaniasis, human African trypanosomiasis and Chagas disease, less than $100 million for helminth infections, $40 million for leprosy, trachoma, buruli ulcer.

So you might have heard the term 10/90 gap; it refers to the fact that we only spend about 10 percent of the world's resources for diseases that disproportionately affect people in low and middle income countries, 90 percent of the world, a 10/90 gap that applies to the big three.

For the Neglected Tropical Diseases, we aspire to get to a 10/90 gap. We are still at a 1/99 gap or a 1/199 gap. So the other very important piece to distinguish the NTDs from AIDS, malaria and tuberculosis is that the commercial markets are essentially zero.

So this is a map to show you the distribution of hookworm. Obviously if you are a CEO of a pharmaceutical company this is not the map you want to see in your

business plan, right where you have got North America and white Europe and white Japan and white -- this is only affecting the bottom billion, the poorest people in low-income countries. And that's been a real challenge.

And the pharmaceutical companies have been wonderful in terms of donating drugs that they've developed for other purposes for Neglected Tropical Diseases. And it's because of their generosity and large financial commitment that they've been able to provide a support for those rapid impact packages, but in terms of investing in R&D, that's still not happening at the level that we want, at least for the truly Neglected Tropical Diseases, and that's where these product development partnerships come in, non-profit organizations that use industry business practices to develop new commercial entities.

Here's a list of PDPs on the right that are primarily focused on the true NTDs. There's not a lot of them. We've heard from DNDi, but there are others as well. Most of them to be headquartered in the United States or Europe with the exception of the International Vaccine Institute in Seoul, Korea.

Now, a number of interesting issues about these PDPs that focus only -- I'm sorry for all the acronyms -- that focus on just the Neglected Tropical Diseases. We tend to be, they tend to be under-resourced and they tend -- often will face a lot -- a lack of a reliable revenue stream. So this is obviously a big problem. The other is, many of the PDPs conduct their manufacturing in what -- that are some times referred to as IDCs, innovative developing countries. These are developing countries with high rates of endemic Neglected Tropical Diseases, yet they've managed to overachieve in terms of product innovation.

So these are the BRIC countries, not so much Russia, but Brazil, India and China, Cuba, Indonesia, and Mexico. So manufacturing has been done in the BRIC countries. And the clinical testing, of course, is being done in resource-poor settings in Sub-Saharan Africa, India, South East Asia, and Latin America.

So an important question is -- it's a genuine question, that you know, we don't have an answer for and it might be something we want to explore today is how should the FDA work with these non-traditional

organizations where there is zero prevalence of these diseases in the Unites States with the exception of the U.S. neglected infections of poverty, where manufacturing is being done offshore and clinical testing is being done offshore. And we certainly do need help at a number of different levels, despite the fact that there is no U.S. involvement in terms of how many of these products will be used.

Remember a lot of these neglected tropical disease products, unlike malaria et cetera, will not even have a military market or a traveler's market as well. So they are only being used for the poorest of the poor. One of the great -- there's several hurdles that PDPs face. One of them is among the different valleys of deaths in product development, this has been a big one that's taken PDPs a lot of time to bridge that discovery of antigens in genes and getting to GMP manufacture, or develop a product development strategy, conduct process development in the case of vaccines, at the 10-liter fermentation scale where you could do this under a quality umbrella and transfer to the GMP manufacturer.

There's a lot that goes into the CMC section

that PDPs are still in the learning stages about. So bridging between basic discovery and good manufacturing practices, we often don't -- the PDPs often do not have special guidance for these non-traditional organizations. And I think we heard this a little bit from DNDi. And it might be worth looking into the possibility of having a mentoring role, for the FDA, for these product development partnerships.

Somebody mentioned what about the pre-IND meetings. Yeah, pre-IND meetings are great. But they are -- and they're very helpful, but there still tend to be somewhat -- it's still a formal process. It's -- you have to ask the question in a certain way, and you feel somewhat obligated to answer it in a certain way. And it'll be interesting to explore whether there could be another venue created which allows that exchange in a less formal manner, because I think the bottom line for the PDPs is they genuinely want to do the right thing.

They want to do everything that a pharmaceutical company is doing in terms of compliance with the FDA, but because they are under-resourced, they are often -- staff has less experience than those with the pharmaceutical

companies, we're kind of searching our way through how to do this the right way.

Another problem is that we don't have access, obviously, to a lot of information from the pharmaceutical industry. We don't have access to their confidential documents. They often don't publish unlike the PDPs. And this is where I bring up this possibility of FDA providing a possible mentoring role to help non-profits and smaller biotechs advance new products.

Another big hurdle that we face is that most of the PDPs because they're working in developing countries, especially in innovative developing countries, are working with -- are submitting filings with the national regulatory agency of those countries; Brazil, India. And it's a little bit of the Wild West out there that we don't really know how to work with many of these national regulatory authorities in large middle-income countries.

It would be also interesting to explore whether the FDA could provide help with that. Since the FDA does have some contact with ANVISA, the national regulatory authority in Brazil or the counterpart in India, how might FDA be useful in going together with PDPs to get some help

on that front.

Another trend that seems to be occurring is that particularly for the worm infections, many of them were actually initially developed for animal health because that's where the money is. You can make more money de-worming livestock than you can people. Sad to say, but so many of the anthelmintic drugs that are currently in existence were developed through the animal health components of large pharmaceutical companies.

However, we have now a number of veterinary products that are still on the shelf that could be developed for human use. And Novartis has an interesting class of acetonitrile drugs for helminth infections. Most of the large ag-vet companies have something that now could be transferred. There has been a lot of interest in product development partnerships or what you do with a dossier that's been developed for animals, what would be needed to transition that into an appropriate IND for humans. Again, providing guidance for that might be very useful.

Clinical Trial Design; again since these are often not killer diseases, some of the endpoints to look

at their disabling features often is unclear. Developing endpoints for clinical trials, I think, could be another very useful mentoring role with the FDA.

I'm getting to the end. There is a wonderful orphan grants program. Currently, in 2008, as I said, two-thirds of the NIH funding for neglected diseases went to AIDS research leaving only about a $100 million for malaria research and $200 million for all the other NTDs. A lot of that is going for basic science; it's not going for product development, I'd say most of it is. So there isn't really large-scale support for product development for Neglected Tropical Diseases coming out of the NIH.

FDA has a very exciting orphan grants program for clinical trials as well as pediatric medical devices. It would be interesting to see whether -- even I realize it's a difficult budget climate, whether FDA could expand its orphan grant program to include other elements of product development.

So in summary, we again -- I want to thank -- I want to personally be here to thank you, but we want to encourage consideration by the FDA for support of malaria, NTD product development activities in multiple areas. The

needs are pervasive; drug and diagnostic and vaccine targets, process development and formulation, technology transfer for GMP pilot manufacturings, regulatory filings with of course you, but also the foreign national regulatory authorities in clinical testing. So thank you so much.

DR. SACKS: Thanks very much, Peter. Irene (phonetic)?

SPEAKER: Yeah. I have a couple of comments and a question. You mentioned in terms of challenges, technical challenges regarding product development the absence of -- you called it of protective immunity being a hurdle to vaccine development. And I was wondering if you could clarify or maybe I should start clarifying from a regulatory perspective.

I mean, what I -- we know that the presence of an -- immune color (phonetic) of protection certainly helps in terms of clinical trial designs, in endpoints that you may choose, if you have a color of protection. But I don't quite understand why you frame it as a hurdle to vaccine development, because from a regulatory perspective, at least, the absence of a color of

protection is certainly not a hurdle because it is not a requirement for licensure. So can you clarify for me --

DR. HOTEZ: Sure.

SPEAKER: -- what you are getting at with that?

DR. HOTEZ: Well, when I say "hurdle" it becomes a challenge scientifically in terms of how you're designing your clinical trials. So for example, you know, if you are making a vaccine for helminth infection or a protozoan infection, we know oftentimes that we're getting protection when we're getting very high levels of antibody. But we don't know exactly how the antibody is working.

And because of the animal models we often don't know what class of antibody we're looking for. So when you're designing a clinical trial and you're selecting adjuvants, what type of -- it makes it a hindrance in your adjuvants selection to decide exactly what type of antibody response that you are looking for, and then the level of antibody that you'll need. The only way to finally know that, and I realize this is not unique to neglected tropical diseases, this is for a lot of pathogens is to actually conduct your efficacy studies and

then start looking at -- and then deriving correlates only at that point. Ideally, it would be nice to have some of those correlates before you go into phase I and phase II trials to get them from your animal studies.

SPEAKER: And I have another comment that perhaps this is somewhat related to that because you -- in one of your slides -- and I have it in front of me -- you were talking about NTDs presenting this unique product development challenges in this -- in that there is a lack of an appropriate animal model for assessing efficacy and for FDA to make allowances for this in terms of regulations. I wonder if you can explain a little bit more for us what you mean by it. Again from a -- animal models for assessing efficacy can be scarce, not even, you know, and it's not quite a unique issue for NTDs.

DR. HOTEZ: I understand that.

SPEAKER: And in terms of, you know, for FDA to make allowance in terms of regulations, I wonder if you can elaborate on that.

DR. HOTEZ: Well, I don't know that we necessarily need you to make allowances for that, I don't know, maybe that's what I wrote there, but I think the

important point being that the animal models for most parasitic infections are highly imperfect meaning that the pathogens themselves are poorly adapted to these laboratory animal models, and so you get enormous inconsistencies in reproducing reliable infections among a group of animals.

So if you might take 10 animals, infect them with a pathogen, some pathogens as you can -- some animals, they're often very heterogeneous, they get high levels of infections or they get low levels of infection and it makes it very challenging to evaluate.

I don't think we need anything right now from the FDA in terms of allowances. I will just keep that in mind that as we move forward the animal models often are not as predictive as we would like of human infection.

SPEAKER: Yeah, I do acknowledge that. I just -- from the vaccines perspective again, I wanted to clarify and I would be interested in hearing some comments from my colleagues at CDER. Again, it is, as you state, very helpful to have an animal model that would predict the efficacy, but in many cases that's just not the case. And apart from talking about the animal rule here, which is

something very different, again from a vaccines perspective, you don't -- you do not need to demonstrate efficacy in an animal model in order to continue developing your product. Animal models are very helpful in terms of demonstrating proof of concept and maybe that's what you are getting at here, but --

DR. HOTEZ: Right.

SPEAKER: -- in terms of the term "efficacy," I think it has a different meaning.

DR. HOTEZ: Sure. Thank you.

DR. SACKS: Sarah (phonetic)?

SARAH: It's about your comment concerning the relationship between NTDs and HIV. You pointed out that it can affect transmissibility, and I imagine there's many other things having to do with --

DR. HOTEZ: Right.

SARAH: The efficacy of treatments or morbidity and mortality. So first, when you're looking at the budgetary allocations, to what extent are the NTD figures -- to what extent are the HIV figures including attention to NTDs in conjunction with HIV?

And the second is in terms of study design, if

one wanted actually look at these more closely together, there's obviously a lot of challenges in the study design, subject population, interpretation of results, et cetera. And I wondered if you had any specific thoughts about the kinds of study design that might better incorporate the connection between these two?

DR. HOTEZ: Yeah, unfortunately, the link between AIDS and NTD pathogens has not really resulted in AIDS money being shifted over to neglected tropical diseases. The AIDS lobby is a very powerful one, and they tend to guard it fairly closely. But there is some really compelling data; now, there's been a Cochrane analysis now looking at parasitic worm infections showing that there people with parasitic worms have higher viral loads, lower T-Cell counts, that's -- looks -- looking very solid now. But in addition is this very worrisome association between female genital schistosomiasis and HIV.

I mean, if you look at a map of the two infections, they have this high rate of overlap and this may turn out to be, as a co-factor, as important as any other in the African AIDS epidemic. So this is going to have to be looked at very closely. What we would like to

see happen are greater links between some of the vertical programs being supported by USAID. So things are somewhat silent, lesser than they were between PEPFAR, the President's Emergency Plan for AIDS Relief, President's Malaria Initiative, and now the Neglected Tropical Disease program.

And yet, these diseases are not occurring in isolation. They are all overlapping, and it would be great to explore operational links. It's not only with HIV/AIDS, it's also with worms and malaria. So if you look at a map of hookworm and a map of malaria, the two are geographically spot-on in that.

What's happening is you're getting anemia from each infection, a malaria from -- a malaria anemia is resulting from hemolysis and splenic sequestration; with hookworm, it's intestinal blood loss, but the two are additive. So you have a pregnant woman in sub-Saharan Africa, who gets what I call the perfect storm of anemia because she has got hookworm together with malaria, and to some extent, schistosomiasis. So looking at the relationships between those pathogens and co-infections is going to be extremely important as we move forward with

large scale control programs.

SARAH: If I can just follow up, just to really clarify, are you suggesting though that when looking at a proposed study design, let's say for prevention of transmission of HIV, that the failure to include something that accounts for the presence or absence of schistosomiasis would mean that the study design is fundamentally flawed and the results would not be optimal?

DR. HOTEZ: Well, if you were to ask me, I'd say absolutely yes. That's a problem. So for instance, the malaria vaccine trials that are going on, is any -- is there controls being put in for whether or not you have hookworm or whether you have other NTD pathogens? Same with AIDS vaccine trials or AIDS drugs studies. Are people looking at the background of these -- this -- the helminth environment of that or other neglected tropical disease pathogen? I personally think it's terribly important.

SPEAKER: I just wanted to share Dr. Gruber's point of view from CDER that certainly animal activity studies are helpful to understand a potential new drug. And from the point of view of drug development it might

help with the selection of a dose to initiate in your first Phase I clinical trial, but it would not be a requirement to submit that to an IND.

DR. HOTEZ: Thank you.

SPEAKER: I just wanted to ask you a little bit about a sort of recurring theme that we're hearing throughout this meeting, and many of the speakers have touched on which is the need for more interaction with FDA, and not before a formal interaction occurs. And I just wonder if you could, maybe explain how you think, from your perspective, how this would happen and when it would happen.

DR. HOTEZ: First of all, I think one of the things that we've learned working with the FDA is that we are deeply appreciative of your time. We know how busy you are and we know you are being pulled in 100 different directions, and like PDPs you are also under-resourced and it's not easy for you to make yourself available for informal consultations.

But questions come up all the time, at product meetings or operations meetings, where, you know, what do we have to do or -- I'll give you an example,

cross-reactivity studies, what do you do if you have homology between a parasite, you know, 15 percent homology, amino-acid homology between a parasite antigen and a host antigen. Do we need to look at cross reactivity, how would we do that, do we need to do immuno-histochemistry studies? Is the Western blot adequate? And to have to ask that -- those kinds of questions in a formal manner each and every time gets to be a little bit cumbersome.

And so if there could be a -- and I guess it would have to be non-binding on both sides, it would have to be truly informal to make it work, if we could get a sense from people with experience, or it might be useful to get input from the FDA when we're dealing with the Brazilian regulatory agency or the Indian regulatory agency. You know, do you think this is going to come up in India? And they say, well, you know, it has come up in the past, but it hasn't come up recently. All of that is useful information.

Now there are consultants out there that can help you with that, but they are obviously very expensive and that's not easy either.

SPEAKER: (Off mike.) One other issue which came up earlier in your talk, something that's pretty much near and dear to our hearts, which is resistance. Obviously, we continuously have to sort of think about this in the realm of bacteria, malaria, TB, et cetera, and obviously now in neglected disease. Do you have any ideas about how FDA could perhaps help in the preclinical, the clinical, and the regulatory realms to deal with resistance in neglected tropical diseases?

DR. HOTEZ: I think it's going to come up mostly in these large-scale implementation programs. So what type of assays and how would you implement them, especially in resource-poor settings, would be very helpful. And I think it would be very interesting -- you know, when you -- one of the things that we have found universally is when we get the chance to talk to people from the FDA offline.

There is a lot of passion for helping work on global health problems, and a lot of interest. They find in -- because these diseases don't come up very frequently in the normal course of work, there is just a lot of inherent interest in something new and fresh. And there

seem to be -- there seems to be a lot of interest and excitement, and we'd love to be able to capture that.

DR. SACKS: There are no other questions. Thank you very much --

DR. HOTEZ: Thank you for the opportunity.

ADDITIONAL SPEAKERS

DR. SACKS: Thank you. Our next speaker is François Verdier (phonetic).

SPEAKER: (Off mike).

DR. SACKS: What?

SPEAKER: (Off mike).

DR. SACKS: I beg your pardon. So I guess we have two speakers who were not previously listed. I guess the first is Theodore Tsai from Novartis.

DR. TSAI: Thanks. I represent Novartis Vaccines. And thank you for the opportunity to comment. My remarks pertain to petitions for prior review voucher status for diseases that are not currently on the list in the agency guidance. And those remarks echo those of previous speakers. The guidance states that the company

can petition the secretary of HHS to add diseases to the list.

However, it's unclear what should be included in the petition to enable for review. We suggest that the agency specify the criteria and their thresholds that would qualify currently unlisted condition for neglected status. For example, in the Delphi process, to prioritize vaccine introductions to developing countries, mortality was given more weight than incidence rates albeit potentials in other indices of disease burden.

And as has been mentioned by previous speakers, there are diseases that have a higher mortality impact in developing countries than those currently on the list. Increased clarity on the definition of market potential in developed countries also would be helpful, specifically on the dimensions by which that potential would be measured.

If, for example, a disease was prevalent in GAVI-eligible countries but also in China -- a country that was one of the original GAVI-eligible countries but now is the world's second largest economy -- and that could provide a significant market potential, would that condition still qualify? Procedurally, what's needed is a

mechanism by which FDA input into the petition is defined.

Specifically, we urge that the FDA be given the opportunity to provide at least one set of questions to the petitioner to enable the petitioner to clarify any unclear elements, and to provide additional information that would help the secretary, with the assistance of the FDA, to make a decision on the petitioner. In addition, petitioner should be granted at least one meeting to discuss the petition with the FDA.

And lastly, timelines by which the secretary needs to respond to the petition should be defined to help petitioners plan their research and development programs. Thank you.

DR. SACKS: Looking around to see if there are any questions from the panel on petitions for new diseases. Not. Don?

MR. BEERS: It sounds like you have an interesting -- perhaps a particular disease or diseases. And some of these process issues, if you included your request with respect to process in the petition itself, that might be a way to get what you want.

DR. TSAI: Thank you.

DR. SACKS: Thanks very much. The other speaker who's requested a time slot now is Emi MacLean, I believe, from Médecins Sans Frontières, Doctors Without Borders.

MS. MacLEAN: Thanks so much for having this hearing, and for allowing me to participate. On behalf of Doctors Without Borders known as MSF, an acronym for our French name Médecins Sans Frontières as some may know, and on the campaign for Access to Essential Medicines, which I also represent within MSF, I'd like to start by thanking the FDA for holding this public hearing.

First, I'd like to say that I'm not a scientist or a doctor and not an expert in the FDA process. So if there are questions that I can't answer, I'm happy to bring them back and provide supplemental information as may be necessary. I'm speaking from MSF's decades of experience running programs and conducting operational research on NTDs where we know that tools exist that are insufficiently available to populations in need, but also that the tools themselves are deficient in many instances.

For example, new medicines for sleeping sickness were not developed for 50 years despite pressing needs, and still need further development. The diagnosis of

sleeping sickness is complicated and often requires a blood sample, lymph node aspiration, and a painful lumbar puncture. There is no test to determine whether patients have been cured of Chagas' disease after a course of treatment.

A diagnostic tool for tuberculosis does not exist in a form appropriate for many populations in resource-poor settings. I think our coming at the end of -- the latter stages of this hearing, I realize that a lot of -- some of the points that I'm going to be making are points that have been made before or are complementary to some of the points that have been made previously.

The populations affected by these diseases are simply too poor to provide adequate commercial incentives for R&D in a system that relies at present almost entirely on the ability to sell products at high prices to incentivize drug and diagnostic development. But what if we could separate the market for medicines production from the market for R&D and encourage robust competition in both?

As a medical humanitarian organization, we've increasingly engaged in these questions because our health

workers on the ground in the Sudan and the Central African Republic, in India and elsewhere, are forced to reckon with empty medicines cabinets and empty drug pipelines for diseases that are killing our patients, and have been for a very long time.

Dr. Hotez spoke about these diseases being represented in the Bible. So the -- without going into too much depth -- the WHO has identified as NTDs 14 major parasitic, bacterial, and viral diseases that are the most common infections of the 2.7 billion people living on less than $2 a day. Those affected are often marginalized and forgotten by governments.

And other diseases like tuberculosis and pediatric HIV/AIDS are also neglected, but are not within the WHO list of entities and are diseases that are dealt with by our health workers on a regular basis. I just like to highlight HIV/AIDS, especially since it was represented quite significantly within Dr. Hotez' presentation, to note that pediatric HIV/AIDS can sometimes be distinguished as a more neglected disease than adult HIV/AIDS when we're talking about where research and development is directed.

Because pediatric HIV/AIDS has been all but eliminated in rich countries, even as a rich country market continues to exist for adult HIV/AIDS medicines the -- there is much more limited R&D attention on pediatric formulations of AIDS drugs and other pediatric HIV/AIDS needs.

MSF has, for many years, provided diagnosis and treatment for individuals afflicted with NTDs primarily focusing on visceral leishmaniasis or kala-azar, human African trypanosomiasis or sleeping sickness, Chagas' disease, and Buruli ulcer. MSF is one of the only actors in the world involved in the treatment of these diseases.

And three of these diseases, as was mentioned by my colleague from DNDi, visceral leishmaniasis, HAT, and Chagas' disease are often fatal if left untreated and have the highest rates of death of all of the NTDs. These four diseases are largely left out of control in treatment programs by health actors and donors, in part because they are considered too difficult and costly to treat.

They're identified as diseases by the World Health Organization that need intensive and integrated disease management because of the limited focus on some of

the other barriers. One of our primary messages to the U.S. government, some of which is related to the FDA and some of which goes beyond, is that the innovation for these diseases is critical, but so too is accessibility of existing tools even where there are limitations to those tools.

It was mentioned earlier that the U.S. government established the presidential initiative on neglected tropical diseases in 2008, which was a very welcome initiative. It however only focused on 5 of the 14 NTDs identified by the World Health Organization. The U.S. speaks about it as representing seven because of how one of the diseases is broken out and did not include any of the four diseases that MSF is engaged in on a regular basis or support for innovation.

As part of the Obama administration's new Global Health Initiative, the U.S. government has now proposed a significant increase in funds for NTDs. We hope still more is possible, although we recognize also the funding environment -- still, would hope that more would be available.

And we would hope that there is an opportunity

now with increased attention on NTDs represented by this hearing and the FDA's engagement as well as a number of other initiatives ongoing, that there is the opportunity to expand the number of diseases that are incorporated within the presidential initiative on NTDs to respond to this ongoing neglect of the four diseases that were identified and really -- and cover the diseases that are identified by the World Health Organization as neglected.

So I'd like to share briefly a bit more on our experience in three particular areas -- Chagas, sleeping sickness, and tuberculosis. Chagas I think has probably been mentioned more than others, including that there is a population in the U.S. that's affected and that it is the largest parasitic killer in the Americas.

For the last decade, MSF has provided free diagnosis and treatment for Chagas in various countries including Bolivia, Guatemala, Honduras, and Nicaragua. I'd also highlight that we're currently exploring the possibility of a project here in the U.S. to improve detection and access to treatment for Chagas that's still in the early stages.

Existing tools can and should be made available

to those with Chagas but as mentioned, they are necessarily insufficient at this stage. In many cases, the endemic countries do not have the necessary facilities or staff available to carry out laboratory tests required for the diagnosis of Chagas.

The two medicines to treat Chagas' disease, benznidazole and nifurtimox, were developed over 45 years ago through research not even specifically targeting Chagas' disease. Presently, neither is adapted for use in small children, although a pediatric formulation is anticipate -- of benznidazole is anticipated soon.

And doctors have been reluctant to administer the medicine because of side effects more common in older patients, and because of the lack of a test of cure. New diagnostic tests, better medicines, a vaccine, and a test for cure are urgently needed to help prevent, diagnose, and treat Chagas.

Sleeping sickness rapidly deteriorates into coma and death, and is quickly fatal if untreated. It's found in 36 countries in sub-Saharan Africa with an estimated 70,000 annual cases and 60 million at risk, although much is still unknown about the numbers and the impact. Ten

years ago, patients with advanced sleeping sickness would have received an arsenic-based treatment called melarsoprol.

It's more than 50 years old and highly toxic, with rising rates of treatment failure. No new treatments have been developed for a half century for sleeping sickness, even though it was killing 1 out of every 10 to 20 patients, and in some affected areas had only a 50 percent effectiveness.

Thanks to the efforts of many partners -- and as was highlighted by DNDi -- including the World Health Organization, Epicentre, DNDi, the Swiss Tropical Institute, and some of the work that we were doing at MSF, NECT exists as a new, safer, and more effective treatment for patients with advanced sleeping sickness.

But despite this new regimen available, the current treatment for sleeping sickness remains long and difficult for both patients and health workers. Both diagnosis and staging, which requires painful lumbar punctures, demand significant technical capacities and are therefore difficult to implement in remote areas where the disease occurs. There is an immediate need to improve

current diagnostic and treatment options, particularly for patients in the advanced stage of the disease.

Lastly, in terms of specific examples, I just like to highlight tuberculosis -- not a neglected tropical disease as identified by the World Health Organization, but from our experience, certainly neglected, though it's a major public health problem with over 9.4 million new cases and almost 1.8 million deaths in 2008 alone.

The most commonly used TB diagnostic test is the sputum smear microscopy. It's relatively fast and easy to implement in resource-limited settings, but it has significant limitations particularly in a lot of the settings in which we work.

It detects fewer than half of all TB cases, and performs even worse than children and people living with HIV who have either difficulties producing enough sputum or do not have sufficient or any mycobacteria in their sputum to be detected under the microscope and it completely misses the extrapulmonary form of TB.

Our patients need a new point-of-care diagnostic test able to diagnose active TB in adults and children who also may be coinfected with HIV. It needs high

sensitivity and specificity. It needs to be simple to use and able to be operated without the need for extensive infrastructure.

A study has estimated that 392,000 deaths or nearly a quarter of all deaths due to TB in the four highest-burdened WHO regions could be avoided by the introduction of a new TB point-of-care diagnostic with better performance speed and accessibility to patients. It was mentioned that neglected diseases can best be thought of as diseases of the bottom billion.

Quite simply, as I think we all know here, people living in developing countries are dying because medicines do not exist due to inadequate incentives for their development, or because they are unavailable in part due to high prices. The system needs to be rectified through innovative mechanisms that do not rely only on commercial incentives.

MSF would just like to highlight the principle of delinkage which should really inform, from our view, the evaluation and development of mechanisms for R&D for neglected diseases. The concept of delinkage fully accepts that R&D costs money, but seeks alternative ways

to fund it separate from high prices that poor patients and developing country governments simply cannot afford.

Rather than relying on high prices charged after innovation, delinkage would seek to stimulate innovation from many sources and consider access issues in advance, a very important point from our view. This approach would broaden incentives for innovation beyond just the profitable diseases, and remove the access barriers created by high prices.

A range of different funding mechanisms that allow delinkage are needed either to push R&D via upfront funding or to pull R&D via incentives that focus investment efforts on products needed in developing countries. MSF's experience of treatment for neglected diseases convince us that we wanted not only to advocate for new tools, but also to engage actively in the development of new tools.

We therefore became a founding member of the Drugs for Neglected Diseases initiatives, and we continue to contribute some funding to DNDi. Because of the limited funding contributed to neglected disease research -- Mary Moran's report highlighted that MSF's

contributions to DNDi make MSF the third largest philanthropic funder of neglected disease research -- quite shocking in our view.

From our experience as a founding member of DNDi, we know that a critical role is played by PDPs and push funding or grants invested into promising candidates for future drugs that we talked about already today. We also know the critical importance of public sector investment in neglected disease research. A quick look at current clinical trials confirms this.

The four diseases which we -- which MSF prioritize in our programming every year and which I've highlighted earlier, each have very limited number of ongoing clinical trials, and all of these clinical trials are disproportionately funded by public funds including the NIH and/or universities or philanthropic organizations, obviously vastly different for other diseases that affect rich country populations.

So because of the barriers that exist for patients with NTDs when there are high prices attached at the end of the day after innovation, it's essential with these push mechanisms that access provisions be considered

from the outset. Our experience also tells us, however, that in addition to these push mechanisms, incentives are needed throughout the innovation process to ensure that the right products reach the end of the pipeline.

For this reason, we recognize that we also need pull funding or incentives at the end of or various stages of the product development process such as the promise of a profitable market or other reward. And we just wanted to highlight here prizes as an attractive option for delinking the markets for R&D and product manufacturing.

Prizes can exist as powerful incentives for innovation, but need to be designed carefully in order to maximize the sharing of knowledge, access to end products, and overall return of the public's investments. Prize designs can vary, and they can also be given for different stages of the R&D process such as identifying biomarkers, or developing a finished product all the way through to the registration process.

Substantial awards for attaining specified milestones along the way to a new drug or health technology could be a useful supplement to grants for diseases for which market incentives are deficient and

where patents are not an effective incentive.

Milestone prizes promise earlier payouts, and are likely to attract new actors such as biotech firms which cannot make major investments in pursuit of awards that may be many years away. However, the advantage of end-stage prizes is they allow the best possible access provisions in return for the prize, whereas prizes for different stages will have some albeit less leverage on the access provisions on the final product.

Some key potential benefits of a well-designed prize include the allowance of R&D efforts driven by health needs, the requirement of payment made only when results are achieved, the encouragement of innovators who would not otherwise be aware of the need, the possibility for incentives for collaboration and knowledge-sharing, and the potential to build in affordable criteria proactively from the start.

Some specific examples of urgent needs identified by MSF and where a prize might have potential were highlighted earlier, the establishment of a point-of-care test that would allow the diagnosis of TB at local health centers and resource-poor contexts and the

development of innovative tools for the diagnosis, treatment and test of cure for chagas disease.

I'd like to highlight that the governments of Bangladesh, Barbados, Bolivia and Suriname have made some proposals to advance development in these areas, including for a TB point-of-care diagnostic and a prize fund for the development of new products that would decrease the burden of chagas disease.

And several discussions to explore de-linkage mechanisms for the technological needs of Chagas are also ongoing at the regional level as part of the Pan American Health Organization's regional implementation of the global strategy and plan of action. These discussions provide a framework for agreement on new incentive mechanisms, including appropriate designs to stimulate innovation.

Mechanisms that spur innovation should be designed carefully to maximize the public interest and be monitored closely so that we learn from the experience and make improvements to policies along the way. As highlighted earlier, and it's clear to people here, the primary incentives in the U.S. for the development of

drugs to respond to rare diseases with relatively few domestic sufferers are established within the Orphan Drug Act.

But the ODA incentive of exclusive marketing protection is largely inapplicable to neglected diseases because exclusive marketing protection as an incentive relies on U.S. consumers being able to pay very high prices during a period of market exclusivity.

The PRV is another important case highlighted already by several speakers prior to myself. Whether companies will actually be motivated by neglected disease drug -- for neglected disease drug development by a transferable PRV is not yet known. As highlighted already, the only existing example for Novartis is Coartem, does not obviously demonstrate this.

And this should be monitored closely but as with any new mechanism to ensure that it meets its intended needs. Some improvements to the PRV from our perspective could make it more promising for neglected disease R&D. An improved PRV would ensure that access considerations are incorporated alongside innovation incentives.

Products developed for neglected diseases could

be made available and affordable to patients in developing countries by tying the PRV to agreements, to license, patents and other intellectual property rights in order to enable generic competition or more efficient procurement of products in developing countries, could eliminate the -- - from PRV-eligibility drugs previously approved outside of the United States, preventing a windfall that rewards companies without spurring innovation, and expand the list of diseases eligible to benefit as highlighted earlier, including chagas disease.

The current proposed legislation, which was also highlighted earlier, aims to resolve the latter of these two problems identified but does not fully resolve the former with regard to the access considerations being incorporated. So an improved PRV, from our view, has the potential to increase innovation for neglected diseases. It also needs to engage with the access considerations as well. And an array of complementary policies is also necessary to ensure effective and affordable new product development for neglected disease as the PRV, given all of the barriers, is unlikely to be sufficient on its own although it's a welcome introduction, especially with the

improvements that could be made.

So just to summarize, MSF asked the U.S. government to include the most neglected tropical diseases from our view and within regard to the WHO classification, Chagas disease, sleeping sickness, Kala-azar and Buruli ulcer within the scope of the GHI and to provide support for improved access to existing health tools and the development and regulatory approval of new and improved ones.

We also urge the U.S. government to craft its policies and mobilize its financial resources to support ambitious visionary approaches to generating medical innovation that can improve the lives of the bottom billion in the world. In particular, this should include relevant discussions at the WHO and PAHO level and the efforts of the consultative expert working group that will be formed in the coming months to analyze new innovation mechanisms in depth as was decided at the World Health Assembly this -- earlier this year.

We need strong political commitment and financial support from government and other donors if we are to make new incentive mechanisms work. There is

increasingly widespread recognition that the existing R&D system is failing and it's past time to consider new approaches. I'd like to also add MSF's strong support for the FDA's engagement, guidance and resources for developing country drug regulatory authorities as was highlighted by my colleague at DNDi as well as, I think, one or two others.

We know that the U.S. government has accentuated increased IP enforcement measures. So the Anti-Counterfeiting Trade Agreement for instance is on the verge of being finalized from what we hear, although most updated version has not been made publicly available. And these can have counterproductive effects on substandard drugs by redirecting scare developing country resources from regulatory processes to ensure quality of medicines towards protecting the private rights of patent and trademark holders.

I'd like to also add our support to the main messages in the recent DNDi report registering new drugs in the African context. It deals well with the best registration strategy for approval of new drugs for NTDs and the best ways to support African regulatory

authorities in the evaluation of new drugs specifically developed to treat their own populations and includes some of the specific regulations -- recommendations of including -- sorry, including regulators from endemic countries in these conversations, supporting regional African centers for regulatory excellence which can aide drug regulation in Africa in the medium and long term.

So the major top line messages that I just would like to highlight in final conclusion from our experience are that innovative incentive measures must be considered urgently for neglected diseases that respond to patient needs in developing countries and the FDA's support of this is very important.

The priority review voucher may respond to this, especially with improvements that are being discussed and if there is a possibility of incorporating access provisions as well. But it won't in itself be enough and other considerations need to be included as well.

Secondly, access considerations must always be present from the beginning or innovation will be fruitless for the patients and health workers on the ground. And lastly, access needs can be hampered by the Anti-

Counterfeiting Agenda which the U.S. is strongly pushing in other countries where there is a real need in terms of responding to substandard drugs to really help strengthen drug regulatory authorities primarily. Thank you very much.

DR. SACKS: Thanks for your presentation. And questions, Joe.

JOE: I just have more of a comment to which you can respond. It's a little bit off subject of your very nice presentation. Thank you.

We heard earlier today that FDA staff should have some training and perhaps a better understanding of health care delivery in resource-poor areas where neglected diseases are common. And your group certainly has experience in the delivery of health care and under extraordinarily difficult circumstances and resource-poor areas.

And I'm just thinking out loud as to how your group can help us understand the delivery of health care in these settings. And what I'm thinking out loud is the adherence to good clinical practice so that in these areas you can have the results of a well-conducted registration

or trials that would streamline drug development and adhere to good clinical practice.

MS. MacLEAN: Yeah, certainly, one of the reasons why I gave the caveat in the beginning that there may be questions that I can't answer is that we have not had such extensive engagement with the FDA. Although we obviously have with a number of other U.S. government agencies where there has been a really valuable interchange where we have been able to provide some of our experience on the ground to be able to help facilitate what we would hope would be better policies that really respond to the patient needs on the ground. And it's certainly something that we would be eager to engage in further conversations with the FDA about.

SPEAKER: I was just curious about the access provisions you talked about. How would that work? I mean, I've never -- you know, we certainly have provisions for expanded access in the United States for people in the United States. But I'm just -- I'm not aware of our ever having been involved in an access program in another country.

MS. MacLEAN: And one of the things that we've

really learned and used as a strong basis for advocacy is, in the last decade was the HIV experience and the barriers that are provided by intellectual property protections. We see that playing out in a very different way for neglected diseases as well.

And one of the things that, you know, where there is tremendous potential within something like the priority review voucher is -- and which has actually happened with some of the product development partnerships is to incorporate from the beginning an obligation that patent protections would not serve as a barrier.

So as long as there is actually some commitment from producer which is another barrier with regard to neglected diseases is because of the limited profitability of neglected diseases; sometimes you can end up with not, you know, not a single producer. But certainly encouraging, you know, developing country producers, in particular by eliminating intellectual property protections is a barrier when there is publicly funded, at that stage when there is publicly funded research and when there is a public contribution at the end of the day. I don't know if that clarifies it.

SPEAKER: Oh, yeah, I realized as you began. I was thinking kind of backwards because we use the term access generally in the pre-approval context. And I would -- and I was just thinking of it in that sense. So you're talking about providing assurance that the company won't just sit on the drug after their --

MS. MacLEAN: Won't sit on the drug and won't market the drug for prices unaffordable.

SPEAKER: Right. Okay.

MS. MacLEAN: So, you know, one of the ways that this has come up is humanitarian licensing provisions which are under discussion and have been, you know, over the last decade really motivated by some of the HIV/AIDS activism because of the recognition that public sector institutions, including the NIH and including universities are involved in a lot of the early state research.

And then once the licensing is -- agreement is made, there is no humanitarian licensing provision. And therefore, you know, all of that publicly funded research notwithstanding that the drugs are not made available for, you know, prolonged period of time in developing countries.

There are ways around that, you know, including special protections for low and middle income countries, and that's something that we would, you know, strongly encourage and demonstrated to be really important within the HIV/AIDS context where, you know, we went from seeing AIDS drugs costing 10 to $15,000 per year because of the rich country market to, you know, now under $70 a year for the most commonly used, although not the preferred AIDS drug regimen.

SPEAKER: I have a question, a question, perhaps a comment and I'm trying hard to formulate it. You had mentioned during your excellent talk, you specifically mentioned tuberculosis and the point-of-care diagnostic. And you also mentioned trypanosomiasis as well, African -- human African trypanosomiasis and Dr. Hotez had mentioned earlier and said the same thing. He was talking about mass drug administration.

But the question I sort of have is, you know, there is not really good FDA model for mass drug administration. And I think it certainly is mass drug administration or other vector controls that have been tremendously successful in African trypanosomiasis, but a

number of diseases have in fact, one would expect, which is why people going to be doing MDAs have tremendous success with a number of the other larger neglected tropical diseases.

As the numbers get down and to use the model that people present their earlier, sort of, as it goes through a surveillance phase, diagnostics become -- the cases become less and less prevalent, diagnostics become more and more important because, of course, mass drug administration as you drop below certain prevalence doesn't become a realistic strategy.

But I've not heard, and I'd be curious, perhaps Dr. Hotez would like to address as well, given these incredible opportunities to look at diagnostics and somebody else alluded to this too, there is not that great incentives. There is a lot of diagnostics ex-U.S. out here ex-U.S. diagnostics which in publications appear to have good performance.

Now, people have, you know, again I know a number of people in the audience are familiar with the malaria experience, when the WHO looked very critically, lot of these diagnostics didn't appear to have much value.

But perhaps you or Dr. Hotez has some thoughts.

How can we promote during what's really very active efforts at eradication or elimination to promote diagnostics like -- as Dr. Hotez had also mentioned -- the possibility of resistance? There is some uncharted territory. What could possibly be a better scenario for studying diagnostics resistance within the setting of some of these programs? Do you have any thoughts or proposals?

MS. MacLEAN: We -- and I certainly welcome Dr. Hotez to contribute to this as well. One of the reasons that I mentioned the TB point-of-care test within the context of this presentation is we're actually currently engaged in the process of trying to create specifications for what a TB point-of-care prize would look like.

Recognizing that there are, you know, limited resources -- limited incentives for the development of TB point-of-care diagnostic, and there is unlikely to be a development of new incentives just from the private sector and from the currently existing mechanisms, but if there are actors that come together to provide support for a prize, the value of that is it encourages actors who would not otherwise be engaged to be engaged and recognize that

there is, you know, at the end of the day, some possible remuneration for the development.

And at the beginning of the day, the other real value of that, which, you know, I highlighted here and also in response to the preceding question is that you can set, you know, certain standards, including the specifications that we recognize as necessary from our experience on the ground working with patients, you know, recognizing where the real gaps are.

And secondly, we can specify at the beginning of the day, you know, what the limitations are going to be in terms -- we can specify access provisions to ensure that after something is developed, presuming something is developed, and you know, if the prize is sufficient enough then you would presume that it would, you know, be helpful in developing something, incentivizing that development. You know, those access provisions can help make sure that it is available to patient populations. Would you like to add something to that?

SPEAKER: I think that's fair, but perhaps I could be more specific, is I think -- and Dr. Hotez has talked about the big three. And in fact just last week

when SEFI (phonetic) had published the expert results, again it may not be -- there may be economic hurdles as you've certainly alluded to, but certainly it is, you know, it addresses some of the -- it may address some of the concerns.

But I'm really more curious about, you know, the -- even though like ascaris can be well diagnosed through microscopy, that may be out of the reach or, you know, perhaps, you know, what thoughts could FDA in the context of this hearing use to promote the development of diagnostics for NTDs.

DR. HOTEZ: Well, your question is very welcome, you know, and I agree with your remarks as well. But there is a huge amount of operational research what we sometimes call implementation science, around strategies of deploying mass drugs. So it's not just simply giving a -- a matter of giving the medicines.

First of all, there is a mapping exercise that needs to be done. And the idea being because you don't often have all seven neglected tropical diseases in the same place so you have three or four, and there is different algorithms for giving the medicines. Required

for that are field-ready diagnostic tests that are better than what we have now.

So, for instance, for looking at onchocerciasis, we're still literally counting palpable nodules on people, looking for the nodules or doing skin snips. I mean, these are diagnostic tests that were developed back in the Pleistocene era.

I mean, we need to bring them to a new level. And you're absolutely right that the incentives for new diagnostics should be just as great for therapeutics and vaccines. So we need better diagnostic for most of the neglected tropical diseases, both in terms of mapping so we know where to do the implementation. And as you also point out, as we -- as the elimination strategies become more and more successful, by necessity it becomes more important to go into the weeds and do diagnostic tests that are more fine level as well and we need better tools.

SPEAKER: Do you have any -- again, I would allude, do you have any suggestions because again that's, I think, a major focus of this hearing where FDA could incentivize these in some way or FDA mechanisms. Perhaps Sally (phonetic) could speak better, but I think everyone

in the room probably recognizes that the device regulations are very different from the drug regulations. And I would like to think without at all casting any aspersions, that they're little easier just by the nature of how devices are regulated --

SPEAKER: Yeah, you know, I don't have a lot of experience with developing diagnostics, so I'm not speaking from experience. The best thing to do is there is a, as you may know, a product development partnership, now that's specifically for diagnostics. There is a couple of them. And PATH has been doing this for years, but also FIND, the Foundation for Innovative Diagnostics based in Geneva. It would be very interesting to have a conversation between you and the leadership of FIND to get their feedback. And if we -- I'd be happy to arrange that.

SPEAKER: Yeah, we do know Mark Perkins fairly well and he has given us input on especially the, some suitable rapid TB test.

SPEAKER: You know --

SPEAKER: But unfortunately they -- you know, we don't see them, they never come through us. I'll tell you

--

SPEAKER: Diagnostics are the orphan products of neglected diseases, if you could believe it.

SPEAKER: Exactly. Yeah, I mean, I'll just give you an example. I mean, dengue has been brought up a huge amount of time. There is dengue here in the United States, and yet we don't seem to be able to encourage a single manufacturer to actually submit either a screening assay for blood here in the U.S. or a diagnostic. And yet there is obviously a market.

So we're looking for some ideas. You know, we -- other than saying, don't need to review at all anything that you've got which is probably what they want us to say, but we are very flexible in diagnostics with what we can do. We will be not quite as hemmed-in with the regulations as perhaps the drug and the vaccine area.

SPEAKER: Well, I'll certainly pass that on to our membership organization and -- as well as colleagues. You know, we do have a critical problem with financing and that's one of the big problems with incentivizing, is lack of financial mechanisms to support product development.

I mean one of the things that we've realized is

we can't rely on the Gates Foundation to be everything to everyone. They -- they're -- they have a lot of outstanding commitments and we're going to need other organizations to step up.

When you look at the numbers, the NIH is probably the largest single supporter of neglected disease research, even greater than the Gates Foundation, but the vast majority of that is for basic science. Outside of AIDS, TB, and malaria it's mostly for basic science. So we don't have a mechanism for supporting product development of neglected tropical diseases.

What's happening in Europe is interesting. The Dutch ministry of foreign affairs and some of the other Nordic countries are now supporting product development through -- not through their traditional science research mechanisms, but through their overseas development agencies actually supporting product development.

The parallel would be if USAID were to support -- start supporting product development, which they do but only through earmarks, through IAVI, the International AIDS Vaccine Initiative, little bit of malaria. So it's kind of a lacuna, it's kind of a gap that we have here in

the United States for that purpose.

I think it would be a great role for FDA, you know, if FDA had the resources to expand its Orphan Grants Program specifically -- not only for clinical trials as it does now, but for product development, for diagnostics; that would be a terrific area for FDA to get involved with.

SPEAKER: Yeah. One area that we've been trying to put some emphasis on is getting good specimens, because we need good specimens to do the validation workout. So we've been trying to sort of encourage the development of good biobanks or good collections specimens from --

SPEAKER: And reference sera also.

SPEAKER: And reference sera and standards, yes.

SPEAKER: Yeah. That's right, yeah.

SPEAKER: So, we have been involved in those areas to try and ease the development process.

SPEAKER: If I could just make two quick comments and perhaps Dr. Sacks would comment, just to follow-up; one is, there has been quite a emphasis in several meetings by FDA of trying to develop biorepositories within tuberculosis, within other efforts.

And this would seem to be a prime effort, especially with MDA because it can -- the more successful MDA is paradoxically, the more difficult it would be to do drug development because then identifying cases becomes the priority for studying diseases.

I don't know if you want, you know, so much of device development, and I don't want to exaggerate this, because -- by overstating it -- but it can be done pre-clinically relative to the clinical trials. It's perhaps maybe slight bit differently in drugs where of course the primary emphasis has to be on clinical trials.

You want to comment, Leonard, at all on the --

MR. SACKS: Sort of cutting the territory. I mean, obviously, biorepositories have many values, not only for the initial diagnosis of the disease, but for development of prognostic biomarkers, for development of toxicity biomarkers, perhaps retrospectively if some toxicity is found in a new drug.

And also for, I guess, detection and confronting resistance where access to the samples may be the crucial issue and people who are doing the trials on the ground can really supply those to the diagnostic industry. So I

guess I'm just sort of --

SPEAKER: I guess in closing I would say certainly if anyone has recommendations, you might just submit it for the docket. I thought that was a very reasonable, concrete proposal that one could, you know, think about including, certainly we would welcome them.

SPEAKER: I think it's a great idea. And you know, we certainly -- I mean, for instance, in our lab we're trying to develop an improved diagnostic kit for toxocariasis, which we think is the most common helminth infection; in the U.S. 3 million African-Americans.

The current state-of-the-art involves taking living worms, collecting their secretory products, wormspit, putting it on an ELISA plate and looking for antibodies. Obviously, you can't standardize that very easily and so that kit's testing is not widely available, that's one of the reasons why it's so neglected.

If you could reproduce it with recombinant engineering, so much the better, but then we need the right standard sera in order to evaluate the test. So if that kind of thing were made available to investigators, I think, you're absolutely right, it would accelerate the

field.

SPEAKER: And I would just thank you for the invitation and certainly communicate with others within our team to see if we can provide some concrete recommendations on the diagnostic question or series of questions.

MR. SACKS: Thanks. Any other questions for the current speakers?

SPEAKER: I have one?

MR. SACKS: Yes?

SPEAKER: I'd just like to ask a quick question getting back to the alternative incentives, and particularly ideas like prizes and various conditions. I know that nobody's done it on the scale that you envisioned, but are there any small scale experiments or programs that have used these?

SPEAKER: There absolutely are, included within the document that you should have in your file --

SPEAKER: Is that in there? Oh --

SPEAKER: -- and I could just direct you to where it is, a whole slew of examples that are cited. In footnote 16 there are a couple of different reports that are cited

which provide that, and I'll just mention a couple of examples that I just cut out of the presentation for lack of time and to not overburden you especially as we approach lunchtime.

The Global Alliance for TB Drug Development, which is a PDP, and the Rockefeller Foundation awarded two prizes for more efficient ways to synthesize a new TB drug candidate, PA-824, and so that was something where quite recently a prize was identified and innovators came forward and the prize was actually awarded at the end of the day.

And I would just also highlight that this is something that is increasingly being considered within the White House as well. There were a couple promising initiatives and statements from the White House. There is a new guidance that was issued on the Open Government Directive supporting the use of prizes to encourage innovation in a number of areas including climate-change technology and promoting open government.

So really it's a fertile area and something where there certainly is experience in the past. It was -- it's something that's being considered, you know, by a number of actors within the U.S. government as well as, you know, on

smaller scales as you mentioned, by you know, philanthropic foundations and elsewhere.

And I would just mention the PAHO, I mean, I gave the PAHO example as well on Chagas, which is another really important potential proposal that is being considered.

MR. SACKS: No other questions. I believe I have the liberty to open this for statements from the floor, not questions, if there are any. These would be unscheduled statements. Is there anybody in the audience who wishes to comment?

MS. WONG: Hi, I'm -- my name is Amy from the Clinton Foundation. I'm program manager of diagnostics there and so -- (tape interruption) --

Hi -- is that better? So, I guess, I also wanted to address diagnostics and -- which in some ways neglected itself. And specifically referring to your question about TB diagnostics and how we can accelerate a lot of the pipeline.

And so I was actually involved in a lot of prize-design for TB diagnostics in a former life. And you know, in trying to talk to not only the users about access and what the product spec should be, but also engaging

with the private sector about what would it take for you to be involved in developing this product, and here's the market, here's the number of people, here are the buyers, here are the PRIZE points; this is the number of patients et cetera.

For them, it wasn't an issue of not understanding that there wasn't a market. They recognize there are people who are sick, they recognize the millions of people who die. And even in this country and in Europe and in the rest of the world, for them it was really, truly an obstacle issue.

So the issues you raised about specimen repositories, there's probably about three or four very small specimen repositories that are very exclusive in this, in -- around the world. And even them are, you know, between specimen repositories, issues about some specimens are characterized in one way and in another way and some specimen repositories have certain kinds of samples and other ones don't. So there's a lot of inconsistency.

And then there's also issues of, well, who's going to evaluate this product and how should we evaluate this product and whether or not the FDA should evaluate or

whether a CE mark is sufficient or whether it's going to be evaluated within a country.

And so I'm not really sure whether or not it's within the FDA's purview to say how should we -- what types of validation for this country especially if the products are not sold in this country. But again, I'd like to emphasize that the FDA working with in-country regulations and strengthening in-country regulation is huge. I mean, it is a lot of products and diagnostics that are sold in other countries.

And even though the FDA is considered, you know, the gold standard and it would be great if all products were sold with the FDA approval, most products in fact just go through in-country registration. An in-country registration is just notoriously very lax, unfortunately.

And so even if you look in China and evaluating a lot of TB diagnostics that go through China, they have very, very lax evaluation criteria. For example, they only test, you know, TB diagnostics in about 100 sera samples with no delineation about what -- how many should be positive, how many should be negative, there are no statistical rigor.

And so if the FDA can work largely in developing the strength of the in-country regulations, I think that would be a big step in preventing poor diagnostics of getting out there.

SPEAKER: If I could probably -- maybe I can? Oh, I can -- . The -- that's a very good comment. A couple things; there are models where this -- I think there's one very successful -- the AsTeC model, the Aspergillosis Technology Consortium, it's within this country, but they all consider it a neglected disease in this country.

There's other examples. Again as I mentioned before, for tuberculosis, I think it is clearly an example there's not much malaria in this country, but FDA has cleared, and which I think is a huge, I think everybody would recognize is a huge breakthrough, which is the rapid diagnostic for malaria.

Your point is very well taken. I guess what I would also say though too is that diagnostics to some extent is an open book. That's a huge amount of guidance and things available. These standards are fairly well worked out and such a -- but your point is very well taken

and we are very willing to work with, you know, we're here to help get it done. So that certainly, you know, we appreciate your suggestion.

MS. WONG: Yeah, I mean, we're also working with companies trying to -- so, again, I'm at the Clinton Foundation, so we're also still trying to work with companies to develop diagnostics, and you know, we talked -- - I don't know if you know Elliot Cowan. We've talked -- had extensive conversations with him, and it always comes down to the sort of chicken and egg problem, is that we ask the FDA to somehow regulate and the FDA asks us how do we want them to regulate.

And so again, it's again echoing what a lot of people have said about streamlining, how we can ask those questions and what -- defining what would be a good evaluation of a product, for the disease-specific and especially diagnostics, which has been such an open book.

SPEAKER: Perhaps we can talk offline --

MS. WONG: Yeah.

SPEAKER: I'm not quite sure what this barrier is, because, you know, we're -- we get paid for this. We're willing to listen.

MS. WONG: Yeah, I know, definitely, and I would hope that we can solidify a lot of our conversations so that it is easier for companies to move forward.

SPEAKER: Well, we'll be here after the meeting.

SPEAKER: And again, that's the pre-IDE meeting that I referred to at the beginning. That's when we do have those discussions.

MR. PERRONE: Yes, my name is Joe Perrone and I'm with SRI International, but in my prior life my business was primarily in a in-vitro diagnostic business. As a matter of fact, I worked for Becton Dickinson, and in 1988 we developed and produced the very first malaria immunodiagnostic test that was ever on the market. So all the ones that are currently on the market whether they're good or not, I consider them my grandchildren.

But having said that, I wanted to reinforce your comment about the importance of diagnostics, because we've heard so much here today on the therapeutic side, and every time I listen to anything about neglected diseases it's very often focused on vaccines or therapeutics.

And I want to remind people in the audience that, and particularly, you know, the folks on the

therapeutic side that in sub-Saharan Africa, about 80 percent of the malaria diagnosis are done using clinical signs and symptoms and not by thick film.

And every study that's ever been published and recently there was a review, the false positive rate, depending on the season, usually runs between 30 and 60 percent. In Kenya, Zambia, and in South Africa, near the Mozambique border in the KwaZulu-Natal region, some years ago we'd done -- we'd performed a lot of blind studies, and at the minimum, throughout sub-Saharan Africa, 25 percent of all antimalarial drugs distributed are distributed to people without malaria.

Now, aside from the possible causes, implications and resistance, the economic burden on the government and those people supplying those drugs is rather significant.

And then also to address the young lady's point before me, I concur with here completely. It's often very much obstacles, and I know many folks in the audience who are from NGOs and I could tell you from a business perspective it's not just a question of developing a test, it's the question of lack of specifications, a lack of

consistency of specifications as to what -- how the product should perform. Very, very important, and very often when we go to the WHO or other organizations they would -- it seemed to be very arbitrary.

And companies shy away from arbitrary specifications, because then you never know whether you're going to win or not. So I would certainly concur that specifications be drafted. I'm not sure that the FDA in this country necessarily can play a role, but perhaps in helping the other organizations develop those, I think, would be very important.

And then also just the normal business aspects that many NGOs don't encounter, when they're doing business in many of these countries; the importation duties and the distribution networks and things along those lines, which are very strong obstacles that a lot of people don't face, but are very important to us from a business perspective as to whether or not, you know, going to pursue an opportunity.

Again, not necessarily for this group, but I think there's also, as we focus towards the FDA and to see how we can do -- how the United States can help, I would

like to make sure that one of the recommendations that was earlier made about partnerships be very much taken into consideration, because I think without indigenous people, and you know, country people working alongside of you, this type of thing will not get implemented and it will be coming from the outside-in.

And plus, I'm of the firm belief that people have to have a stake in their own future and I think that's critically important to give them an incentive to move forward. But thank you very much for this opportunity today.

MR. ZELDIS: Hi, my name is Jerry Zeldis, I'm CEO of Celgene Global Health. I have a few comments about the Priority Review Voucher program. The obvious statement is that if you -- if a company were to use the voucher, they better be certain that the review is not going to end up in a complete respond to nonapproval, relative to worthless.

So yes, there's tremendous value to the priority review if the company is absolutely certain, or as soon as they can be, that it will undergo a good expedited review.

The second point I want to make about this is by

having a higher filing fee that also adds to the whole calculus as to when to use the PRV. And I wonder, since this is a mandate from Congress, and I do understand that you have to use your filing fees to pay for the review of drugs and by having a PRV it adds to the burden, is it possible to get Congress to agree perhaps with this new bill that's pending in the Senate that Congress will pay for the difference in the cost of executing a priority review.

So did, it is -- the burden doesn't lie on the FDA, it comes out to Congress. After all, there's only been one PRV given out to any company yet, which gets me to the other point which has me a little concerned about, the Senate bill.

And I realize this is, perhaps I should talk to BIO ventures and not the FDA, but something to consider, even if a product is not "innovative," the cost of running very well-conducted trials, to give the level of evidence that you would need to assess a therapeutic as being safe and effective, usually runs in the tens of millions of dollars. It is not just taking -- dusting off something and getting it approved. Just the cost of filing is a

many -- is a multiple, multiple million dollar event.

And what I would hope is that by wrapping ourselves with a PRV and saying it must be innovative, we are actually decreasing the number of therapeutics that could be approved for neglected diseases.

Again, this -- I may be talking to the wrong audience, but at least I want to publicly voice that concern.

MR. SACKS: No comments from the panel? Yes?

MR. GAUTIER: Francois Gautier, (phonetic) Centre fe Pestelle (phonetic). I think most of the issue is related to the development of vaccines or drug for neglected tropical diseases have been mentioned. However, I would like to add perhaps two remarks. One is regarding the possibility to consider a conditional approval for such drugs or such vaccines before the end of large efficacy trials because today the time needed to complete the large efficacy trial may impair the access for new drugs or new vaccines.

And therefore, would it be possible to evaluate perhaps a pathway, which would allow conditional authorization, which is also perhaps useful for regulatory

authorities in developing countries to start the evaluation of Feducia (phonetic). Some of these countries do not want to start the evaluation of a new drug or a new vaccine before the registration of these drugs or new vaccine in reference countries. So perhaps agencies such as the FDA or the EMEA can play this role. I mean, we mentioned this morning the Article 58, there are perhaps other possibilities similar to this Article 58 pathway.

The other remark is concerning the certificate of analysis. A lot of regulatory authorities in developing countries also request a certificate of analysis from a country of origin. And I think it could be big agencies, such as the FDA, may play a role in order to facilitate the obtention of certificate of analysis from the country of origin in order also to accelerate the registration of a new drug or a new vaccine in developing countries. Thank you.

MR. HUGU: My name is H.S. Hugu (phonetic). I'm an independent consultant; I'm a native of sub-Saharan Africa. In listening to the testimony today, it occurs to me and seems to me that there are participants from the regulatory -- from the public-private sectors, NGOs

involved in the development of these neglected tropical diseases -- therapies for, and diagnostics for, prevention for neglected tropical diseases.

And I'm wondering would there be value in having a focal point within the FDA similar to what eventually came about in the area of the combination products. People who remember, years ago, a firm was developing a combination product here for the U.S. market involving different centers. You know, one had to deal with multiple centers. And I'm not proposing that CBER or CDER would not perform their review functions.

But I am wondering, since -- in looking at the suggestion for more informal mechanisms, for communication with the agency by developers rather than the formal structure pre-IND, pre-NDA type meetings. Would there be value, as I said, to having some focal point within FDA that could clear, clarify, interact on some of the issues that arise? Thank you.

DR. SACKS: Thanks. I see there are no comments from the panel, but thanks for the suggestion. It looks like we have time for maybe one or two more speakers. So perhaps those will be the last two.

MS. PUVA: Okay, thank you. Vereli Fay Puva (phonetic) I'm from Sanofi-Aventis in access to medicine departments. I would like to address some remark about the Article 58, there are -- there were a lot of recommendation to build something quite similar to the Article 58, but today the Article 58 is not a real success.

There was not a lot of product that were going through this process. And one of the reason is that the countries, the endemic countries, think that Article 58 is quite a different standard because companies commit themselves not to market the product in Europe. So in that case, the national regulatory authorities of the countries think really that it is a different standard; it is not a marketing authorization, but just an opinion. So I think that this should be taken into account.

The other thing linked to the Article 58 is that full ICH and European guidance apply. And we have seen in the various intervention that it is not really possible to apply ICH, and U.S., and the European guideline because there are some specificities linked to the field realities for the development of drugs.

There was also one thing related to the fees because for the submission of the Article 58, you needed to pay for fees. And we know that there is no real return on the investment for this disease. So probably exemption from fees for this type of submission should be welcome.

Just another comment we have had during the intervention, also comments about the importance of sharing information between FDA and endemic countries. It's clear it's a good thing, but I think that we need to build tools about confidentiality because there is no insurance of confidentiality when we submit or share data with the endemic country.

And lastly, a comment about the priority review voucher. My understanding of the priority review voucher is that it is to encourage research and development for new chemical entity. However, we have already drugs available on the market never developed in neglected tropical disease, and that could be included in development plan, clinical development plan, for this specific indication.

It is -- it could be in one way rapidly available for the population because there is no real need

except if the dose is not the same, but no real need of pre-clinical development, full pre-clinical development. We have already an idea about the safety. There is already a pharmaceutical form available. So my question is that could we improve the priority review voucher and open it to product already registered under other indication. Thank you very much.

SPEAKER: So -- and we had news from, I mean, the vaccine development section Office of Biodefense, DMID, NIAID, and there's a lot -- I want to talk about this issue with -- interaction with FDA because there's been a lot of comments on that. So I thought I'd relate some of my experience because I think there's a lot of similarities between biodefense counter measures and what we're talking about today.

So within OBR and DMID, we have several different product lines that involve CBER and CDER, and every one of them has a different paradigm in the way we interact with CDER and CBER, FDA in general. Admittedly, there are some differences between us and private companies. A lot of our efforts are government funded, so it's -- and we, of course, are sister agency with FDA. So

I think that facilitates things as well.

But mainly what I wanted to say is though we have many different paradigms that we've used, by far and away, the most successful has been the one where very few persons at FDA in -- on one project have been involved in an informal scientific basis for years. I mean, literally from the beginning of the project. And this involves teleconferences, team meetings, some -- many meetings were with product sponsors, some weren't.

And I'm just saying that just one or two key people from FDA involved in a product development team and working group. I mean, there's all kinds of consortia here. Product development partners presumed that they all have product development teams and meetings; some informal representation from FDA in these meetings. Through the whole process, I think it is very valuable.

And I'm not talking about a lot of people. Just one or two key persons. And I know FDA is over-tasked, like all of us are, but hopefully, with the recent HHS review and all this talk about regulatory science for FDA, that's an area where, you know, maybe increased staffing could help provide more interaction between FDA and the

product development teams.

Now, the other aspect of a center or a point of focus, and I think CDER did this with Octet for bio defense. The danger at some point, of course, becomes when you go from informal scientific interchange and to the regulatory binding guidance. So that's -- and I appreciate that's a sensitive line. But I think if there's someone involved in these teams informally that could help develop and determine when more formal meetings and interchange is needed, that could also be helpful.

I mean, there is a line there. I get that. But you know, it's -- right now where I think we're at two extremes, either a lot of informal exchange in very few cases or only formal mechanisms. And I think there's ways to do -- there's ways to, you know, kind of bridge this gap without the huge impact, and might be a large return.

SPEAKER: Thanks for that appeal for resources. You got a comment? Sure.

SPEAKER: Thank you for these comments. I'd like to briefly actually comment on this as well. You mentioned the engagement of one or two FDA key people and scientific working groups, you know, for some of the

medical countermeasure products that are being developed and the success there often. At the same point, you also mentioned or cautioned perhaps a little bit of where's the line between, you know, what is a scientific advice that is nonbinding and informal, and what is regulatory biding advice.

That is something that can however be an issue. We -- I just wanted to -- I don't want to discourage that -- these interactions; I think have been very helpful and very productive. But there have also been instances where there was misunderstanding, that the scientific consultation provided by the FDA was mistakenly taken for regulatory binding advice by -- on the side of the applicant, and it was somewhat rocky. So I think, I mean, basically I want to support that -- this type of interaction, but I think, you know, from the get-go, what it means, the boundaries have to be made very clear.

The other thing is that you mentioned was the incentive, you know, and the various reviews that have been taking place and the monetary incentives now being put into the agency that could provide for additional staffing, so that FDA folks really have time and can

engage in these type of collaborations. It's an interesting idea and we also have actually discussed that internally.

The problem is, you know, you hire more staff, but they need to be trained in a certain way too. So you have a number of key folks at FDA and this is still limited what we have in terms of providing the much needed and necessary expertise. And so I think hiring initiatives are -- solve only part of the problem because you really need training, you need well experienced and versed staff to really sit on these committees. And just hiring a lot of new people doesn't quite solve that problem.

SPEAKER: Well, and maybe I should refine what I said because I think it will address both points. And I probably over emphasized the input that we get -- we've gotten from FDA on these points. I think the real benefit potentially is for FDA, especially in the diseases where there isn't a lot of knowledge and expertise within FDA. I think FDA gains from this kind of relationship by increased awareness on their own part.

So if someone is involved early, and often even

someone new, it's training in itself because they learn the disease and product-specific issues. Even if they don't say anything, I mean, we have lots of meetings, and I don't expect the FDA representatives to say anything.

In fact, I never ask questions. If we're on a conference call, especially if sponsor is involved, I never -- one of my rules is we don't ask the FDA person questions. We don't want to put them on the spot. We realize there's no binding guidance given anyway. This, I'm speaking for myself now. This is the way we've done our thing.

So -- but they are there. They hear the issues. They learn the issues as they come up; what can be solved, what can't be solved. And you know, down the road, I think there is a payoff there. So I guess I'm suggesting it's -- this is as beneficial for FDA maybe more so than the sponsor. I think the sponsor or the product developer will get a payoff when the formal meetings do occur.

SPEAKER: I actually just had a quick question for the previous speaker regarding Article 58. And my question was whether she had any suggestions about how to improve on that without creating a double standard and the

same time short of making this a full approval process. Any thoughts on how that Article 58 could be improved on?

SPEAKER: Well, I have not the solution, but one thing is clear, that it is not a marketing authorization and it is -- well, there is two thing. The first one is that there is a choice from the authorities for this guidance not to deliver a real marketing authorization, and just take into consideration the indication and the population to evaluate really the drug for the target population.

This is really a choice. I think that the main issue is that there was no communication at all about the Article 58 and there is a real misunderstanding about this Article 58. One of the best thing is that experts from the authorities can be involved in the assessment.

They have no right, they do not participate to do the vote or in fact to the retail assessment, but they are here to see how the product is assessed and to give to the assessor their feedback about the reality of the field. And I think that we have already spoken about that, that stringent authorities know how to evaluate the drug, but what they don't know is the reality in fact of

the field, of the population, of the economical condition, and so on.

So for me, I think that the main issue is the communication about the Article 58, that there was no communication at all, no presentation to the various authorities, to companies and so on. So we are working, of course, on that. We have had a meeting with DMA to see how we can improve that. But there is no solution up to now.

SPEAKER: Thanks very much. We'll -- if there are no further comments from the floor, I just wanted to say that this has been an enormously helpful hearing to us. We certainly acknowledge many of the points, which will be included in our report, and many of the suggestions, which we're going to take up further. I hope that this is a beginning of a process rather than the end of it.

I think we have a lot of work ahead of us in developing products for these important diseases. I wanted to take the opportunity to thank the speakers in particular for their very helpful and instructive presentations. I wanted to thanks the panel members for

taking the time off and contributing to the meeting.

I wanted to thank the audience for their participation. And finally, I wanted to thank the colleagues in my office in particular and staffing for putting the whole meeting together. And I believe this, in our view, was very successful. Thanks to you. The meeting is adjourned.

(Whereupon, the PROCEEDINGS were adjourned.)

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