

**Stakeholders' Meeting: Presidential Initiative for Neglected
Tropical Disease (NTD) Control**

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Working Paper 2: Drug Supply and Delivery

*Provision of Essential Medicines
for Preventive Chemotherapy for
Neglected Tropical Diseases*

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Summary of Abbreviations

Drugs

IVM	ivermectin
ALB	albendazole
DEC	diethylcarbamazine
MBD	mebendazole
PZQ	praziquantel
AZI	azithromycin

Diseases

ONCHO	onchocerciasis (river blindness)
LF	lymphatic filarasis
BT	blinding trachoma
SCH	schistosomiasis
STH	soil transmitted helminths

Organizations

IFPMA	International Federation of Pharmaceutical Manufacturers Associations
PhRMA	Pharmaceutical Researchers and Manufacturers of America

Introduction

On February 20, 2008, President Bush challenged the world to reduce and eventually control and eliminate the burden of neglected tropical diseases (NTDs) as a major threat to health and economic growth in the developing world. The new Presidential Initiative for NTD Control ("the Initiative") will increase the United States' commitment to NTDs from \$15 million in 2008 to a total of \$350 million over five years. These funds will provide more than 300 million integrated treatments to patients in Africa, Asia, and Latin America. (Note: the estimated treatment figures and drug forecasts in this paper were calculated using 300M cumulative treatments as a conservative baseline; however, recent USAID NTD project statistics indicate the potential for the Initiative to achieve higher treatment targets.) In addition, the new Initiative will expand the targeted number of countries from 10 in 2008 to approximately 30 by 2013.

Table 1: Summary of funding and treatment estimates projected via the Initiative

Year	2009	2010	2011	2012	2013	Total
Funding	\$25M	\$70M	\$80M	\$85M	\$90M	\$350M
Treatments						300M

The Initiative will build on U.S. Agency for International Development (USAID) investments in NTD control and will target seven major diseases:

- lymphatic filariasis (elephantiasis);
- schistosomiasis (snail fever);
- trachoma (eye infection);
- onchocerciasis (river blindness);
- three soil-transmitted helminths (hookworm, roundworm, and whipworm).

Approximately one billion people, mostly in the developing world, suffer from one or more NTDs. Seven of these diseases - the seven targeted by the new Initiative - can be controlled and in some cases even eliminated through targeted mass drug administration. Most of these diseases either blind, deform, or debilitate their victims. In addition, they can contribute to limited school enrollment, diminished childhood growth and cognitive development, and reduced economic productivity in adults. Treating the millions of people who suffer from NTDs will help to change these negative effects and to improve not only personal health, but also economic growth at large.

USAID began an integrated NTD control program in 2006, focusing initially on five countries in Africa - Burkina Faso, Ghana, Mali, Niger, and Uganda. In its first full year of implementation (2007), this program delivered more than 35 million NTD treatments to more than 14 million people. The program is now expanding to Haiti, Sierra Leone, and southern Sudan, and at least two additional countries will be added in 2008. USAID has invested \$30 million to date in this NTD control program.

Drugs for NTD Control

The purpose of this paper is to examine the demand forecasts and other related quantitative and qualitative issues concerning the anthelmintic drugs necessary for the success of the Presidential Initiative for NTD Control.

WHO recommends a strategy of preventive chemotherapy which targets a group of NTDs and at-risk populations rather than specific diseases or infected individuals, since NTDs tend to occur together in the same geographic cluster. Preventive chemotherapy, even when deployed without other complementary interventions such as improved sanitation, vector control and health promotion, can lead to a significant reduction of morbidity and transmission of helminthic diseases. Therefore, a precondition for success of this NTD Initiative is reliable, uninterrupted access to good quality medicines in order to reach high coverage of populations at risk.

The devastating toll of these NTDs can be dramatically reduced with mass drug administration (MDA) using a combination of medicines from a group of six highly effective anthelmintic medicines. Each medicine has an

excellent safety record that has accrued from the use of millions of doses. Most drugs needed to treat these NTDs have been donated in some measure by pharmaceutical companies, including GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., and Pfizer Inc. These donations are valued at hundreds of millions of dollars each year, and may reduce the estimated cost for other program components to between 40 cents and slightly more than one dollar per person, per year, in Sub-Saharan Africa.

Drug Donation Programs and Other Access Mechanisms

Pharmaceutical companies recognize that drug donation programs "are not and should not be promoted as the solution to the global health crises. However, appropriate donations do serve as an effective, sustainable mechanism for providing access to needed medical supplies not available by any other means" [Partnership for Quality Medical Donations]. Therefore, many companies have formed partnerships to enable access to certain medicines in cases where there is no viable commercial or other solution. Since those donation programs are drug specific and disease specific, it is helpful to view a summary of donations broken down by each NTD. (Table 2)

For those NTDs without drug donation programs, drugs are commercially available, although large-scale procurement may be limited. WHO has been involved in facilitating procurement for some of the non-donated, commercially available product, as indicated.

Table 2: Comparison of NTD with treatment regimen and drug procurement options.

NTD	Annual therapy	Availability
Onchocerciasis	3 tabs IVM 3mg	Open-ended donation commitment from Merck & Co., Inc., since 1987
Lymphatic filariasis	1 tablet of ALB +	GSK donation for global elimination of LF since 1998
	3 tablets of IVM ; or	Merck & Co., Inc. open-ended commitment for African countries with onchocerciasis co-endemicity
	2.5 tablets of DEC	No donation. Commercial availability. WHO procured 85M tablets from generic suppliers (2006)
Schistosomiasis	2.5 tablets of PZQ (for school-aged children)	Merck KGaA donation of 200 million tablets of PZQ for treatment of Schistosomiasis through 2017. Commercial availability from MedPharm, others. WHO procured 324,000 tablets in 2006 from generic suppliers. Also, the Schistosomiasis Control Initiative has provided 40 million treatments procured from commercial sources (MedPharm)
Soil Transmitted Helminths (STH)	1 tablet ALB ; or	No donation. Commercial availability. WHO procured 261,000 tablets in 2006 from generic suppliers
	1 tablet MBD	Johnson & Johnson commitment of up to 50M doses / year. Also, WHO procured 2.4M tablets in 2006 from commercial suppliers.
Trachoma	3.8 tablets AZI	Pfizer Inc. committed to donating 33 million treatments / year (2008)

Demand Forecasting

An estimate is needed of the drug needs for the years 2009-2013 – the period of the new Initiative. Drug needs are based on the disease burdens of the populations to be treated in the specific countries that will be selected for implementation during the Initiative. Since those countries will not be known until the Initiative has begun, and will develop during the 5 years of the program, an initial estimate can be made using a global disease burden provided by WHO. WHO's calculations are based on an affected population of 2.046 billion people in the developing world. For this paper, that larger population was modified in Table 3 to reflect a burden that corresponds to the estimated population to be reached through the Initiative (i.e., 300 million total cumulative treatments.)

Table 3: Burden of NTDs associated with the Presidential NTD Initiative (interventions per disease)

NTD	Drug(s)	2009	2010	2011	2012	2013	Total
ONCHO	IVM	1,254,542	3,517,408	4,021,570	4,273,650	4,514,007	17,581,176
LF	ALB+DEC	4,088,406	11,462,821	13,105,826	13,927,328	14,710,621	57,295,003
LF	ALB+IVM	3,136,355	8,793,519	10,053,924	10,684,126	11,285,017	43,952,941
STH	MBD	7,336,395	20,569,332	23,517,602	24,991,738	26,397,309	102,812,375
SCH	PZQ	2,246,069	6,297,391	7,200,017	7,651,330	8,081,652	31,476,459
BT	AZI	3,338,232	9,359,529	10,701,061	11,371,828	12,011,395	46,782,045
							300,000,000

NTD drug therapy "overlap"

The population estimate in Table 3 does not account for overlap of NTDs requiring the same drug therapy since the degree of overlap will not be known until actual country selection. For example, IVM needed for ONCHO would be accounted for in IVM needed for LF in an area where ONCHO and LF overlap. In that case, the same IVM meets the need of the ONCHO and the LF treatment, and listing it separately would constitute 'double counting.' Similarly, in areas of LF and STH overlap, the ALB used for STH obviates the need for separate MBD for STH, again presenting a case of possible 'double counting.' Therefore, this projection represents a conservative maximum, upper limit of the drug needs for the Initiative.

Also, it is important to note that STH can be treated with either MBD or ALB; however, for purposes of these calculations MBD will be displayed as the primary therapy since the primary pharmaceutical industry-sponsored STH drug donation program uses MBD (Johnson & Johnson's Children Without Worms program.)

From patients to treatments

The next step is to compress table 3, above, by combining the IVM and ALB lines to give a summary demand of drug treatments per product, where one treatment is defined as the application of one dose of a given drug.

Table 4: Projection of TREATMENTS needed for the Initiative

	2009	2010	2011	2012	2013	Total
IVM	4,390,897	12,310,927	14,075,493	14,957,776	15,799,023	61,534,117
ALB	7,224,762	20,256,341	23,159,750	24,611,454	25,995,637	101,247,944
DEC	4,088,406	11,462,821	13,105,826	13,927,328	14,710,621	57,295,003
MBD	7,336,395	20,569,332	23,517,602	24,991,738	26,397,309	102,812,375
PZQ	2,246,069	6,297,391	7,200,017	7,651,330	8,081,625	31,476,459
AZI	3,338,232	9,359,529	10,701,061	11,371,828	12,011,395	46,782,045

Finally, these figures are translated to product quantities based on the average number of tablets per treatment of each drug.

Table 5: Projection of TABLETS needed for expanded USAID NTD funding

		Projected Tablet Demand Per Year					
Tablets / treatment		2009	2010	2011	2012	2013	Totals
IVM	3	13,172,692	36,932,781	42,226,480	44,873,329	47,397,069	184,602,352
ALB	1	7,224,762	20,256,341	23,159,750	24,611,454	25,995,637	101,247,944
DEC	2.5	10,221,016	28,657,054	32,764,565	34,818,320	36,776,552	143,237,507
MBD	1	7,336,395	20,569,332	23,517,602	24,991,738	26,397,309	102,812,375
PZQ	2.5	5,615,174	15,743,477	18,000,043	19,128,325	20,204,129	78,691,148
AZI	3.8	12,685,282	35,566,210	40,664,033	43,212,945	45,643,303	177,771,772

Drug Availability Analysis

IVM (ivermectin) – The projected tablet demand for the Initiative falls within the current forecast for the MECTIZAN Donation Program for the time period under consideration. Therefore, it is expected that Merck & Co., Inc. will be able to meet this demand. Applicants for support through the Initiative should ensure that their IVM forecasts and applications are adequately communicated to Merck & Co., Inc.'s MECTIZAN Donation Program to ensure timely availability.

ALB (albendazole) – The projected tablet demand for the Initiative falls within the current forecast for the time period under consideration. Therefore, it is expected that GlaxoSmithKline (GSK) will be able to meet this demand through their donation via the WHO. Applicants for support through the Initiative should ensure that their ALB forecasts and applications are adequately communicated to GSK and WHO to ensure timely availability.

DEC (diethylcarbamazine) – The projected tablet demand for the Initiative will not be met by any current donation program. Therefore, the Initiative will have to rely on commercial sources for this drug. WHO has experience in sourcing generic DEC, having procured 85 million tablets in 2006.

MBD (mebendazole) – As shown in Table 2, Johnson & Johnson pledged donations of up to 50 million tablets of MBD / year through their de-worming program (Children Without Worms). It is not clear if the drug needs of the Initiative will be included within those 50 million tablets since Children Without Worms is an independent program with its own application and approval process. Therefore, efforts should be made to align the needs of the Initiative with the Children Without Worms' provision mechanism. This paper assumes a once yearly treatment schedule for STH; however, in certain areas with high prevalence treatment may be necessary twice a year. If the Children Without Worms program is unable to meet the full MBD demand associated with the Initiative, a commercial procurement solution will be necessary. Should this be the case, WHO has experience sourcing ALB commercially, which is a suitable MBD substitute for STH programs. Additionally, generic levamisole or pyrantel may also be used instead of MBD for STH programs.

PZQ (praziquantel) – Merck KGaA has committed to a donation of 200 million tablets of PZQ for treatment of SCH through 2018. The Merck KGaA donation program is in partnership with WHO; therefore, close coordination is recommended between USAID, WHO, and the Initiative's implementation mechanism to ensure alignment of drug needs with the donation program. There is commercial availability of PZQ from MedPharm and other suppliers and manufacturers. Also, WHO procured 324,000 tablets in 2006 from generic suppliers.

AZI (azithromycin) - Pfizer Inc. is committed to donating ~33 million treatments / year (~125.4 million tablets AZI) through the International Trachoma Initiative. Given Pfizer Inc.'s current level of donation at approximately 21 million treatments of AZI in 2007, it is likely that the AZI needs for the Initiative will not be accommodated within the current donation program, making a commercial sourcing solution necessary.

Approaches to Facilitate and Expand Drug Provision

Given the clear need for additional quantities of drugs for the Initiative, specific steps can be taken to facilitate their timely availability. For donated drugs that contain the needs of the Initiative within existing forecasts, the supply chains still must undergo significant scale up to meet the required quantities. For drugs that (in the current environment) will require commercial procurement solutions, creative approaches are needed. A few mechanisms to enable the provision of necessary drug supplies through donations and purchases, are discussed below.

WHO global procurement partnership

As one mechanism to address the gap, WHO is exploring the development of a global partnership for procurement of essential medicines for the expansion of preventive chemotherapy programs. Such a partnership aims to mobilize public and private resources to ensure that national NTD programs will have sufficient quantities of the medicines referenced in this paper. The partnership will also promote integrated delivery strategies to improve the cost-effectiveness of in-country programs. Finally, the partnership aims to develop and implement an information system to track the progress of NTD programs in order to provide a better basis for future drug demand forecasting.

Donor funding of Active Pharmaceutical Ingredients (API)

The Initiative may consider directing some funds to offset manufacturing costs by purchasing Active Pharmaceutical Ingredients (API). The API would be used by a pharmaceutical company to increase the overall production level, using existing resources for formulation, tableting and packaging of the final product. From the perspective of the United States government, this could potentially be facilitated via USAID's Global Development Alliance, an innovative public-private approach to combine complementary assets for effective problem solving and deeper impact.

Mitigation of shipping and customs expenses

NTD drug donation programs by pharmaceutical companies typically cover the shipping costs for delivery of medicine to the port of entry of each program country. Given the high cost of shipping product from manufacturing facilities to developing world distribution locations, the Initiative may consider ways to offset these costs. For example, the Initiative could include annual grants to the shipping organization (e.g., pharmaceutical company, WHO) at a flat level, or as a percentage of overall shipping expenses associated with the Initiative. Alternatively, the various partners to the Initiative could engage in negotiations with a logistics firm to secure advantageous rates for shipments in support of the Initiative.

Regarding customs, in the case of donated product all shipments should enter duty-free. Therefore, the country partners involved in the Initiative must ensure agreement by the local finance and customs authorities that the shipments will be permitted to enter duty-free. This assurance is currently a standard requirement in the individual applications for most pharmaceutical firm disease-specific NTD drug donation programs. Given the need for cooperation between national Ministries of Health and Ministries of Finance on this issue, the topic often must be re-addressed as part of the national budget cycle. For additional or scaled-up donations and shipment in support of the Initiative, this assurance will be critical to help to avoid the potential for inappropriate and restrictive customs payments.

Leveraging of resources amongst pharmaceutical companies

The Initiative provides an exceptional opportunity for the pharmaceutical industry to display a united front for global health through a commitment to meet the drug needs associated with carrying out the \$350M pledge. A joint commitment to ensure sufficient and regular provision of the full spectrum of necessary drugs, through donation or commercial arrangements, would illustrate the vision of the pharmaceutical industry to support global health. Furthermore, it will create leverage for other global stakeholders to dedicate complementary resources to capitalize on these currently available solutions.

Other (non-quantitative) Issues Surrounding Drug Provision

The pharmaceutical industry members involved with these disease-specific control and elimination programs are committed to contributing to the Initiative in partnership with other global NTD stakeholders. Due to the special nature of pharmaceutical products, donors and commercial providers of anthelmintics are concerned with unique

issues that must be acknowledged and addressed by all levels of the supply chain. These issues include SAE reporting, general supply chain issues, program-related research issues, and disease-specific program objectives.

Serious Adverse Events management and reporting

WHO has developed a standardized form for reporting serious adverse events (SAEs). This form is designed for use in MDA situations and covers albendazole, DEC, ivermectin, mebendazole and praziquantel. The form facilitates direct reporting of SAEs and directs users to submit the report form directly to the responsible drug donation program or pharmaceutical company for recording and forwarding to the appropriate surveillance agency. The form is part of WHO's guidebook Preventive Chemotherapy in Human Helminthiasis, available online at http://www.who.int/neglected_diseases/preventive_chemotherapy/pct_manual/en/index.html.

For azithromycin from Pfizer Inc. via the International Trachoma Initiative (not included in the WHO guidebook), physicians should follow local regulations regarding the reporting of SAEs to local authorities or to Pfizer Inc. directly.

Through the mechanism established to carry out the Initiative, field-level implementing partners should confirm their awareness of and adherence to proper procedures for SAE reporting. Direct assistance from the pharmaceutical companies or the associated drug donation programs is available to navigate any SAE reporting issues that may arise.

Supply chain issues

Any drug supply chain has challenges, given materials, storage conditions, etc., especially in the developing world where physical infrastructure and human resource capacity may not be fully optimized. The Initiative must recognize these challenges through the screening process for implementing partners to ensure they have the capacity to properly manage drug supplies. Some of the issues to be addressed are listed below. Additionally, the Initiative should recognize the tremendous opportunity presented for health care capacity building through this program. Since many of the areas that will be reached through this Initiative are naïve to this level of health care service, the Initiative should capitalize on opportunities for training of health care workers and community volunteers. Quantification of such activities should be a reporting metric for all program partners.

- shipment coordination to synchronize MDA in country
- securing sufficient warehouse space
- limited supply of commercial air carrier or ocean freight space
- different lead times for manufacturing
- periodic and unpredictable shortage of global active pharmaceutical ingredient
- consistent product presentation among the same medicine and sufficient product differentiation between different medicines
- training on supply chain, reporting and inventory management
- extreme temperatures and humidity of many countries / rainy seasons
- product security in failed states and conflict zones; general leakage and theft
- lack of personnel and equipment (e.g., forklifts)
- managing various shelf lives
- error detection, correction and remediation

Program related research issues

Ongoing program related issues of interest to pharmaceutical company supported drug donation programs include monitoring of drug efficacy, pharmacokinetic studies needed for integrated delivery, evaluation of treatment coverage strategies where drugs are not equally indicated for all demographics (e.g., age). Many of the disease-specific drug donation programs already have guidelines in place for these issues, but coordination between programs is necessary to ensure that any new issues are identified and addressed in a jointly acceptable manner.

Disease specific programs - objectives and approvals

The Initiative is one element of a global movement focusing on integrated NTD control and elimination. In the activities of various stakeholders involved in NTD programs, integration of programs and co-implementation of drug therapies is accepted as an effective and efficient approach that will have the greatest reach in the global efforts to combat NTDs. However, it is also important to maintain a focus on the individual diseases being addressed since

many of the diseases have specific global targets linked to the programs and commitments of pharmaceutical donors. Therefore, the implementation mechanism for the Initiative must align program operations with individual disease programs and their associated disease control / elimination targets.

Onchocerciasis: Merck & Co., Inc's donation of MECTIZAN is for the elimination of onchocerciasis as a public health problem globally. In Latin America, the objective is full elimination of transmission with an endpoint to treatment. In Africa, donation will likely continue under a program of disease control, as full elimination of transmission may be possible only in isolated areas. www.mectizan.org

Lymphatic filariasis: World Health Assembly resolution WHA 50.29, issued in 1997, called for the elimination of LF as a global health problem. This objective is supported by the Global Program to Eliminate LF (GPELF), and is supported by GSK's donation of albendazole and Merck & Co., Inc.'s donation of MECTIZAN, in addition to commercially available DEC.

GSK's donation of albendazole for LF elimination is made to the WHO under a Memorandum of Understanding between the two organizations. The application process is managed by WHO via a set of Regional Program Review Groups (R-PRGs). The R-PRGs are made up of regional public health/LF experts with a remit to review country LF elimination plans and albendazole applications, and make recommendations to WHO for supply of albendazole. In LF / oncho co-endemic countries in Africa there is a dual approval process whereby applications are submitted to the MECTIZAN Donation Program and WHO.

It can be noted that the global LF program has an objective of elimination of the disease and halting MDA once disease transmission is eliminated. Studies are ongoing to determine appropriate endpoints to treatment. Should formerly LF endemic areas achieve elimination of transmission and subsequent halting of LF MDA, this would imply the removal of ALB chemotherapy, thereby creating the possible need for a new approach to STH MDA in those areas.

Trachoma: Pfizer Inc.'s International Trachoma Initiative (ITI) (www.trachoma.org) is the mechanism through which Pfizer Inc. provides azithromycin for trachoma programs. The program maintains its own application and oversight process.

STH: Through Children Without Worms, Johnson & Johnson is donating mebendazole to 8 countries (by end of 2008) in Africa, Asia, and the Americas. An independent, authoritative body of experts called the Mebendazole Advisory Committee (MAC) advises the Task Force and Johnson & Johnson on technical and strategic aspects of the program, and recommends policies and procedures to ensure safe and effective use of the donated mebendazole. www.childrenwithoutworms.org

Conclusions

The goals of the disease-specific NTD control and elimination programs supported by the members of the pharmaceutical industry are aligned with the objectives of the Presidential Initiative for NTD Control. Indeed, for more than 20 years, major industry members have been fully engaged and invested in NTD programs. To cite a few examples:

- 1987 – Merck & Co., Inc establishes the MECTIZAN Donation Program for onchocerciasis
- 1998 – GSK, and later Merck & Co., Inc., establish donation programs for lymphatic filariasis
- 1998 – Pfizer Inc. initiates the International Trachoma Initiative
- 2007 – Merck KGaA donates 200 million tablets within a period of 10 years to the WHO. Tablets will be used exclusively for affected children in the poorest developing countries
- 2007 – Johnson & Johnson commit to STH program through donations of mebendazole

This history represents an unparalleled track record of partnership and leadership in global public health. These and other contributions from the pharmaceutical industry will be enhanced further through the catalytic activities of the Initiative.

And while the most visible and well-known contributions from pharmaceutical companies to global NTD programs take the form of product donations, companies can (and often do) offer additional, valuable contributions. These have taken the form of direct financial support for program implementation, supply chain expertise, guidance on research, general management support, and engagement on important policy and advocacy issues.

To address the issues presented in this paper, there is a clear need for an active Working Group on Provision of Drugs for NTD Programs. WHO is well-positioned to serve as the convener of such a group given their cross-cutting involvement in drug provision / procurement and NTD program implementation, in all regions and across all NTD disease categories. An informal industry group, the Partnership for Disease Control Initiatives (PDCI), together with PhRMA and IFPMA, should also be a part of the Working Group in view of their active drug donation programs and partnerships, in addition to their contributing role on policy and industry-wide advocacy efforts. Furthermore, should WHO's proposed partnership for drug procurement be developed, it will work in conjunction with the industry-supported Working Group to advance the collective aims of the stakeholders in support of the Presidential Initiative for NTD Control.