

# THE MECTIZAN® (IVERMECTIN) DONATION PROGRAM

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**FOR RIVERBLINDNESS AS A PARADIGM FOR  
PHARMACEUTICAL INDUSTRY DONATION PROGRAMS**



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## TABLE OF CONTENTS

	<u>Page</u>
1. INTRODUCTION	3
2. TYPES OF DONATIONS	4
3. DESCRIPTION OF THE MECTIZAN DONATION PROGRAM	8
4. WHO BENEFITS?	13
5. MEASURES OF SUCCESS AND ACHIEVEMENTS	14
6. QUESTIONS AND CRITICISMS	17
7. WHAT WORKS	18
8. APPLICABILITY TO OTHER SITUATIONS; FRAMEWORK FOR FUTURE DRUG DONATION PROGRAMS	21
9. CONCLUSION	24
 BIBLIOGRAPHY/REFERENCES	 25



## 1. INTRODUCTION

The debate over pharmaceutical pricing policies and access to AIDS-related drug treatment has greatly intensified over the past year. In this context, along with a succession of price reductions, several research-based pharmaceutical manufacturers have instituted donation programs as a response to the need for improved access to these drugs by HIV-infected persons in the developing world.

In her last editorial as Editor-in-Chief of the New England Journal of Medicine, entitled "The Pharmaceutical Industry: to Whom Is It Accountable?" (NEJM, 342(25): 1902-4, 22 June 2000), Marcia Angell delivered a harsh assessment of the pharmaceutical industry's pricing and marketing practices. In one of its only complimentary concessions, the editorial's penultimate paragraph stated:

The recent decision by five drug companies to cut the price of HIV drugs in Africa was a good but small start. There have been other generous actions by drug companies, notably Merck's 1987 decision to donate millions of doses of ivermectin to treat onchocerciasis and lymphatic filariasis in underdeveloped countries. These are examples that the rest of the industry might do well to emulate in an organized way.

To replicate a program such as Merck's is certainly a laudable goal, for this program is widely considered to be a highly successful example of private-public partnership in international health. How, then, should the pharmaceutical industry go about emulating this program? Should this be the model in all circumstances, or are there characteristics of this disease (onchocerciasis) and this drug (ivermectin) that make this program unique? What are the critical elements that have resulted in this success?

The purpose of this paper is to examine Merck's Mectizan<sup>®</sup> (ivermectin)\* donation as a successful paradigm for pharmaceutical industry donation programs: what characterizes it, what it responds to, how it was instituted, who implements it, who benefits, and how to measure its impact.

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\* The proprietary name 'Mectizan' is a registered trademark of Merck and Co., Inc. for its donated version of ivermectin for human use. The generic name of the compound, ivermectin, will be used in this paper at the same time that the acronym 'MDP' will be used to indicate the Mectizan Donation Program, since the program from its inception has, quite logically, utilized the proprietary name for the donated product.

## **2. TYPES OF DONATIONS**

When attempting to characterize a pharmaceutical industry-sponsored donation such as that of Merck, it is important to recognize that different types of donations are made in response to different types of situations. These can be in either a disease-specific context, or in the setting of an emergency situation (e.g., a natural disaster or complex emergency).

### **a. Disease-specific**

In contrast to donations by pharmaceutical companies in the context of emergency situations, numerous examples exist in which specific therapeutic products are donated to address specific diseases. At present, the International Federation of Pharmaceutical Manufacturers Association (IFPMA) lists the following disease-specific donation programs:

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## Product-Specific Donation programs and Pharmaceutical Industry Sponsors

Disease	Donated Product		Company
	Trade name	Generic name	
African trypanosomiasis	Ornidyl	eflornithine <sup>1</sup>	Aventis
African trypanosomiasis, leishmaniasis	Pentam	pentamidine	Aventis
HIV/AIDS	Crixivan	indinavir	Merck and Co., Inc.
	Stocrin	efavirenz	Merck and Co., Inc.
	Videx	didanosine	Bristol-Myers Squibb
	Zerit	stavudine	Bristol-Myers Squibb
	Megace	megestrol acetate	Bristol-Myers Squibb
	Fungizone	amphotericin B	Bristol-Myers Squibb
	Viramune	nevirapine	Boehringer Ingelheim
	Retrovir	zidovudine (AZT)	GlaxoSmith Kline
	Eпивir	lamivudine (3TC)	GlaxoSmith Kline
	Combivir	AZT + 3TC	GlaxoSmith Kline
Leprosy	Rimactane	rifampicin	Novartis
	Lamprene	clofazimine	Novartis
Lymphatic Filariasis	Zentel	albendazole	GlaxoSmith Kline
	Mectizan	ivermectin	Merck and Co., Inc.
Malaria	Malarone	atovaquone + proguanil	GlaxoSmith Kline
Onchocerciasis	Mectizan	ivermectin	Merck and Co., Inc.
Polio		oral polio vaccine	Aventis Pasteur
Trachoma	Zithromax	azithromycin	Pfizer
Vitamin A deficiency		vitamin A	Hoffman-LaRoche

SOURCE: [www.ifpma.org](http://www.ifpma.org), accessed 30 May 2001

1. Bristol-Myers Squibb also contributes to this eflornithine donation program.

As this list demonstrates, the research-based pharmaceutical industry is involved in a wide range of product-specific donation programs. These are considered to be 'non-emergency' in nature, as they are not a response to a specific natural disaster or complex emergency.

In some donation situations, the drug product has had an established commercial niche before its donation was contemplated (e.g., albendazole). In others, there was no commercially viable market for the product at the time the donation was initiated. Indeed, in some circumstances the very need for a donation program is due to the fact that the donated pharmaceutical product has no commercially viable market (e.g., eflornithine).

Such product-specific donations can be utilized in two fairly distinct programmatic settings: either in a public health modality, or in an individual patient, therapeutic modality.

#### **i. Therapeutically-oriented programs**

In a therapeutic program, use of the donated product is generally on a patient-by-patient basis, requiring individualized diagnosis prior to treatment. Consequently, the individual patient is the one who most directly benefits from treatment with the donated product.

An example of such a therapeutically-oriented program is the Malarone donation program sponsored by GlaxoSmithKline. In order to be treated with Malarone, the patient must be diagnosed with malaria and must have failed primary therapy. This program, quite appropriately, does not call for the presumptive treatment of patients or communities *suspected* of having malaria. The donations of eflornithine and pentamidine by Aventis and Bristol-Myers Squibb (respectively) for treatment of African trypanosomiasis are additional examples of therapeutically-oriented donation programs.

Since such donation programs are based on individual patient diagnosis, treatment, and follow-up, they are much more reliant on the presence of a functioning medical infrastructure than would be a public health-oriented donation program (see below). The type and sophistication of the required infrastructure will depend on the drug(s) being donated, as well as the disease(s) being addressed.

#### **ii. Public health-oriented programs**

In a public health-oriented program, the donated product is administered to an entire community, based on an epidemiologic threshold that warrants mass treatment. Although individuals may well benefit, on a 'patient-by-patient' basis, from such mass treatment, the community at large is a targeted beneficiary, and reduction of disease transmission is an important goal.

Merck's Mectizan Donation Program (MDP), as implemented through such programs as the African Program for Onchocerciasis Control (APOC), the Onchocerciasis Control Program of West Africa (OCP), and the Onchocerciasis Elimination Program of the Americas (OEPA), is an example of a public health-oriented donation program. Rather than diagnose and treat individual members of a community, the decision to initiate annual treatment with ivermectin is made by performing a survey of the community members to determine what proportion has palpable onchocercal nodules. Once a

threshold level of onchocerciasis is diagnosed in this manner, the entire community of eligible recipients is given annual therapy. The benefits of such annual mass treatment are felt at both the individual and the community level. Individuals with heavy infections of onchocerciasis are spared from the inexorable progression to blindness, and those persons with dermatologic manifestations are provided relief from the chronic debilitating pruritis associated with this disease. The community as a whole benefits, both from the increased productivity of its members as well as from the impact on disease transmission. (In program areas in which vector control activities have greatly reduced the density of *Simulium* vectors, the marked decrease in skin microfilariae brought about by annual ivermectin treatment enhances the overall interruption of disease transmission.)

Similarly, the Lymphatic Filariasis (LF) program, to which both GlaxoSmithKline's albendazole and Merck's ivermectin are donated, is an example of a public health -- oriented program. Indeed, this program's primary goal is interruption of disease transmission and thus the prevention of new cases: not unlike the goal of a vaccination program. As in the onchocerciasis program, initiation of mass chemotherapy for LF is based on the result of disease surveys in endemic areas via sampling of the population. (The survey methodology in this case is by an antigen card test that requires a small blood sample.) The individuals in the community who are infected with LF will not be cured of their disease by this intervention, since the chemotherapy being administered is effective against the blood microfilariae but not against the disease-producing adult worms resident in the host lymphatics.

#### **b. Emergency**

Although not the focus of this paper, pharmaceutical companies routinely respond to requests for product-specific donations in the context of natural disasters and other types of emergency relief efforts. Vaccines, along with pharmaceuticals, are additionally important commodities in the public health response to such emergencies.

In a recent survey of donors conducted by WHO (see "First-year experiences with the Interagency Guidelines for Drug Donations", WHO/EDM/PAR/2000.1), less than 20% of the responding donors stated that their donations were made for acute emergencies. Of the total annual value of donations (US\$ 298 million) reported by donors responding to this survey, 76% (US\$ 228 million) was from the pharmaceutical industry.

WHO, the pharmaceutical industry, and NGOs have sought to develop guidelines to ensure that such donations are 'appropriate'. In crafting such guidelines, participants seek to adhere to the four 'core principles of good donation practice', which are that all product donations:

- are of maximum benefit to the recipient;
- respect the wishes and authority of the recipient;
- strictly avoid any double standards in quality;
- are based on effective communication between donor and recipient.

Since the WHO first proposed guidelines for drug donations in 1994, consensus has been sought amongst the various organizations and companies involved in both the donation and the distribution of such products in emergency situations. All seek to optimize the matching of need with availability.

### **3. DESCRIPTION OF THE MECTIZAN DONATION PROGRAM**

#### **A. History and Institution of the Program**

Merck analyzed Japanese soil samples in 1975 for action against parasites and discovered the highly active chemical family of avermectins. By 1978 it had derived ivermectin and discovered that it was effective against horse worms related to the *Onchocerca volvulus* that causes river blindness in people. As the drug was progressing toward regulatory approval (it was approved as a veterinary drug in 1981), Merck began to consider the use of ivermectin as a human drug. Two phase 1 clinical trials, both funded by Merck, demonstrated the initial safety and promising efficacy of ivermectin in patients with onchocerciasis. In order to more definitively study safety and effectiveness, Merck approached WHO, and they conducted collaborative human trials from 1982 to 1985. The careful conduct and regulatory acceptability of these large trials was facilitated by the TDR-funded Onchocerciasis Chemotherapy Research Center in Ghana. These trials confirmed the safety and efficacy (and ease of administration) of ivermectin, leading to the first regulatory clearance of the human formulation of ivermectin, Mectizan®, by the French drug regulatory authority in 1987.

Merck then had to decide how to use this discovery. It first proposed selling ivermectin at a price based on market conditions – related to what other anti-parasitic agents sold for at that time -- of \$3 ; but the people who could benefit from this medicine were the least able to pay. Next it tried to find third-party payers such as the U.S. government and international organizations, but was unsuccessful even though it eventually offered to discount the price to \$1. Abandoning the drug was unattractive both in terms of health benefits denied to suffering people in Africa, and in terms of characteristics of Merck and its situation: its corporate culture, its already-existing donation programs, and also its image now that many knew of the existence of this breakthrough.

The final option, donation, also had actual or potential difficulties and disadvantages for Merck and possibly others. These were:

- (a) Risks if Mectizan caused unexpected adverse reactions
  - (b) Manufacturing and administrative costs of long duration and potentially large total amounts
  - (c) Possible creation of expectations that future medicines would also be donated not sold; this could create new, or aggravate existing, disincentives to research against tropical diseases
  - (d) Providing the drug was necessary but not sufficient – it would also be necessary to ensure the existence or creation of an effective distribution system to get the drug reliably
-

to millions of affected persons in 35 countries all over Africa, as well as Latin America and Yemen, for at least a dozen years.

Reportedly Merck paid little attention to the financial implications of this donation program at the time of taking its basic decision. Hitherto its donations had been largely in response to requests made by private voluntary organizations for use in their overseas health programs, or in response to disaster situations (although it had generously made available streptomycin to Japan after World War II). Its view at the time apparently was that the company's financial performance had been and was good, and it could afford the donation program. While the maximum financial size of the program could have been estimated more or less, such a calculation does not seem to have played any part in the decision. Nor was there reportedly any consideration beforehand of the tax deductions that might be available to reduce the net cost of the program.

Merck finally chose in 1987 to donate the drug to all who need it for as long as needed.

One feature of drug donation programs that may be of increasing relevance today is whether the idea for the program originated with the pharmaceutical industry sponsor, or whether it was a response to a request from outside the industry.

The initiative to develop ivermectin for human use came from Merck. The decision on a donation program came only after Merck pursued unsuccessfully both commercial sales at market prices and third-party payers at either market or discounted prices. Ultimately, though, Merck CEO Roy Vagelos decided that an open-ended donation should be instituted.

The drug donations were fitted into the ongoing internationally sponsored Onchocerciasis Control Program (OCP) for 11 West African countries (covering the years 1974-2002) as well as the ongoing efforts of several NGDOs working to combat blindness in Africa, later consolidated and strengthened under the African Program for Onchocerciasis Control (APOC) for 17 other African countries (intended to cover the years 1996-2007). The availability of donated ivermectin also enabled the initiation of the Onchocerciasis Elimination Program of the Americas (OEPA), covering 6 Latin American countries. Thus, together with Yemen, the Mectizan Donation Program covers a total of 35 countries considered to be endemic for onchocerciasis.

## **B. Organization and Administration: Roles and Responsibilities**

A pharmaceutical donation program for developing countries has many actual and potential actors. These actors may be grouped as follows: the private sector (in this case Merck); autonomous programs to implement the donations; ministries of health in recipient countries; non-governmental development organizations; and international organizations. All of these play roles in the Mectizan Donation Program.

a. Private Sector Pharmaceutical Company (Merck)

i. Corporate donations office

Merck's Corporate Donations office plays an important coordination role in the conduct of the program. Since shipment and customs responsibilities for the donated product are handled by Merck, there is a need for close coordination between the Mectizan Donation Program (MDP) office in Atlanta (where requests for Mectizan are reviewed and, in consultation with the Mectizan Expert Committee [see below] , approved) and the site of final drug product manufacture and packaging in France. The corporate donations office also:

- helps set the strategic direction for the program (for example, the decision to expand the donation to include Lymphatic Filariasis as well as onchocerciasis);
- ensures that the donation process and procedures adhere to Merck corporate policies and agreed-to commitments;
- gathers, validates, and disseminates accurate data regarding quantities shipped, and related information relevant to the conduct of the program;
- provides brochures and related educational materials which describe the purpose and accomplishments of the Mectizan program; and
- engages in the business of building and maintaining the vital 'public/private partnership' between Merck, the affected African communities, the involved NGDOs, and the international organizations (WHO, World Bank) who together form the Onchocerciasis partnership.

ii. Regulatory affairs

From a regulatory standpoint, the fact that Mectizan happens to be donated rather than sold does not change Merck's corporate responsibilities in the area of drug safety monitoring and reporting. One of the most important yet most overlooked aspects of Merck's participation in this donation program has been its continued role in meeting this important public health obligation. Any adverse drug effects noted to occur in the context of the APOC or OCP programs are investigated and reported to the appropriate drug regulatory authorities (e.g., the Food and Drug Administration in the US). For example, reports of adverse events in Cameroonian patients given ivermectin for onchocerciasis when co-infected with a different filarial worm (*Loa loa*) have prompted a series of careful on-site investigations, as well as the convening of expert panels to advise on the optimal measures needed to ensure the safeguarding of the local population and the appropriate conduct of future investigations.

iii. Medical/scientific

Merck has kept its own scientist/clinicians involved in the donation program since its inception. This has been important for the continued success of the program, particularly

since ivermectin had not been in clinical use prior to the creation of the Mectizan Donation Program (MDP). As with any newly-approved drug for human use, it was very important to monitor for side effects as the number of people treated with the drug expanded beyond the numbers included in the clinical studies conducted for regulatory purposes. As the drug's wide margin of safety was reaffirmed, its broader distribution by community-based distributors (who lacked formal medical training) could be contemplated. Merck clinical scientists also play an important liaison role on the Mectizan Expert Committee (MEC), a committee of tropical disease experts which independently oversees the conduct of the Mectizan Donation Program (see Autonomous Programs, below). More recent issues, such as the need for more field-appropriate drug stability testing and the programmatic need for a 3 mg tablet rather than a scored 6 mg tablet, have also greatly benefited by the ongoing participation of Merck scientists in the Donation Program.

#### b. Autonomous Programs

The Mectizan Donation Program required both an oversight organization and a credible body to make a sizeable number of decisions each year on which individual ministries of health, local health agencies, or NGOs in Africa and Latin America would receive ivermectin. Merck sought the creation of a program organization, external to the corporation itself, that would give the program high standing, independence, and distance from Merck as a corporate entity. The resulting entity, the Mectizan Donation Program, was established as part of the Task Force for Child Survival and Development headed by Dr. William Foege. Along with his leadership of the MDP and direction of the Task Force, Dr. Foege also maintained close professional links to the Carter Center.

For project decisions and other technical functions of the program, Merck formed the Mectizan Expert Committee (MEC), an independent group of experts in tropical medicine and public health. This committee, which meets twice annually, consists of seven voting members and three liaison, non-voting members representing WHO, the Centers for Disease Control and Prevention, and Merck. Its charter states that the main goal of the MEC is "to facilitate the earliest and widest possible application of Mectizan in public health programs consistent with good medical practice and the approved prescribing information in all areas where onchocerciasis is endemic".

#### c. Ministries of Health in Recipient Countries

The ministries of health of the endemic African countries play a variety of roles. Most countries have established a national onchocerciasis task force (NOTF), which is an in-country partnership comprised of the MOH, the local and international NGOs involved in onchocerciasis control efforts, and WHO. The NOTF approves APOC programs within its territory, helps to provide the strengthened epidemiological surveillance capability that will continue to be required through 2007 and beyond, and also has important roles in relation to ivermectin and the Mectizan Donation Program. It can facilitate the licensing of ivermectin for human use in its country and its listing on that

country's Essential Drugs List. It is also the ultimate guarantor of performance on the program in its country. It facilitates part of the ivermectin distribution through its own staff at various levels down to communities. It also oversees ivermectin distribution and use through non-governmental development organizations (who are represented on the NOTF) that operate projects in its country.

d. Non-Governmental Development Organizations (NGDOs)

International NGDOs from Europe and the USA especially concerned about blindness and other eye problems have been active for some time in West Africa and, since the inception of the MDP in 1987, in supporting onchocerciasis control programs. By now there are over 30 NGDOs that are active partners in APOC. They are particularly important in countries where local health services are weak; in some countries there would be no effective onchocerciasis program without them. They both train community distributors and supervise the Community-Directed Treatment with Ivermectin (CDTI). To discuss subjects of common concern, learn from each other, and pursue common interests with other partners, they have established the NGDO Coordinating Group for Mectizan Distribution. To carry out their distribution role, the NGDOs have raised millions of dollars from their donors. They have developed a valuable resource for the programs in their field staffs. The NGDOs have also gained recognition and credit from the program's successes.

e. International Organizations

In the Mectizan Donation Program, as for OCP and APOC in general, WHO has played the lead technical role, while the World Bank has played the lead financial role on the two programs. In addition, FAO has played a minor role in the area of land resettlement and agricultural production.

WHO is the Executing Agency for both OCP and APOC. It was involved from the start with the research effort on ivermectin, and has remained involved through its Expert Committee on Onchocerciasis Control; Tropical Disease Research (TDR) research programs and studies, especially in recent years on community-directed treatment with ivermectin; and its role in the OCP and APOC organizations. It will remain involved with the OCP countries even after donor financing for OCP ends, through its sub-regional support center and through its country offices.

The World Bank has administered the Onchocerciasis Trust Fund, as well as the similar fund for APOC. It gradually increased its staff input, then set up a dedicated unit for this administration and for fund raising for the whole program that has functioned very efficiently. It has been a major donor itself to both programs. Furthermore, through its convening power it has been able to take responsibility for and succeed in resource mobilization and donor coordination for the two programs. This is carried out predominantly through the Committee of Sponsoring Agencies which groups the donors for program monitoring, management issues, input to the OCP Joint Program Committee,



and resources. The Bank's internal unit has provided the liaison to Merck and to the Mectizan Donation Program, assuring information flows, periodic problem solving, and other general facilitation.

#### 4. WHO BENEFITS?

##### A. Patients and Healthcare Systems in Developing Countries

*i. Communities otherwise lacking access to appropriate pharmaceuticals:* the most important and most numerous beneficiaries of this donation program are the 25 million individuals who reside in onchocerciasis-endemic communities and are currently under annual community-directed treatment with ivermectin. In the absence of the Mectizan Donation Program, and its effective implementation in APOC and OCP countries, these individuals would otherwise totally lack access to an effective and safe anti-microfilarial drug. The old drug that had been used for treatment of filarial infections, diethylcarbamazine or DEC, was cheap and generically available but potentially dangerous to use in persons with intense onchocerciasis infections. (Indeed, the evocation of an adverse response to this drug in onchocerciasis-infected individuals is so predictable that the phenomenon is sometimes used as an evocative diagnostic test in cases of occult onchocerciasis.)

*ii. Agencies wishing to address certain diseases but lacking financing to purchase appropriate pharmaceuticals:* The removal of any need for funds for purchase of anti-onchocerciasis medications has greatly facilitated the sustained interest of NGDOs in these programs. Even if the decision of Merck had been to initiate a greatly reduced-price program of \$1 per 6 mg tablet in 1987, rather than an outright donation, this would have necessitated an additional \$55 million, in the year 2000 alone, for the acquisition of adequate numbers of 3 mg tablets (assuming 50¢ per tablet), in order to conduct the APOC and OCP programs at their present levels of drug distribution. Such an additional funding burden would have placed additional demands on both the participating NGDOs and the bilateral and multilateral donors that would undoubtedly have been difficult to meet.

*iii. Health care systems:* An equally important contribution of this program in the endemic countries has been the creation of a grass-roots, community-based, demand-driven 'system' that forms the rudimentary basis for a functioning health care system. By demonstrating that such a 'system' can indeed work, the Mectizan Donation Program and APOC have enabled participants at all levels to consider the use of this paradigm to address additional disabling endemic diseases. As these communities broaden the scope of their 'community-directed' treatment schemes, they become more active participants with their Ministries of Health in laying the foundations of a functional health care system from the ground up.

## **B. Pharmaceutical Industry Members, their Employees and Stockholders**

*i. Corporate image:* Over the years since initiation of the Mectizan Donation Program, Merck has greatly benefited from being seen as a 'good corporate citizen' because of its willingness to establish and maintain such an effort. Recognition and awards have come from a variety of sources, some of which include: Helen Keller International (1989), the National Council for International Health (1990), the Corporate Social Responsibility award (1992), the Institute on African Affairs (1993), and the American Foundation for the Blind's(AFB) Helen Keller Achievement Award (1999).

*ii. Employee satisfaction:* A positive corporate image engenders enhanced employee satisfaction. The sense of mission and contribution to an important disease control activity, exemplified by the Mectizan Donation Program, provides a sense of ownership to all employees of Merck, whether or not directly involved in the conduct of the program. The enhanced morale resulting from such a sense of pride and ownership is beneficial to the company as a whole and can have a 'trickle-down' effect as well. (For example, the daughter of one Merck employee with a longstanding involvement in the Onchocerciasis program decided, in part based on her knowledge of her father's experiences, to become a Peace Corps volunteer in one of the onchocerciasis-endemic countries of West Africa.)

*iii. Tax incentives:* The U.S. tax benefits that Merck has received on account of the Mectizan Donation Program have substantially reduced the net financial cost of the program to the company. While Merck shareholders might have been expected to query, either at or since the start, an open-ended commitment of significant but uncertain magnitude and duration, in fact their reactions to Merck's humanitarian gesture have been overwhelmingly positive. Further, given Merck's continuing good financial performance, any extra profit foregone because of the donation program does not seem to have been missed.

## **5. MEASURES OF SUCCESS AND ACHIEVEMENTS**

### **A. Measures of Success**

The OCP program and the APOC program (first phase) have a large number of achievements to their credit. These achievements are in the areas of health gains, economic gains, efficiency, institutional, capacity building, and sustainability. The health and economic gains lend themselves to quantification, the others are qualitative. Some of these achievements are also those of the Mectizan Donation Program, but the latter has additional achievements of its own.

## B. Achievements -- OCP and APOC

In the area of health gains, OCP and APOC exemplify:

- successful single-disease categorical control programs
- basis for integrating disease control in rural Africa
- promotion of strengthened health system – e.g. epidemiological surveillance
- care to avoid ecological damage e.g. from spraying operations for vector control
- basis (OCP) for creation of program for surrounding countries (APOC), also to protect OCP gains
- support to participating countries to take over residual onchocerciasis control activities within framework of their own national health systems, with the results that:
  - a large proportion of the population at risk, currently greater than 25 million people, are now being treated
  - more than 2 million people have been freed of their infections
  - tens of millions have been or will be protected from infection, including about 15 million children, and a million people have been or will be protected from going blind

In the area of economic gains:

- prevention of premature deaths and increased productivity of the living will increase output and living standards
- resettlement of land freed from disease (25 million hectares in OCP countries) will bring further major benefits
- the cost of protection per person is under \$1 per year
- cost-benefit analyses -- slightly optimistic in that they omit Merck's costs -- yield highly satisfactory internal rates of return of 20% for OCP and 17% for APOC

In the area of efficiency, OCP has exemplified:

- cost-minimization, in vector control
- efficient distribution, of ivermectin.

OCP and APOC are models of a whole series of difficult institutional achievements and relationships:

- effectively functioning global partnership
- UN family partnership
- cooperation among African countries
- cooperation between African countries and donors
- long-duration cooperation and aid
- comprehensive regional approach to multi-country problem
- successful operating international institution, with highly motivated staff
- involvement of private sector and of international scientific community with international organizations and others.

In the area of capacity building, OCP and APOC have provided:

- training, through over 500 fellowships for high-level staff
- on-job experience of field activities, for over 1,000 professionals
- empowerment of communities, through CDTI
- training of 30,000 community distribution workers
- a cadre of African scientists who have become recognized world experts on onchocerciasis.

Finally, in the area of sustainability:

- the OCP countries will take over surveillance, maintenance, and prevention of the return of the blackfly to liberated areas
- national health services and NGOs will continue to supervise a low-cost and implementable distribution system for ivermectin.
- a framework is in place through which delivery of additional health interventions (vitamin A supplementation, other antiparasitic drugs) can be introduced.

### **C. Achievements -- The Mectizan Donation Program**

The Mectizan Donation Program has shared in this impressive overall success, especially as regards its record of long-duration cooperation with recipient countries, NGOs, the scientific community, and international organizations. It has also recorded a number of important and specific successes of its own:

- more than 10 years' production of ivermectin on an increasing scale
- creation of a lasting mechanism (the Mectizan Expert Committee), external to the company and involving respected independent scientists and public health officials, for evaluating and selecting recipients using objective criteria, thus achieving the allocation of ivermectin to the "best" users
- efficient distribution of ivermectin from Merck via developing country ports into the hands of the using bodies
- efficient distribution of ivermectin to ultimate beneficiaries by indirectly assisting in the building of a cadre of 30,000 community-level distributors (a cadre that may offer the potential for other public health interventions at community level all across Africa)
- creation of a mechanism allowing Merck to learn of, and react responsibly to, unexpected adverse events (side effects on users)
- keeping any drain on company profits over a long period within the range of tolerance of its major stakeholders (shareholders, bond markets...) by efficient manufacture and distribution and by offsetting tax benefits, and making them more acceptable also by the favorable effects of the program on Merck's public image and on employee pride and motivation
- setting an example of a model donation program for other pharmaceutical firms, in particular as regards: unconditional guarantee of supply in any amount needed for as

long as needed; mechanism external to the company to select recipients; and responsible attitude towards possible adverse events,

With the result that millions of people have enjoyed:

- ▶ significant early reduction of the risk of developing eye lesions and blindness;
- ▶ alleviation of intense and chronic discomfort (itching) caused by their infection;
- ▶ and a significant advance of the date by which transmission of the disease will be interrupted.

## 6. QUESTIONS AND CRITICISMS

Remarkable as the program is both in itself and as a model for other donation programs, there have been or could be questions and criticisms along the following lines, about either the program itself or its possible wider impacts.

Final success of the program and of onchocerciasis control will only be assured if the effort is sustained until the job is done. Organizationally, the question is whether there has been or will be sufficient integration of (a) onchocerciasis monitoring and prevention of recrudescence, and (b) community treatment activities into the national health systems of the endemic countries. The NGDOs may still be critical to success, rather than relying only on Ministry of Health distribution and supervision systems that remain weak in most if not all countries. Financially, the question is whether the countries will prove able and willing to provide the financial resources required to meet the non-Merck costs of the program once donor funding ceases (at the end of 2002 for OCP and 2007 for APOC).

A possible economic query from a global viewpoint re the OCP program that would require further evaluation is the possibility that the internal rate of return of adding ivermectin distribution to already-existing vector control activities has not been all that high. The benefits of adding ivermectin are a major advancement of the eye disease benefits but only a limited advancement of the interruption of transmission of the disease, while Merck's costs have been omitted from the cost-benefit analysis. (The relevant costs are the real economic costs: the opportunity cost of the resources Merck has used for the Mectizan program, not the financial costs to Merck.) In the case of the APOC program, where ivermectin is the main source of the total benefits, the internal rate of return from a global viewpoint is also lower than estimated hitherto, in that cost-benefit analyses have excluded Merck's real resource costs.

Finally, there may have been some exaggeration of the donation or "sacrifice" by Merck, in several regards. The program has had no known impact on its actual or potential markets for ivermectin (neither veterinary nor human). The company has taken the available U.S. tax deductions for its donation over the years, thus minimizing the net financial cost of the program to itself while, more recently, prompting some organizations to question the rationale of the US Government in granting such deductions. Finally, the boost to its corporate image from its participation in the program may well be very

valuable to it in terms of generating additional commercial business and/or investor interest, further offsetting any net costs of the Mectizan Donation Program itself.

Two other possible adverse impacts of the program, which were much discussed before its inception and could have implications for future programs of this type, can be re-evaluated now in the light of experience. The first was whether the example of the program would create more requests or pressure for donations not commercial sales of other drugs (by Merck or others). Merck itself has experienced little such pressure, and apparently not related to Mectizan but in the form of more general requests to provide funding. However, there seems to have been an effect on other pharmaceutical companies, through the promotion of the Mectizan program as a model for other such programs that have emerged recently; these other companies have been stimulated to emulate Merck. To the extent this has occurred, it should be regarded as good on balance, not bad.

The second possible impact that was feared was on Merck's and others' willingness to undertake research and development against tropical diseases, if there was a chance that only a donation program rather than commercial revenues would result. While such R & D has continued to be limited until the last few years, and has been stimulated mainly by the availability of new sources of donor financing (Gates Foundation etc.), it does not appear that the Mectizan Donation Program played any adverse role here. Such an effect has not been visible, but whether there was one ultimately may never be known.

## **7. WHAT WORKS**

### **A. Success Factors – OCP and APOC**

The first success factor in OCP was a fairly precise long-term strategy.

*i.* The efforts of Robert McNamara, the president of the World Bank who in 1972 visited onchocerciasis-devastated areas of West Africa, set in motion the detailed project preparation work which formed the basis for the Bank's willingness to commit to the concept of a regionally-focused Onchocerciasis Control Program. This commitment was crucial vis-à-vis both WHO and other donors.

*ii.* The willingness of donors to undertake a 20-year commitment was crucial. This willingness was partly due to the fact that there was a time limit, set not by governments but by technical factors. It was also facilitated by the contribution of the Mectizan Donation Program to the possibility of eventual devolution from OCP to the African countries; the MDP's continuation meant donors knew there was a way to safeguard their investment.

*iii.* Implementation was not dependent on government follow-through, but was under the control of an organization with considerable autonomy. In the governance of this institution there was a balancing of WHO influence by that of the World Bank, which also appealed to other donors.

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iv. OCP itself was also an important success factor for the Mectizan Donation Program. The organization had a culture of effective working and tangible accomplishment. Its staff was highly committed.

## **B. Success Factors – Mectizan Donation Program**

The success of the program has depended on a number of factors.

i. One of the most important has been that there has always been the same clear and specific goal, namely to distribute ivermectin to the affected populations until onchocerciasis was no longer a significant public health problem. In other words, Merck has adhered to the view that this is not ‘just’ a *donation* program, but rather a *distribution* program within the context of a broader public health initiative.

ii. A very important success factor has been the nature of the drug ivermectin itself. Firstly, in relation to the disease, it has several outstanding properties: one annual dose is enough, and it has a quick effect both on itching and on preventing eye lesions/blindness. It can be easily transported, stored, and distributed given its compact pill form and lack of cold chain requirements. It is easy to administer (the pill form, and once per annum requirement, again) and stable under field conditions. It has also turned out to have a very wide margin of safety and thus requires little in the way of post-treatment monitoring. As a result, treatment is possible in the most remote places, far away from formal health facilities, by community members rather than trained health personnel in areas where little or no health care infrastructure exists.

iii. Public education of communities in Africa about the importance, availability, and benefits of Mectizan was also necessary and was carried out (by NGOs and community distributors in particular). Once treatment began, word of mouth helped to multiply these efforts.

iv. A crucial success factor was Merck’s unconditional guarantee of the necessary quantities of Mectizan for as long as necessary (and free). This gave all partners the assurance to make long-term plans. It also made it more worthwhile to invest substantially in the creation of a distribution system, and of solid systems for the training and supervision of all personnel, particularly the thousands of community distributors.

v. Another highly important factor was that the program led Merck to become a real stakeholder in onchocerciasis control, leading to its becoming involved in a variety of ways. There was and is enthusiastic Merck headquarters support and scientific underpinning for the program. Merck has had to make investments in additional ivermectin production capacity more than once to meet the increased needs of the donation program. It was willing also to change the product formulation (from 6 mg to 3 mg tablets) to suit field conditions.

*vi.* The success of the Mectizan Donation has also depended on a high degree of public-private partnership. Three dimensions are noteworthy. First has been the willingness of the NGDO community to serve a vital role, as demonstrated by the Task Force on Child Survival and Development's willingness to host the Mectizan Expert Committee and the MDP secretariat, as well as by the NGDO Coalition's pooling of resources to fund an NGDO coordinator position at WHO Geneva. Second has been the willingness and ability of African communities to organize community-directed treatment with ivermectin (CDTI) – this local control has increased local commitment to the program. Third is the willingness and ability of the African Ministries of Health and the NGDOs to undertake the technical supervision of CDTI necessary to assure high quality of services. The involvement of these diverse organizations – from the affected communities, local and international NGDOs, Ministries of Health, and financial donors (both individuals and countries), to multilateral institutions such as WHO, UNICEF, and the World Bank – in partnership with Merck – has been the hallmark of this highly successful effort.

*vii.* The regional character of the program has also contributed importantly to its success. Merck did not have to deal with each country individually. It or the Technical Coordinating Committee of APOC was able to set standards and issue guidelines valid for all. This wholesale rather than retail approach also prevented inconsistencies among countries with different provisions. It also permitted the standardization of training. These were all considerable efficiency gains. In fact, it would have been very difficult to organize the program on an individual nation basis.

*viii.* A number of organizational and health-related arrangements, made to suit or reassure Merck, have also contributed importantly to the success of the program. The first was the institution of the Mectizan Expert Committee to select recipients, to give Merck distance from itself having to take judgments as to whether whole countries/health systems and individual NGDOs were suitable recipients of drug deliveries. The second was setting up systems, again outside Merck, for the local Ministries of Health and NGDOs to supervise community distribution, so the drug would arrive where it could have impact. Third was a system of monitoring adverse events, which served to preserve Merck's reputation and limit its risks.

*ix.* There are also market and financial features of the program that have served to prevent any loss of business for Merck and to minimize or even offset entirely its net expenditures for the program. The human drug distribution did not interfere with Merck's existing or future markets for the well-established veterinary form of the drug. There was also little prospect of a future commercial market for the human form of the drug, as Merck had already discovered at the beginning. At commercially profitable prices the drug was unaffordable by the very poor rural sufferers from the disease (its incidence in urban areas is negligible), and no third-party payers were willing to step in. Finally, whatever Merck's real manufacturing, administration, and shipping costs were and are, it has taken advantage of U.S. tax deductions to minimize its net costs.

*x.* In fact there were and are advantages to a donation program which make it a win-win situation compared to a program of commercial sales. There could have been no APOC

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program, and no successful closure of the OCP program as currently planned, and hence a question whether transmission of the disease could ever be interrupted, without the large quantities of drug that Merck has donated through the program. The company benefited through positive publicity as well as through increased motivation of its employees, without even mentioning the tax benefits that offset Merck's financial costs of carrying out the program. Finally, having committed to make donations in an open-ended manner gave and gives Merck an incentive to succeed as soon as possible in the efforts against the disease, to limit its final liability and costs. A program of sales would have conveyed precisely the opposite message.

*xi.* Finally, from the viewpoint of the African countries, program costs have been minimized by several factors. These have been: the availability of Merck's free supplies and shipping, donor financing, common standards guidelines and training, low-cost community directed distribution of ivermectin, and sharing of the costs of training and supervision of CDTI workers with international NGOs (and hence with their donors). This has minimized both organizational/personnel and financial costs to the countries.

## **8. APPLICABILITY TO OTHER SITUATIONS; FRAMEWORK FOR FUTURE DRUG DONATION PROGRAMS**

### **A. Applicability to Other Situations**

The success of the Mectizan Donation Program naturally inspires the question of the potential for more such successful drug donation programs. A number of authors cited in the bibliography have already examined preconditions for and necessary characteristics of such programs (Frost et al, Lucas, Kale); some additional points on these aspects follow below. Meanwhile, a number of other drug donation programs have started or are being discussed for implementation.

A duplication of such efforts is not necessarily desirable. Many in the international health community fear the resultant 'stove piping' of individual, disease-specific programs and the opportunity costs such a phenomenon can place on already-struggling ministries of health. A more appropriate approach worth consideration is that of using the Community-Directed Treatment with Ivermectin (or CDTI) approach as an 'entry point' at which additional yet equally safe and efficacious public health-oriented interventions might be introduced. In using such an approach, the community-based distributors of ivermectin can serve as 'seed crystals' around which the beginnings of a grass-roots health care infrastructure, it is hoped, can start to develop.

The number of diseases for which a promising candidate drug exists or may soon become available for a public health program, i.e. one requiring community-level mass distribution, is unfortunately somewhat limited. The most promising such candidate to date appears to be albendazole, which since 1998 has been donated by (what is now) GlaxoSmithKline for the intended elimination of lymphatic filariasis. In Africa, considerable overlap in disease distribution exists between onchocerciasis and lymphatic

filariasis; the two drugs can be safely co-administered; and, when dosed once annually, these two drugs not only address onchocerciasis and lymphatic filariasis, but have beneficial effects against a variety of additional parasitic infestations. Co-distribution of these two donated, broad-spectrum antiparasitic drugs has already begun in Nigeria, Tanzania, Togo, and Ghana. A second example of such an 'entry point' approach is the ongoing use in Nigeria, Cameroon, Mali, and the Central African Republic of community-based distributors of ivermectin for the concomitant distribution of vitamin A supplements to infants and children, thus protecting them from the onset of xerophthalmia and other disorders associated with a dietary deficiency of vitamin A.

## **B. Framework for Future Drug Donation Programs**

Even when a promising disease/drug combination exists, several of the aspects that have been tackled successfully in the Mectizan Donation Program will need to be covered anew if a program is to succeed. These include:

- an organized international effort which recognizes the burden a particular disease places on the world's poor, raises the awareness of the international community to that situation, and begins to marshal the needed financial and intellectual resources.
- the availability of a functioning public health system in which to insert the program. This includes the acceptance by the recipient country health authorities that this program and drug are parts of their priority health actions. It also includes the existence of capabilities for technical support and supervision of community-level work, in either ministries of health or other partners, especially NGDOs. Finally, it should include a system for monitoring adverse events.
- the availability of sufficient resources. This includes an unconditional commitment on the part of the donating company to supply the necessary quantities of the drug for the time period necessary to achieve the program's health goals. It also includes commitments as to the availability of sufficient financial resources to cover the non-drug costs of the program, from governments, NGDOs, communities, donors, multilaterals, private foundations, or other sources.
- the process of approval of drug shipments to particular recipients (automatic or discretionary? if the latter, by the donating company or by others? etc.)
- the extent of the logistical and financial responsibilities of the donating company (product only? shipping? handling through customs and port? internal distribution in recipient countries? tracking and monitoring systems for both the drug distributed and the populations treated? etc.)

- the presence of an effective program monitoring and evaluation strategy, and the ability to adapt new methodologies based on the resultant recommendations; and
- the availability of a community-level distribution system which can take on the program. This last point is discussed further below.

Ministries of health in developing countries have their networks of paid staff who generally cannot reach far beyond existing fixed health facilities for lack of transport and budget, competing priorities, and time constraints. Many countries also have networks of community-level workers, related either to the communities themselves or to locally-active NGOs; these networks usually achieve partial coverage of the thousands of villages in each country. The donating company and its partners in the Mectizan Donation Program have shown that a new large network (over 30,000 workers in numerous countries) can be created and the necessary training provided within a reasonable period of years.

Now that the considerable investments have been made and this network for community-level distribution exists in large parts of Africa, it is natural to hope that CDTI can be used as an 'entry point' for other primary health care interventions, including other drug donation programs, and that this can be done at low or even no additional cost. As mentioned above, a first such commitment has been made, namely to channel the donated drug albendazole for lymphatic filariasis (elephantiasis) through the system that has been created for Mectizan for river blindness, so it can be delivered to sufferers from the disease along with Mectizan, as is needed for optimal effectiveness. Many of the NGOs participating in the onchocerciasis programs are sight-oriented, and thus have interest in incorporating other vision-related activities such as distribution of Vitamin A capsules and the use of patient encounters in the context of CDTI as an opportunity to identify persons who might benefit from cataract surgery.

However, this is not a straightforward matter. Even if the logistical part of getting the drug or other product to the recipient countries is solved, there remains the question whether the community-level distribution system (and its technical support and supervision system) can handle whatever extra workload is implied by adding the new product. It would be necessary to examine this extra workload, see whether and how it can be minimized, and see whether the existing number of community agents and their supervisors could in fact take it on -- without becoming overloaded and detracting from the quantity and quality of their work on the Mectizan Donation Program. Then the recipient country governments and the donors would have to agree that this addition was a good change from a health goal point of view and acceptable. The need to go through a process like this will probably slow the addition of new items to the Mectizan Donation Program structure even if a number of promising candidates emerge.

## 9. CONCLUSION

The partnership which has formed to address the scourge of onchocerciasis in Africa has become a paradigm for successful public-private partnership in the international health arena. The success of the Mectizan Donation Program, one component of this partnership, has resulted from a convergence of several factors. Any chance of successfully building upon, expanding, or otherwise duplicating the Onchocerciasis Programs to address additional diseases of public health importance depends upon understanding these various factors and how they have coalesced over time. The dedication and long-term vision of the sponsoring corporation(s), the donor community, and the implementing organizations, underpinned by solid science and results-oriented operational research, all have combined to make onchocerciasis control in Africa a highly successful international effort. Now more than ever, there is a need to apply the lessons of this successful undertaking to additional public health initiatives.

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2. Charles Fettig, formerly Senior Director, Marketing, Merck, March 28, 2001
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**WEB SITES**

**International Federation of Pharmaceutical Manufacturer Associations**

[www.ifpma.org](http://www.ifpma.org)

**Lymphatic Filariasis Program**

[www.filariasis.org](http://www.filariasis.org)

**Malarone Program**

[www.malaronedonation.org](http://www.malaronedonation.org)

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[www.taskforce.org/MDP/](http://www.taskforce.org/MDP/)

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[www.merck.com/overview/philanthropy/mectizan/p1.htm](http://www.merck.com/overview/philanthropy/mectizan/p1.htm)

**Trachoma Initiative**

[www.trachoma.org](http://www.trachoma.org)

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