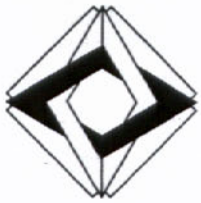

Merck & Co., Inc. (B)

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Merck Decides to Develop Mectizan

In 1978, Dr. P. Roy Vagelos, then head of Merck's research labs, approved initial funding for research into a potential treatment for river blindness.

Vagelos believed there were several reasons Merck ought to go forward with the research, first being the potential impact of a negative decision on the Merck culture. Failure to investigate Dr. Campbell's tantalizing hypothesis could demoralize Merck scientists, especially since the inquiry focused on a widespread, intractable disease that produced great suffering.

Vagelos also believed that the prevalence of the disease in the Third World would motivate someone - Third World governments, private foundations, or even the U.S. Government - to buy a successful drug and donate it to the victims.

The fact that a successful drug for onchocerciasis would not generate much revenue for Merck was a secondary concern to Dr. Vagelos and his associates. "Until you can demonstrate that the drug is capable of doing something," Dr. Vagelos noted, "you don't even bring the marketing people into it. Because, until you can characterize a drug, they can't put numbers on it." Dr. Vagelos admitted, however, that "we knew that it was going to be a borderline economically viable project at the start."

Finally, Dr. Vagelos believed the company should proceed because the project would further Merck's knowledge of parasitology, already an established field in Merck. Even if the research failed to produce a treatment for river blindness, it might produce findings of future use to

the company.

For Dr. Vagelos and Dr. William C. Campbell, the scientist who had proposed the research, investing in the development of the drug for this dread Third World disease was an irresistible possibility. "Emotionally, you become very involved in what you can accomplish, as a research group and as a company," Dr. Vagelos explained. "And so we could hardly wait to start these experiments." It made sense for Merck, Dr. Vagelos believed, to learn as much as possible about its fledgling class of compounds, avermectins, as possible.

Clinical Trials Approved

By 1980, ivermectin had traversed quite a distance on its journey to becoming a river blindness therapy: from the original parasitological research (led by Dr. Campbell) to the microbiology and chemical identification programs (led by Drs. Tom Miller, Richard W. Burg and Georg Albers-Schonberg) to the chemical synthesis of ivermectin (Drs. John C. Chabala and Michael H. Fisher) to development of the animal drug formulations. Eighteen months had elapsed since the compound's potential human application was first suspected.

Then, in January 1980, the baton was passed to Dr. Mohammed A. Aziz, senior director of clinical research at Merck. A quiet man of steely determination, Dr. Aziz was widely credited for championing the drug, which would come to be known as Mectizan, within Merck and shepherding it past numerous scientific and corporate obstacles. His obsession with developing Mectizan, cited by all who knew him, was due in large part to his personal background. As a tropical disease expert, native of the region now called Bangladesh and former World Health Organization (WHO) scientist with experience in Sierra Leone, Dr. Aziz knew firsthand what river blindness meant for Third World people. Dr. Aziz got his chance to proceed in January 1980, when Merck research management agreed to move forward with human clinical trials.

It was a momentous decision for Merck. The company was now committed to a lengthy, expensive set of tests for a drug that was not likely to generate much, if any, revenue. "We had never undertaken the development of a drug that was going to be broadly used, such as 18 million patients, with the idea that we were not going to make money," Dr. Vagelos later explained. In general, drugs that earn $20 million or less a year are at risk of being discontinued, he said, and certainly no one expected Mectizan to generate a fraction of that sum.

"On the other hand," Dr. Vagelos continued, "the company is so large and the laboratories so prolific, that one can never guess what is going to come out." A clinical investigation of ivermectin, however problematic, could yield useful knowledge.

At the outset of research, Dr. Bruce M. Greene, a prominent university scientist associated with the development of Mectizan recalled there was "a lot of turmoil in the company [in the early 1980s] about whether we should expose this fabulous commercial product to the risk of human usage." Dr. Vagelos, who had become chief executive in 1985, quieted the debate, and as it turned out, Merck's concerns regarding negative side effects of ivermectin on humans were unwarranted.

The clinical trials would pose a special challenge. Victims of river blindness rarely lived within hailing distance of modern medical facilities. Yet clinical trials needed to be held in such settings to ensure proper medical oversight of test subjects and collection of rigorous data.

Cooperation with WHO

Realizing that it would need help in this phase of the drug's development, Merck turned to the World Health Organization (WHO), the Geneva-based consortium of 166 member nations. Talks began in July 1982 to determine the most appropriate approach to the problem — from medical, political and commercial points of view.

There was a certain incongruity in Merck working closely with WHO. On some policy issues, the U.S. drug industry and WHO had had bitter disagreements. In the 1970s and 1980s, for example, multinational drug companies generally resisted WHO-backed standards for international drug marketing. They also denounced a WHO "essential drugs list" initiative designed to help Third World nations spend their limited resources on the most basic, widely needed drugs.

Notwithstanding such policy clashes, WHO had often collaborated with private drug companies to develop drugs for Third World nations, which typically did not have the marketplace clout, de-

spite their large populations, to stimulate such research. According to a 1988 WHO report, less than 4% of the global drug industry's research expenditures focused on diseases endemic to developing countries, even though 25% of the world's population lived in the Third World. In developing ivermectin, Merck and WHO complemented each other's needs quite well. Merck had a compound that might treat river blindness, and WHO had access to a global network of government health officials and scientists who could help run clinical trials.

Despite these common interests, the initial collaboration between WHO and Merck was at times strained. WHO was already deeply invested in a $26 million a year program to eliminate black flies through aerial larvacide spraying. WHO officials were initially concerned that this program might be abandoned if ivermectin looked promising. Merck officials reassured WHO that they would continue to support spraying as well as the development of the new drug.

WHO scientists also questioned the medical promise of ivermectin. "Initially, when Merck came to us and said it had this fancy new drug," recalled Dr. Duke, who then headed the WHO filariasis disease program, "my reaction was, 'We've got several drugs and they all incite violent reactions.'" There was skepticism that any drug could overcome the side-effects induced by these drugs, which required close medical supervision. Furthermore, WHO scientists believed that any new drug for river blindness must attack the adult parasite, not the microfilariae offspring, because only then could new generations of microfilariae be conclusively stopped.

Notwithstanding periodic clashes of scientific judgment and institutional cultures, a working collaboration evolved over time. Working with Professor Michel LaRiviere of the University of Paris, Dr. Aziz eventually decided to conduct the first human tests of ivermectin at the University of Dakar, Senegal, in February 1981. Merck supplied the drug, grants-in-aid for the studies, and the resources to apply for regulatory approval; WHO provided scientists and research facilities.

Dr. Aziz and his associates moved ahead with great caution, administering extremely small doses. One scientist recalled how Professor LaRiviere personally stayed up all night with test subjects to monitor for adverse reactions. By the end of 1981, the early results were promising: no adverse reactions, and a single, extremely small dose of ivermectin dramatically reduced microfilariae counts. A second study in Paris was conducted to confirm the Dakar results.

But the skeptics remained. In November 1982, Andre Rougemont, a highly respected scientist at the University of Geneva and former WHO official, wrote a stinging letter to *Lancet*, the prestigious British medical journal. Rougemont charged that ivermectin "brings no really new or interesting feature to the treatment of onchocerciasis," and accused Dr. Aziz and his colleagues of being "over-optimistic."

Prodded by such a public attack, Dr. Aziz redoubled his efforts to prove that ivermectin was indeed superior to the existing drug of choice, DEC. With the help of Drs. Bruce Greene, Hugh Taylor and other university scientists, Aziz plunged ahead with Phase II tests in Senegal, Mali, Ghana and Liberia in 1983-1984. The complex tests further confirmed the promise of ivermectin, and led to a subsequent set of trials in 1985. With mounting excitement, Dr. Aziz and his associates planned the final, Phase III tests the following year with 1,200 patients in Ghana and Liberia. These tests succeeded in establishing the optimum dosage level and in further confirming the drug's safety.

Application for Approval of Drug

By early 1987, nearly seven years after Merck executives had authorized the first clinical trials and nearly ten years after Dr. Campbell first proposed the research, the company had the clinical data needed to seek final regulatory approval for Mectizan. The materials were submitted to the French Directorate of Pharmacy and Drugs, whose judgments are widely accepted by Francophone African nations where onchocerciasis is a major public health program. Final approval came in October 1987.

It was a buoyant time at Merck, especially for Dr. Campbell, Dr. Aziz and Dr. Vagelos. It was also a critical turning point. Less than two months after the last regulatory hurdle had been cleared, Dr. Aziz died at age 58 of cancer. And Merck, which had spent nearly a decade developing a remarkable treatment for river blindness, could not simply bask in the glory of its triumph. Its achievement

would be of little consequence unless it could surmount another daunting challenge — delivering the new wonder drug to the people who needed it.

Selling the Drug

As early as 1982, after Dr. Aziz's first clinical trials proved successful, Merck knew that some unorthodox plan to distribute Mectizan would be needed. Early research confirmed what many had suspected: no conventional market for the drug was likely to materialize. The victims were too poor; they lived in utterly isolated locations; and they had no access to pharmacies or routine medical care.

From this point on, according to Dr. Vagelos, Merck moved forward in developing Mectizan with a blind faith that some third party, at some point in the future, would step forward with funding. The anticipated funders included foundations, international health or development organizations, Third World governments, and the U.S. Government.

When regulatory approval for Mectizan seemed certain in 1986, Dr. Vagelos, then Chairman and CEO, set out on a series of trips to Washington, D.C., searching for parties to buy and distribute Mectizan. His first stop was Deputy Secretary of State John Whitehead. Later he visited Donald Regan, then President Reagan's White House Chief of Staff. "Each of these people understood the potential importance of the drug, and they thought it must be distributed," recalled Dr. Vagelos. "And each of them referred the project to the U.S. Agency for International Development" — a foreign assistance agency that makes grants and loans for various Third World development projects.

Whitehead introduced Dr. Vagelos to M. Peter McPherson, the head of U.S. AID at the time. As Dr. Vagelos recalled, Whitehead said, " 'Now, Peter, we've got to do this program.' And McPherson looked up at him and said, 'Mr. Secretary, we don't have any money.' " Follow-up conversations yielded the same answer.

Dr. Vagelos was highly skeptical — and disappointed. The proposed distribution program would require an initial commitment of only $2 million a year, eventually growing to a sum of $20 million a year. It would be hard to imagine a more cost-effective way for the U.S. to curry goodwill with Third World nations.

Dr. Vagelos was disappointed by the U.S. Government's failure to come up with funding because he was spending so much time on the matter. He felt that it was beginning to detract from his normal responsibilities as Merck Chairman and CEO. "I was doing more for this than I'd done for any other drug," he said. "I mean, this [advocacy for a specific drug] is normally covered by our regulatory affairs and marketing people."

A series of visits to other potential funders — African health ministries, foundations, and others — were also to no avail. Merck even called upon noted international figures to advise them, but none of these efforts succeeded.

Should Merck Simply Give the Drug Away?

At this point, an impertinent, offhand suggestion made several years earlier resurfaced at Merck headquarters. In 1983 or 1984, Dr. Brian Duke had made a provocative suggestion — with no authorization from WHO — that Merck simply donate Mectizan outright. To his chagrin, Dr. Duke saw his casual remark to a reporter turn up in print in *South*, a Third World business magazine. The suggestion was not appreciated by Merck management who were still hoping to find third-party funding.

"That's not the way you do things in a commercial organization," Dr. Vagelos said in 1991. "You don't start out by thinking you're going to give something away....We hadn't gone through our process of determining what it would take [to distribute the drug]." When the search for third-party funding failed, however, Dr. Duke's suggestion began to sound much more plausible. Dr. Aziz had long favored such a solution. As Dr. Campbell recalled, "Aziz was constantly pushing the idea that Mectizan should be given away with pride."

The idea of a drug company donating an unlimited supply of a breakthrough drug to millions of people was unprecedented. It was a proposed commitment that would prompt any company to think long and hard. As senior executives debated the issue internally and consulted with peers in the drug industry, they wondered: Would this set a "bad precedent" — an expectation that future drugs for Third World diseases should also be donated, which could itself discourage companies

from conducting research on such diseases? Would Merck face intolerable legal liability if some Mectizan recipients suffered adverse reactions? Would the sheer cost of administering such a program and manufacturing the drug be prohibitive?