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CASES IN GLOBAL HEALTH DELIVERY

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Investing in Global Health: Botanical Extracts Ltd.

"Botanical Extracts is encouraging economic development through creating jobs and building skills, capacity, and a life around reducing the burden of malaria. It has to be done and it feels good to be contributing. The bitter part is the massive cost of doing this business."

—Patrick Henfrey, Chief Executive Officer of Botanical Extracts Ltd.

Looking back from 2008 on his involvement in the artemisinin industry, Patrick Henfrey, CEO of Botanical Extracts Ltd. (BE), had fond memories. BE began exploring the cultivation of *Artemisia* in 1994, just as the leaf was emerging as a potential marketable product for treating malaria. Henfrey had visited farms in rural areas of East Africa and watched farmers lead donkeys laden with bags of dried *Artemisia annua* ("*Artemisia*") leaf for sale. Artemisinin, the key anti-malarial compound extracted from *Artemisia,* was used to manufacture artemisinin-based combination therapies (ACTs), recently recognized as the most effective anti-malarial treatment. By 2008 BE had grown substantially and was in a position to meet a significant share of the market demand for pharmaceutical-grade artemisinin. Nonetheless, BE was extracting artemisinin well below its factory's capacity of approximately 40 tons per year, and the company's future was uncertain due to the industry's unpredictability. Facing demand shortfalls, heavy financial burdens, and unnerved farmers, the company leadership needed to move quickly to stabilize the business of artemisinin production.

Malaria

As reported in the 2008 World Malaria Report, there were an estimated 247 million cases of malaria and 805,000 malaria-related deaths in 2006.[1] People with underdeveloped or stressed immune systems, including children younger than five (especially malnourished children), pregnant women, and previously

Kileken ole-MoiYoi and William Rodriguez prepared this case for the purposes of classroom discussion rather than to illustrate either effective or ineffective health care delivery practice.

unexposed travelers or migrants to malarious regions were particularly susceptible to severe malaria. Of total malaria-induced mortality, 90% of deaths occurred in sub-Saharan Africa, and 85% were children. Nearly one in five child deaths in sub-Saharan Africa were due to malaria, with a child under five dying from malaria approximately every 40 seconds (see **Exhibit 1** for more on mortality in children under five).

Though most people will survive a bout with malaria, it is a life-threatening illness. Malaria causes flu-like symptoms, marked by fatigue, headache and muscle aches, with intermittent periods of high, wracking fevers, and profound malaise. If untreated, a subset of people progress to severe malaria, marked by severe anemia, kidney failure, coma, and eventually death. In malaria-endemic areas, repeated episodes can lead to partial immunity; older children and adults in endemic areas generally tolerate chronic malaria infection, although they still suffer from mild to moderate degrees of anemia.

Mosquitoes acquire immature forms of the malaria parasite during blood meals from infected humans. Malaria parasites then complete their reproductive stage in the mosquito's gut and begin to mature in the insect's salivary glands. After piercing human skin during a subsequent blood meal, the mosquito transfers the parasites into the human bloodstream. Only a few parasites need to be transmitted; these multiply rapidly in the human host until tens of billions of parasites are circulating in the blood and causing disease (see **Exhibit 2** for the mosquito life cycle). The larval stage of the mosquito life cycle requires relatively stagnant bodies of water, such as swamps, ponds, and irrigation ditches or potholes, discarded cans, and tires that fill with water after rains. As a result, malaria transmission typically increases exponentially after heavy rains when the mosquito population surges.

Historical Context

Malaria significantly altered the course of human development as populations migrated to avoid the deadly disease. It is likely that throughout human history, malaria has prevented millions of people from escaping poverty. The marshlands of the Roman Empire were an epicenter of malaria, and some historians believe that a malaria epidemic in 79 CE was partially responsible for the fall of Rome.[2] Numerous Roman officials linked the symptoms of malaria to the proximity of foul-smelling swamps and stagnant water. By the fourteenth century, foreign Catholic popes were barred from residing in Rome for fear that they would succumb to "Roman Fever," which became more commonly known as *mal'aria*, or "bad air."

Malaria purportedly led to the deaths of several Catholic popes, Alexander the Great, St. Augustine, Genghis Khan, Dante, the Roman Emperor Charles V, the Ethiopian Emperor Minas, and the British leader Oliver Cromwell. As of 1750, malaria was prevalent throughout Africa, Central and South America, almost all of Asia, and Europe extending as far north as England and Denmark. Much of North America was also malarious, stretching as far north as New England (see **Exhibit 3** for global distribution of malaria). Several United States presidents suffered bouts of malaria, including George Washington, James Monroe, Andrew Jackson, Abraham Lincoln, Ulysses S. Grant, Theodore Roosevelt, and John F. Kennedy. Only the latter two purportedly acquired the disease outside the United States.[3]

Long before the relationship between malaria and mosquitoes was understood, swamp drainage was known to be an effective strategy to reduce its impact. Some projects successfully controlled the local mosquito population and broke the transmission cycle, although swamp drainage became increasingly costly and environmentally destructive. A better understanding of the parasite's life cycle at the start of the twentieth century led to major efforts to eliminate malaria in Europe and North America.

Swiss chemist Paul Herman Müller's Nobel Prize-winning discovery of dichloro-diphenyl-trichloroethane (DDT), an insect neurotoxin, in 1939 revolutionized malaria control. DDT enabled the widespread spraying of mosquito breeding grounds and residential areas. Armed with this new tool and

with the drug chloroquine — the first widely available treatment for malaria — in 1955 the newly formed World Health Organization (WHO) launched its Malaria Eradication Program (MEP). The MEP was the first coordinated effort to eradicate malaria; it relied heavily on the spraying of DDT and treatment with chloroquine. Treatment of malaria broke the transmission cycle at a second point by removing the reservoir of infected humans who could otherwise infect mosquitoes with malaria parasites. Despite its stated goal of malaria eradication, WHO's efforts largely overlooked sub-Saharan Africa because of the region's underdeveloped health systems, its poor infrastructure, and the perceived difficulty of implementing treatment and prevention programs on the continent.

After some early successes — notably, the elimination of malaria from Europe, North America and Australia — DDT was removed from the MEP when it became apparent that mosquitoes had developed widespread resistance to the insecticide. Some studies had also linked DDT to toxic effects in animals and plants, and some also suggested chronic exposure to DDT could be toxic to humans.[4] Over time, WHO and its partner organizations concluded that, given DDT resistance, poverty, and poor health infrastructure in the world's persistently malarious regions, malaria eradication was not feasible. In 1969 efforts to eradicate malaria were largely abandoned, although the MEP never officially ended. Few alternative strategies to control malaria were proposed. Throughout the 1970s, funding for malaria interventions steadily decreased, and WHO dramatically scaled back its malaria control efforts. Consequently, in areas where the disease was only partially controlled, malaria incidence began to rise again, and resistance to chloroquine spread.

By 1990 every country in sub-Saharan Africa had reported chloroquine resistance (see **Exhibit 4** for map of chloroquine resistance). Unfortunately, because chloroquine was inexpensive, it remained both widely used and increasingly ineffective. Other drugs suffered similar fates. Sulfadoxine-pyrimethamine (SP; also known as Fansidar®) resistance was reported throughout Southeast Asia only five years after its introduction in the late 1970s.[5] Resistance to SP was also common in sub-Saharan Africa by the 1990s. As a result of chloroquine and SP resistance, malaria treatment failures became increasingly common. Meanwhile, no new drugs had been developed, and there were few effective alternatives to chloroquine and SP. Severe malaria could still be treated effectively with intravenous doses of quinine, but this was not always easy to acquire, had several serious side effects, and often required hospitalization (see **Exhibit 5** for malaria treatment options).

Since the 1970s, malaria had been largely restricted to low- and middle-income countries. In addition to the loss of life, the economies of the poorest countries suffered from the workforce's lost time and efficiency. In endemic regions, public and private organizations were forced to budget for lost productivity, inefficiency, and company expenditure on malaria treatment and prevention for employees. In some countries, low-income families spent up to one-third of their household income on malaria treatment and prevention, generally to the detriment of spending on education and food.[6] Some health economists purported that malaria cost sub-Saharan Africa an estimated 1.3% of its GDP, or approximately USD 12 billion each year.[7] A well publicized, but debated, study reported that Africa's GDP in 2000 would have been 32% higher — USD 300-400 billion — if malaria had been eliminated from the continent in the 1970s.[8]

Reinvigorated Efforts to Control Malaria

In 1998 WHO, the United Nations Children's Fund, the United Nations Development Program, and the World Bank decided to revive the concept of malaria control and launched the Roll Back Malaria Partnership (RBM). In its first decade, RBM made some progress in coordinating global institutions, but its overall success remained limited by the ineffective implementation and delivery of curative and preventive measures, particularly in sub-Saharan Africa. Death and disease from malaria remained high throughout endemic areas, and widespread resistance to anti-malarial drugs remained a significant obstacle.

By the end of 2008, several countries, including Ethiopia, Ghana, Rwanda, and Zambia, had shown progress in their efforts to control malaria. Rwanda and Ethiopia had successfully reduced malaria-induced under-five mortality by more than 50% largely due to funding from WHO and the Global Fund to Fight AIDS, TB and Malaria (Global Fund).[9] In addition to increased financing, programs were more comprehensive and better coordinated to deliver integrated malaria treatment and prevention strategies. These strategies included: indoor residual spraying of insecticides, treatment with artemisinin combination therapy (ACT), the distribution of insecticide-treated bed nets, and, more recently, long-lasting insecticidal bed nets, and intermittent presumptive therapy for malaria in pregnancy. Rapid diagnostic tests were introduced to better inform the use of ACTs and to improve accuracy in reporting the incidence of malaria. Some studies indicated that the introduction of rapid diagnostics alone decreased the reported incidence of malaria; previously all childhood fevers were assumed to be malarious and were treated and reported as such. Accounting for these results, the RBM short- and long-term objectives were updated in the 2008 Global Malaria Action Plan (see **Exhibit 6** for Global Malaria Action Plan objectives).

Artemisinin-Based Combination Therapy

History of Artemisia and Artemisinin

The emergence of resistance to inexpensive treatments such as chloroquine and, later, SP necessitated the development of new anti-malarial medications that could offer a greater barrier to drug resistance.

During the Vietnam War, American bombing campaigns had cut off North Vietnam from South Vietnam. The only link between the two was a corridor through dense and mosquito-infested jungle known as the Ho Chi Minh Trail. The trail functioned as a crucial passageway for the transfer of North Vietnamese troops, ammunition, communications, and supplies. However, malaria posed a great threat to those who traveled the Ho Chi Minh Trail. Despite daily malaria prophylaxis, as many as 10% of all those who walked and rode the trail succumbed to the disease.[10] In response, North Vietnam's leader Ho Chi Minh contacted Chairman Mao Zedong of the Communist Party of China and asked for help with a cure to the disease that was killing thousands of his forces and leaving others incapacitated for days or weeks.

In May 1967 the Chinese established Project 523 with the goal to develop an effective anti-malarial from traditional Chinese medicines.[10] *Artemisia annua*, also known as 'Sweet Annie' or Wormwood, was an annual herb native to China and parts of Southeast Asia, where it was known locally as *qinghao*. *Qinghao* had been used in China to treat chills and fevers as early as 168 BCE.[11] Wormwood extract had long been brewed as a tea to treat intermittent fever and achy joints. By the late 1960s Professor Zhou Yiqing and his team of scientists from the Chinese Academy of Military Medical Sciences confirmed that *Artemisia annua* was an effective remedy for malaria. They isolated the active compound and named it artemisinin.

Professor Zhou and his team were well aware of the problem of drug resistance and the proven strategy of combining two drugs to delay the onset of resistance to any one drug. They isolated four derivatives of artemisinin (dihydroartemisinin, artesunate, arteether, and artemether), all of which proved effective against malaria and would later become the active pharmaceutical ingredients of various artemisinin-based combination therapies (ACTs). In consultation with the London School of Hygiene and Tropical Medicine, the Walter Reed Army Institute of Research, and WHO, the Chinese scientists developed the first ACT by combining artemether with lumefantrine, an unrelated synthetic anti-malarial which they had developed in the 1970s, which was similar to mefloquine, quinine, and halofantrine.[12] The artemether lumefantrine combination (AL) was later developed into a fixed-dose combination (both compounds

combined in a single tablet). Professor Zhou[1] believed that they "had a great drug for treating malaria in China, and [his] hope was to make it available to all the people who were suffering from malaria. ... [he] wanted to ease their suffering and give them new opportunity."[11] With this in mind, in the early 1990s the Chinese granted Ciba-Geigy, later Novartis AG, rights to evaluate the AL combination. After confirming the efficacy of AL in two clinical trials in China, Ciba-Geigy and the Chinese partners signed a licensing pact for joint development, testing, and manufacture of the AL combination.

Artemisinin Supply Chain: Cultivation and Extraction

Among high-volume medications, ACTs have remained one of the few for which the active pharmaceutical ingredient is still extracted directly from a plant rather than synthesized chemically. This dependence on agricultural production and processing created an extremely complex, labor-intensive, and time-consuming supply chain that required expert management in cultivation, chemical extraction, and manufacturing, as well as a keen sense and anticipation of market behavior.

Artemisia grew in temperate and high-altitude tropical climates. It thrived in relatively fertile soil but required periodic rainfall, especially during its first seven weeks as a seedling. *Artemisia* was largely resilient to disease and insect infestation, and it did not require fenced in plots because animals generally did not eat it. Full growth of the plant, however, required six to eight months; healthy *Artemisia* grew up to two meters tall and was green and lush with a pleasant scent (see **Exhibit 7** for an image of the *Artemisia* plant). During harvest, the plants were typically cut at the base and laid out in the fields to dry. At this stage, it was crucial that drying plants did not get wet because the middle and upper leaves with the highest concentrations of artemisinin could rot, rendering them useless for extraction. Once plants were cut and dried in the fields, farmers separated the dried leaves from the stalks and collected the leaves in sacks. The sacks were weighed, and the dried raw material was delivered to *Artemisia* intake centers where it was assessed for artemisinin content. Once accessed at intake facilities, the raw material was transferred to extraction sites, where it was soaked in various solvents to extract the artemisinin from the dried *Artemisia* leaf and separate it from various impurities, such as oils and waxes. The impurities had to be removed because they could negatively affect both the efficacy and the shelf life of ACTs. The solvent was then processed through carbon filtration to isolate the artemisinin. Solvents used in the extraction process were generally reused to minimize waste and costs. Despite these efforts, the various methods of artemisinin extraction and purification were uniformly expensive and time consuming, and artemisinin yields could vary significantly.

Even more challenging, was the length of production. From the time *Artemisia* seeds were planted in nurseries to when the finished co-formulated ACT was packaged and shipped, production of an ACT like AL required at least 14 months (see **Exhibit 8** for production timeline). The supply chain could be further complicated by the geographical distribution of the various production stages: *Artemisia* cultivation, artemisinin extraction, derivation of the final purified active pharmaceutical ingredients, co-formulation with a second compound, and final ACT manufacture, packaging, and delivery (see **Exhibit 9** for a geographic supply chain of Novartis' AL combination, Coartem®).

Most *Artemisia* was grown in China, Vietnam, and East Africa. In all three regions, smallholder farmers, as opposed to large commercial cultivators, were responsible for a significant proportion of *Artemisia* cultivation. In East Africa, to ensure compliance with Good Agricultural Practices, farmers typically received selectively bred, high-artemisinin-yielding *Artemisia* seedlings directly from extractors before each planting season. At the end of the planting season, each farmer's crop was weighed and assessed for quality. In East Africa, usable raw material had to contain a minimum of 0.8% artemisinin.

[1] In 2009 the European Commission awarded Professor Zhou Yiqing "Inventor of the Year" in the non-European category for his work on developing the AL combination.

Artemisinin-Based Combination Therapies and Monotherapies

As Novartis and its Chinese partners were completing the clinical development of AL, the effectiveness of ACT against malaria was becoming increasingly clear. In 2000 at a WHO meeting convened to review anti-malarial drugs, the RBM advocated strongly in favor of ACTs and the concept of combination drugs. As a result, in 2001 WHO conducted an extensive evaluation of the effectiveness of ACTs in sub-Saharan Africa.[13] The drugs proved remarkably effective, especially AL, with cure rates ranging from 94% to 100%, even against chloroquine- and SP-resistant strains.[14] Additional studies demonstrated the impact ACT treatment could have on malaria control programs. The combination of indoor insecticide spraying with DDT and treatment with Coartem® (Novartis' trade name for AL) reduced malaria incidence in KwaZulu Natal, South Africa by 86% and decreased hospital admissions by 82% (see **Exhibit 10** for notified malaria cases in KwaZulu Natal over time).[15]

By April 2002 WHO had recommended ACTs as the preferred treatment in malaria-endemic areas where drug resistance was widespread.[16] WHO recommended specifically that malaria be treated only with a combination of two or more drugs, one of which was artemisinin-based: AL, artesunate/mefloquine, artesunate/sulfadoxine-pyrimethamine, or artesunate/amodiaquine. When using most donor funds, national malaria control programs could only purchase ACTs from manufacturers who had been approved by WHO's stringent pre-qualification process. By the end of 2008, however, there were very few pre-qualified ACT manufacturers and only two producing a fixed-dose combination ACT — Novartis and Sanofi-Aventis.

ACTs, including AL, were also the most expensive anti-malarials on the market. As a result, price-conscious national programs chose not to adopt AL immediately as first-line treatment in their national malaria control programs. Attracted by the high prices of ACTs, however, and the tremendous promise of artemisinin-based therapy, several small manufacturers began producing artemisinin "monotherapies"— drugs that contained a single artemisinin derivative and were neither co-formulated nor co-blistered with a second anti-malarial. Artemisinin-based monotherapies were effective and less expensive than ACTs, but they significantly increased the risk that malaria parasites would develop resistance to all artemisinin-based anti-malarials, including ACTs. As a result, WHO called publicly for all pharmaceutical companies to cease the manufacture of artemisinin-based monotherapies. This was an unprecedented intervention by WHO in the pharmaceutical marketplace and showed a new level of commitment to ensure the long-term effectiveness of ACTs. Despite these efforts, in late 2008 evidence of delays in parasite clearance after treatment with artemisinin emerged from the Thai-Cambodian border, where artemisinin-based monotherapies were widely available.[17] A ban on artemisinin monotherapies was expected to be enacted in the region by mid-2009, although it would likely be very difficult to enforce.

Novartis and Coartem®

With the increasing awareness of the importance of AL and other ACTs to global malaria control, Novartis faced critical decisions. The company formed in 1996 following the merger of two leading Swiss chemical companies, Ciba-Geigy and Sandoz Laboratories. Following the merger, Novartis quickly became one of the world's largest and fastest growing pharmaceutical companies. Its portfolio included leading drugs for heart disease, arthritis, asthma, cancer, hypertension, skin conditions, and infectious diseases. The Novartis Group's business soon achieved 8% annual growth with net annual sales of nearly USD 40 billion and annual net profit of USD 12 billion. Novartis' annual research and development investments in 2007 amounted to approximately USD 6 billion (see **Exhibit 11** for Novartis financial highlights).

In May 2001 Novartis entered into an agreement with WHO to add Coartem® to WHO's Essential Medicines List.[2] At the time, the recently established Millennium Development Goals[3] created extreme downward pressure on the pricing policy for global health commodities like anti-malarials. Novartis' initial agreement with WHO stipulated that Coartem® be supplied to the public sector in developing countries on an at-cost basis and be distributed by purchasers free of charge in public-sector facilities. With assisted financing from the Global Fund, in September 2006 Novartis reduced the average public-sector price of Coartem® from USD 1.57 to USD 1.00. Following improvements in production efficiency, outsourcing active pharmaceutical ingredient production, prices dropped again in 2008 to an average of USD 0.76.

Despite Novartis' initial pricing, many national malaria programs were hesitant to make the AL combination their preferred malaria treatment. Even at the public sector price of USD 1.00, AL remained expensive relative to other anti-malarial drugs like chloroquine and SP, which, though less effective, cost as little as USD 0.30 (see **Exhibit 12** for antimalarial private sector prices). Particularly in areas of high drug resistance and high transmission, health planners were forced to balance the costs of AL and other ACTs against their efficacy (see **Exhibit 13** for ACT prices).[18] As ACT prices dropped further, the number of countries adopting them as first-line treatment increased.

During 2007 Novartis expanded its Access-to-Medicine project to reach 66 million patients, of whom 65 million received Coartem®.[19] Coartem® became Novartis's largest product in terms of patients reached; given its low price, however, it accounted for only USD 190 million of the Access-to-Medicine Project's total value of USD 937 million (see **Exhibit 14** for Novartis Access-to-Medicine Projects).

From a production perspective, Novartis and other ACT manufacturers initially relied heavily on WHO's non-binding demand forecasts. Although WHO recommended ACTs in 2002, its forecasts anticipated that orders for ACTs would not increase significantly in the first few years of availability. This was due to the time required for countries to change their malaria treatment policies, allocate funds, and tender bids. At that point, however, WHO expected demand to grow rapidly, especially in the public sector (see **Exhibit 15** for ACT forecast). By 2005 anticipated demand was as high as 60 million annual doses.

In 2002, however, the global supply of artemisinin was extremely limited. If forecasts were to be believed, to meet the expected surge in demand a considerable increase in the cultivation of *Artemisia*, extraction of artemisinin, and manufacture of ACTs would be needed to avoid a massive global shortage. Given the 14-month production cycle, time was short, and there was significant uncertainty. The forecasted surge in demand resulted in an exponential increase in the market price of artemisinin, incentivising farmers and extractors to rapidly increase production.

ACT manufacturers found it difficult to accurately determine how many ACTs to manufacture. Adding to the industry's complexity, the risks — financial, reputational, and poor health outcomes — of failing to deliver sufficient quantities of ACTs to the people in need were daunting.

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[2] Essential medicines are "those that satisfy the priority health care needs of the population." The list guides the medicine portfolios for governments and the major public and private health care organizations around the world. Medications are evaluated based on their public health relevance, efficacy, safety, and comparative cost-effectiveness.

[3] The goals were to: eradicate extreme poverty and hunger; achieve universal primary education; promote gender equality and empower women; reduce child mortality; improve maternal health; combat HIV/AIDS, malaria and other diseases; ensure environmental sustainability; and develop a Global Partnership for Development.

Botanical Extracts, Ltd.

Botanical Extracts, Ltd. (BE) was an early mover in artemisinin extraction in Africa. The founders of BE began by producing plant extracts, such as essential oils and perfumes, in Kenya in the late 1980s. BE leaders first heard about *Artemisia* in the early 1990s and recognized its potential as a profitable product that also could help relieve the local burden of malaria. As a result of their experience with plant-derived products, they carried out preliminary studies on *Artemisia* cultivation in the highlands of East Africa. In 1994 they planted small plots of *Artemisia* in Tanzania to assess the commercial potential of the cultivated plant. Two years later, BE leaders established African Artemisia Ltd., which would become a subsidiary of BE dedicated solely to the commercial production of *Artemisia* for artemisinin extraction. The African Artemisia Ltd. management team spent the late 1990s carrying out agricultural experiments to develop resilient and high-artemisinin-yielding plants well suited to East African growing conditions. The founders hoped that these early efforts would enable them to play a significant role in the artemisinin market if ACTs were to become first-line treatment for malaria. Although they were aware of some uncertainty in the industry, they were drawn to it by their entrepreneurial nature and the potential to generate profits from a product with high social and economic benefits to the region that they called home.

Once WHO reached non-binding forecast agreements with Novartis and recommended ACTs for the treatment of chloroquine- and SP-resistant malaria, it expected that the demand for artemisinin would increase significantly. The perceived global scarcity of artemisinin and the subsequent increase in price motivated BE to scale up production of artemisinin in East Africa. In 2002 BE processed 250 tons of *Artemisia*, and its scientists and engineers spent the next two years refining their extraction process in an effort to improve quality and reduce operating costs. As a result of this work, in 2004 BE formed East African Botanicals Ltd. in Kenya to manage the agricultural aspects of *Artemisia* production. One year later, East African Botanicals Uganda was formed to manage both the production of *Artemisia* and the extraction of crude artemisinin.

How well and how quickly *Artemisia* farming and artemisinin extraction would scale was one of the main unknowns in WHO's ACT demand forecasts. Novartis, which initially sourced its artemisinin exclusively from China, wanted to diversify artemisinin extraction to other regions of the world to both mitigate risk and cut costs. Given BE's experience in farming and processing *Artemisia*, WHO and Novartis quickly recognized that BE might be in an excellent position to supply artemisinin. In 2004 BE signed a preliminary supply agreement with Novartis for artemisinin production, and in 2005 it made its first sale to Novartis. Although BE had originally intended to produce 10 tons of artemisinin annually, market demand was poised to grow quickly, and Novartis felt that it required much larger volumes to fill orders for the final ACTs. Novartis supported the development of a new *Artemisia* processing facility in Athi River, Kenya, known as Botanical Extracts Export Processing Zone, Ltd. (BEEPZ) to meet the anticipated higher volumes. Without assistance from Novartis, the up-front capital investment for high-end purification equipment was prohibitive for BE, which had been limited to producing crude artemisinin in Kenya and Uganda, and exporting it to Europe for purification to pharmaceutical-grade artemisinin.

In 2007 operations began at BEEPZ, and BE made its first shipments of pharmaceutical-grade artemisinin to Novartis. At this point, BE was able to purchase raw material from farmers in Kenya, Tanzania, and Uganda, produce crude artemisinin at East African Botanicals Uganda, and produce pharmaceutical-grade artemisinin at the BEEPZ facility in Athi River, Kenya. Between 2006 and 2007, BE's artemisinin production grew from 1.45 million to 22 million treatment equivalents, the vast majority of which was purchased by Novartis to manufacture Coartem®.

Key Considerations for Botanical Extracts, Ltd.

Uncertainty in the ACT Industry

Despite having built the extraction capacity for 120 million ACT treatments — enough artemisinin to meet a significant portion of the worldwide demand in 2007 — BE held only an estimated 20% market share. Large Chinese and Vietnamese producers continued to supply a purported 70% of the artemisinin market; small suppliers held the remaining 10%.[20]

The artemisinin industry was undergoing dramatic shifts concurrent with BE's major investment to expand its production capacity. Due to considerable delays in national adoption of new malaria treatment policies and logistical challenges beyond what WHO anticipated, actual ACT demand in 2004 and 2005 was well below what was forecast. Meanwhile, spurred by the forecasts, prices for artemisinin futures had soared to artificially high levels and had created incentives for thousands of farmers and a large number of extractors around the world to significantly increase *Artemisia* cultivation and artemisinin production. When the forecast demand failed to materialize, the massive oversupply of artemisinin caused the market price to collapse — from its highest level of USD 1,100 per kilogram to its lowest level of USD 155 per kilogram in less than two years. Since then it had somewhat stabilized to roughly USD 300 per kilogram. As a result of the price collapse, many smaller companies throughout the ACT supply chain were suddenly in financial distress and collapsed. WHO was forced to reduce its forecast of orders for ACTs (see **Exhibit 16** for change in orders and price).[4]

The difficulties involved in forecasting were particularly problematic given the long lead time for production. ACTs were unlike most pharmaceutical products because their complex supply chain was dependent on agricultural cultivation. The ACT market initially matured more slowly than anticipated, and the highly volatile market price resulted in a cyclical market for which forecasting demand was complicated. BE and its investors had assumed significant financial risks to increase manufacturing capacity, and like the other extractors in the industry, BE found itself in a potentially calamitous position. Although BE had the capacity to supply a significant percentage of the global demand for artemisinin, it was forced to cut back production considerably. It became harder for BE to secure financing to complete the construction of the BEEPZ factory and improve its efficiency to better compete with Asia-based suppliers. Absent its contractual agreements with ACT manufacturers, BE would likely have been unable to sell its pharmaceutical-grade artemisinin and may not have survived the devaluation of artemisinin. However, ACT manufacturers, particularly Novartis, absorbed much of the financial loss associated with the collapse in artemisinin's market price.

Although the eventual rise in uptake of ACTs brought the market price of artemisinin back up to roughly USD 300 per kilogram by the end of 2008, the early instability and price collapse had already created significant hardship at the bottom of the supply chain. Many smallholder farmers had planted *Artemisia* on the promise of high prices, only to see most of their potential profits disappear. Extractors such as BE had invested heavily in increasing capacity, creating relationships with stakeholders and training farmers to ensure that it could meet supply agreements with ACT manufacturers. Given the market volatility, most companies were either unable to continue or reconsidered embarking on artemisinin extraction. Shielded somewhat by its contracts, BE was actually able to continue its plans to build the BEEPZ factory in the midst of the market shifts between 2005 and 2007. The BE leadership viewed its venture as a

[4] For a teaching case on Novartis and Coartem®, see Prof. Debora Spar and Brian Delacey, "The Coartem® Challenge," HBS No. N1-706-037 (Boston: Harvard Business Publishing, 2006).

long-term investment that could only pay itself off after the market matured past the initial instability. ACT manufacturers, particularly Novartis, bore some of the significant risk associated with BE's capacity expansion. After concluding the negotiations, Mr. Patrick Henfrey, CEO of BE, remarked:

> Novartis has proven to be our most important partner as we move to large-scale production of artemisinin in East Africa. … By placing firm orders for extracted artemisinin, providing financial support for infrastructure improvements, and delivering technical support and know-how, Novartis has made a major contribution to creating a sustainable market for this key natural ingredient. As a result, BE will end up being a significant manufacturer of artemisinin in East Africa.[21]

Without initial guaranteed purchasing and price agreements, BE's manufacture of pharmaceutical-grade artemisinin would have been too risky a business venture for such a small company in a developing industry. However, BE still faced challenges closing out its financing and navigating the market turbulence.

Competition

Even with Novartis' support, the artemisinin glut and resultant price collapse placed relatively small, new active pharmaceutical ingredient producers like BE in financial difficulty, particularly given their competition with larger, established artemisinin extractors in China and Vietnam. Despite BE's early market entry during the time of high demand forecasts, the manufacturers in China and Vietnam had assumed a dominant market position due to their head start of several years, and had established cost-effective extraction technology and raw material supply chains. The extractors in China and Vietnam were not eager to share their techniques or exchange information, and BE had to develop an entirely new supply chain for raw materials in East Africa. It took several years and significant investment for BE to establish supply networks, scale up capacity, and improve efficiency and quality. As of May 2008, BE was still having difficulties in achieving its target extraction yield and in ensuring consistent high artemisinin quality.

In 2003, following the rapid artemisinin price increase, other companies in India, Nigeria, Mozambique, Malawi, Zambia, Ghana, Rwanda, South Africa, Madagascar, and Senegal began exploring the potential cultivation of *Artemisia* and extraction of artemisinin. It was not clear how many of these companies lost interest or ceased operations in the context of price volatility and high start-up costs for extracting and purifying artemisinin. However, after the market price collapsed, several companies dumped their excess artemisinin inventory on the market and left the industry. This reinforced the low prices and exerted additional financial pressure on the remaining extractors and ACT manufacturers. By May 2008, artemisinin was manufactured in China, Vietnam, Kenya, Uganda, India, and Madagascar, although the latter two manufacturers were in an exploratory phase and not actively marketing their artemisinin.

For companies like BE that were heavily invested in the industry, establishing and enforcing universal, stringent quality standards for ACTs was paramount. Since an industry-wide minimum standard for the amount of artemisinin needed for anti-malarials had not been established and enforced, some ACT manufacturers unilaterally reduced the artemisinin concentrations in their tablets, presumably to cut costs. WHO-qualified ACT manufacturers and artemisinin extractors advocated for universal and clear minimum quality standards for ACTs along with their enforcement. Additionally, counterfeit ACTs appeared, often containing little or no artemisinin; instead, they contained antipyretics, ineffective anti-malarials, or antibiotics, which were either ineffective or temporarily alleviated the symptoms of malaria without treating the disease.[22]

Raw Material Supply Chain Management

Unlike Novartis, one of the world's largest pharmaceutical companies, BE had few resources in reserve to manage risk, sit on inventory, and ride out major market shifts. Its supply chain was particularly complicated due to the volatility of *Artemisia* cultivation and artemisinin extraction.

During its early stages of development and expansion, BE faced two strategies for the production of raw material:

1. Take ownership of the cultivation, controlling farms and farmers, and developing standardized techniques to ensure good agricultural practices and consistent quality
2. Contract cultivation to farmers, who would assume responsibility for all matters related to cultivating a healthy *Artemisia* crop and drying the raw material

When Novartis first signed supply agreements with BE, there had been much talk about promoting local economic development. Malaria disproportionately affected Africa, so it seemed logical that African companies should be involved in addressing the problem. Although both business models would expand local economic opportunity and create several new high-skilled jobs, outsourcing *Artemisia* farming posed greater upfront challenges due to the logistical complexity, lack of consistency in the quality of raw material, and unpredictable supply. The primary benefits of cultivating the crop itself were that BE would be able to manage inputs (such as adequate irrigation) and better regulate production timing and quality. BE initially pursued a 50/50 model, doing half of the cultivation itself and working with contract farmers for the other half. Although it proved cheaper to cultivate *Artemisia* itself, BE initially lacked the resources to do so at the desired scale. The most significant constraint on contract farming was ensuring adequate crop irrigation, which led BE to select contract farmers in growing regions with sufficient precipitation.

When the price of artemisinin fell and questions arose about BE's financial stability, BE's ability to manage its raw material supply chain became even more challenging. Recruitment and retention of *Artemisia* farmers became a major challenge. In 2007 and 2008, Kenyan and Tanzanian farmers began voicing concerns about insufficient training and technical support from BE and its subsidiaries; a lack of compensation for harvested *Artemisia* that was destroyed by rain while drying in fields; delayed payments; and differing opinions on quality. Some farmers began claiming that the unfavorable artemisinin market conditions made it more profitable and less risky to grow potatoes.

Financing Operations

Establishing a raw material extraction, processing, and purification factory for pharmaceutical-grade artemisinin in East Africa was a costly venture. Although the Novartis supply agreement facilitated the sale of BE's artemisinin, high capital costs for manufacturing equipment and high financing costs remained significant obstacles to BE's financial solvency.

When Henfrey and his partners founded BE, it had been significantly undercapitalized. The favorable demand forecasts and artemisinin's high market price led them to believe that they would be able to raise funds, increase their manufacturing capacity, and repay their loans relatively quickly. However, it took BE much longer than anticipated to complete and commission the factory and to develop the technical capabilities and infrastructure required to increase production capacity and efficiency. The sharp downturn in the market and considerable shortfall in anticipated demand placed BE in the unenviable position of maintaining a factory with excess capacity. There were few buffers in the artemisinin industry, and excess capacity was difficult to carry. Henfrey believed that "unless there [was] a stabilized pricing structure between a grower, an extractor, a drug manufacturer, and an end buyer, this would remain an extremely cyclical business."

In other emerging sectors of African economies, businesses involved in social enterprises had been calling for increased access to "patient capital," or flexible financing. Henfrey believed that patient capital would allow companies similar to BE "to develop and build a foundation of skills and mental rigor in what would become an upward spiral of economic development" and that cyclical industries like his needed strong and stable companies with financing that enabled the development of products and systems to "ride out storms."

Interaction with Novartis

Novartis was an unusual business partner for BE in that it absorbed many of the industry losses that might otherwise have fallen on BE. Flexible funding from Novartis sustained BE during the crippling price fluctuations and enabled BE to continue producing pharmaceutical-grade artemisinin. From the beginning Novartis was proactive and took on significant risks; Henfrey noted, "There was a lot of talk, but Novartis was one of the few organizations that made very significant commitments." Between 2004 and 2005, based on WHO forecasts, Novartis had increased production of Coartem® by 725%, from 4 million to 33 million treatments. Due to the slow maturation of ACT demand, Novartis sold only 9 million treatments, resulting in significant losses that threatened to derail the global push for ACTs (see **Exhibit 17** for Coartem® scale-up). However, Novartis absorbed the majority of the losses and maintained its commitment to the Coartem® program, to BE, and to its other artemisinin suppliers. Henfrey reflected:

> It was only the goodwill of a few organizations — the Acumen Fund,[5] Cordaid, and GTZ [German Agency for Technical Cooperation] along with Novartis — and the cast-iron determination of some individuals that kept BE alive. The factory should have died; by normal measure it should have died a long time ago.[6] It would have been a casualty of that over-hyped market expectation and BE's desire to do something of significance. We should have been more measured and acted much more calmly. People underestimated the time it takes change to happen— even if it is very important change. Even when things are of life and death significance, change does not happen overnight, and when you try to plan any kind of transition, you must understand the human elements that are involved to allow that to happen. This business is like a tanker, not a speedboat.

Public-Private Partnerships

As BE was framing its investment in artemisinin production in East Africa, the marketplace was undergoing an even more fundamental change on a broader scale. In their attempt to help countries achieve the objectives set forth by the Millennium Development Goals, The Global Fund, the World Bank, private foundations, and other bilateral and multilateral institutions had all significantly increased the amount of funding made available to improve health care delivery in resource-limited settings. However, it was very difficult for a private business involved in the manufacture of health care commodities to access this funding directly. Despite Novartis' memorandum of understanding with WHO, its Malaria Initiative operated at a loss, and was viewed as a corporate social responsibility project in the Access-to-Medicine Project. Henfrey often wondered whether it would have been more realistic to register BE as a not-for-profit company and increase its chances of benefiting directly from donor funds.

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[5] The Acumen Fund is a non-profit global venture fund that focuses on alleviating global poverty through enhancing local economic development. For a teaching case on Acumen Fund, see Alnoor Ebrahim and V. Katsuri Rangan, "Acumen Fund: Measurement in Venture Philanthropy," HBS No. 9-310-011 (Boston: Harvard Business Publishing, 2009).

[6] In April 2008, the Aga Khan Foundation, Industrial Promotion Services, and the International Finance Corporation joined BE as equity partners to further stabilize its financing.

While both BE and Novartis endured difficulties in the industry, BE found itself in a long period of financial distress, barely able to pay the farmers and cover its own expenses. As appealing as the public-private partnership between Novartis, WHO, and the Global Fund appeared on paper, potentially conflicting incentives, priorities, resources, and responsibilities created an environment of disparate risk allocation. One of the most significant challenges to the industry was the strong downward pressure on price, which was intensified by the various actors' incentives within the partnership. The private, for-profit actors faced significant hurdles to accommodate this downward pressure and maintain financial security, particularly the farmers and small companies involved with the cultivation of *Artemisia* and extraction of artemisinin, who could not sustain losses. Henfrey remarked:

> When you talk about the chain of structuring public-private partnerships and trying to use some combination of commercial business and not-for-profit money, anybody who is actually trying to play in that pool, or trying to shape it, needs to take the time to be very aware of those businesses. They are different worlds with different pressures.

The nature and strength of public-private partnerships was such that they brought groups together that did not typically collaborate with one another. The public sector was a necessary mediator between for-profit actors and end-users who desperately needed the products, but could not afford them. However, not-for-profit and public buyers — acting essentially as market brokers — operated with different incentives from the companies themselves. Amidst significant downward pressure on the price of artemisinin and ACTs, there was broker pressure to increase rapidly the quantity of treatments available under a fixed amount of funding and limited support for the required capital investments and risk capital. This put pressure on the for-profit actors to operate as not-for-profit entities — in the case of Novartis, to offer Coartem® below cost to the public sector, and initially to operate at a loss. How was this sustainable?

BE Restructuring

In May 2008, BE was restructured, with the involvement of the International Finance Corporation and the Industrial Promotion Services to enhance its financial stability. Its primary objective remained to produce pharmaceutical-grade artemisinin at reduced production costs and potentially to diversify into a range of other related products.[23]

Despite the volatile and turbulent path, BE had a significant impact on the East African economy. In addition to owning and operating the BEEPZ in Athi River, Kenya, BE wholly owned three other subsidiaries that produced *Artemisia* according to international Good Agricultural Practice guidelines: East African Botanicals in Nakuru, Kenya; African *Artemisia* Ltd. in Arusha, Tanzania; and East African Botanicals Uganda Ltd. in Kabale, Uganda, which also extracted crude artemisinin (see **Exhibit 18** for timeline of BE activities).

Between 2005 and 2008, BE more than doubled its land under cultivation from 1,660 hectares (4,100 acres) to roughly 3,400 hectares (8,400 acres) and contracted roughly 6,000 farmers in Kenya, Tanzania, and Uganda to grow and harvest *Artemisia*. The four subsidiaries had more than 250 full-time employees. BE's introduction of a new commercial crop and associated farmer training workshops created new technical and agronomical skills, provided farmers with indirect access to international markets, and the potential to increase their income. Farmers were supplied with high-yield hybrid seedlings, and a team of agricultural advisors provided technical support and ensured that Good Agricultural Practice guidelines were followed. In addition to working with thousands of contracted smallholder farmers in East Africa, BE also cultivated *Artemisia* on its subsidiary commercial plantations: two in Kenya and one in Uganda. In all, BE had invested more than USD 20 million in the economies of Kenya, Tanzania, and Uganda.

Moving Forward

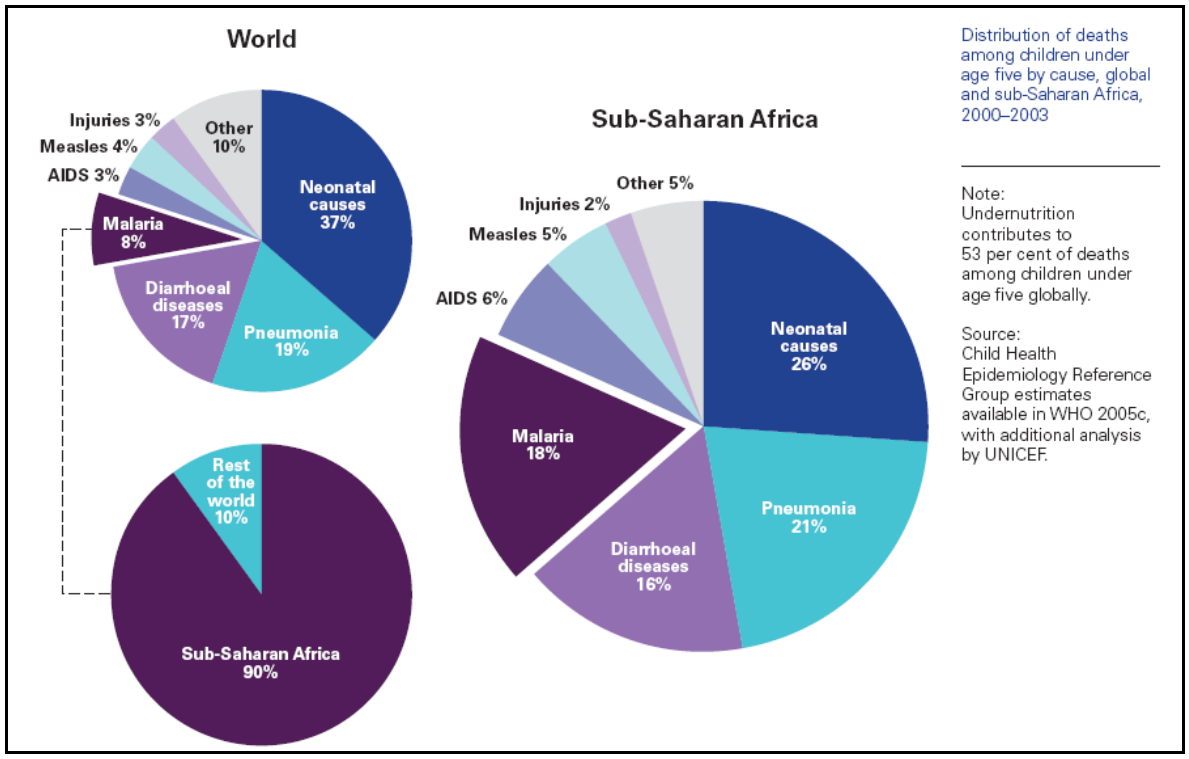
Botanical Extract's leaders were entrepreneurs, but even they pondered whether they had made the right move by investing in the ACT industry at such an early stage with rapid scale-up. It was very difficult for a small company to take on the considerable start-up costs and risks in the context of an underperforming and unpredictable market. When the forecasts for 2005 failed to materialize, the shortfall in demand resulted in significant losses for artemisinin manufacturers who were directly accountable to farmers. Henfrey remarked, "BE was not a big corporation, and this was a challenge for a big company, not for a few people."

Despite the challenges in the industry, the company remained committed to the multiple social benefits of developing artemisinin extraction capabilities in East Africa. Henfrey believed that once the prices stabilized, Africa would catch up quickly with the Asian manufacturers. However, in such a cyclical market, he believed that it would be difficult for companies that relied solely on producing artemisinin to survive. Henfrey was considering diversifying his manufacturing portfolio to include not only the active pharmaceutical ingredient derivatives of artemisinin, but also other plant extracts. Additionally, two research institutes were pursuing the production of semi-synthetic and artemisinin-mimicking compounds intended to supplement the supply of plant-derived artemisinin.[24] Although this would be unlikely to occur before 2012, Henfrey believed that if synthetic artemisinin became available, BE needed to be in a position that it could remain a profitable and competitive business with a diverse product portfolio. There was also a need to increase investment in the company to further improve the recovery rate of artemisinin from the crude extract and to ensure consistency and quality of the end-product.

Although the price fluctuations and questionable quality standards across the artemisinin market created significant challenges for BE, Henfrey was equally concerned with how the principal actors in the industry could have a lasting impact in controlling malaria and ensuring that the life-saving medications actually reached those in need. Although these concerns went beyond the capabilities of BE, the future of the business depended on the ability of people, particularly in sub-Saharan Africa, to access life-saving ACTs.

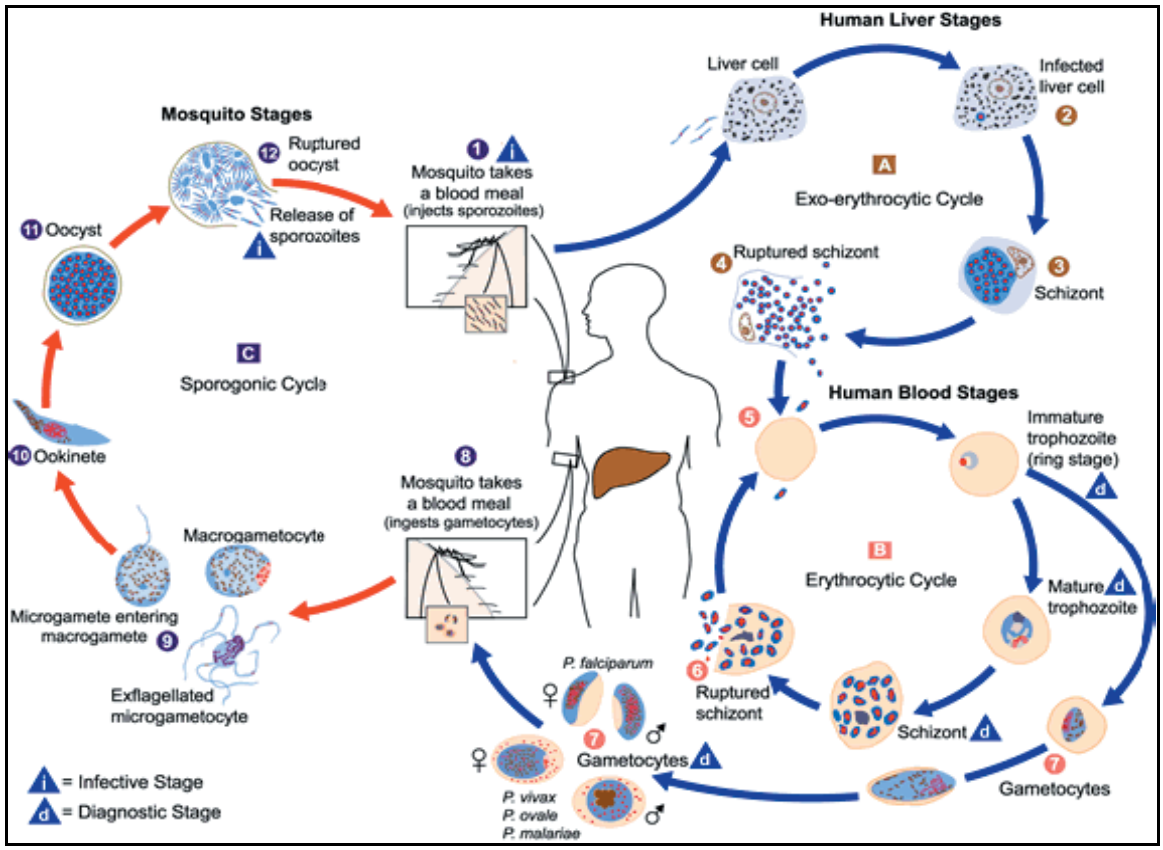
With the help of its financial partners and advisors, and through the determination of its managers, BE had endured the market fluctuations and unrealized forecasts. Henfrey and the BE management team had learned quite a bit from the experience; however, the costly endeavor nearly caused the demise of the company. Henfrey reflected: "I hope we'll look back at all of this and say, 'Yeah, that was a wild ride, but it was a hell of a good thing to do.'"

Exhibit 1 *Causes of Mortality in Children Under Five (2000-2003)*



Source: Malaria & Children: Progress in intervention coverage. UNICEF and RBM, 2007.

Exhibit 2 Plasmodium falciparum *Life Cycle*



Source: *Killer Number One: The Fight Against Malaria*, United Nations Integrated Regional Information Networks (IRIN), February 2006.

Exhibit 3 *Malaria Global Distribution (1900-2002)*

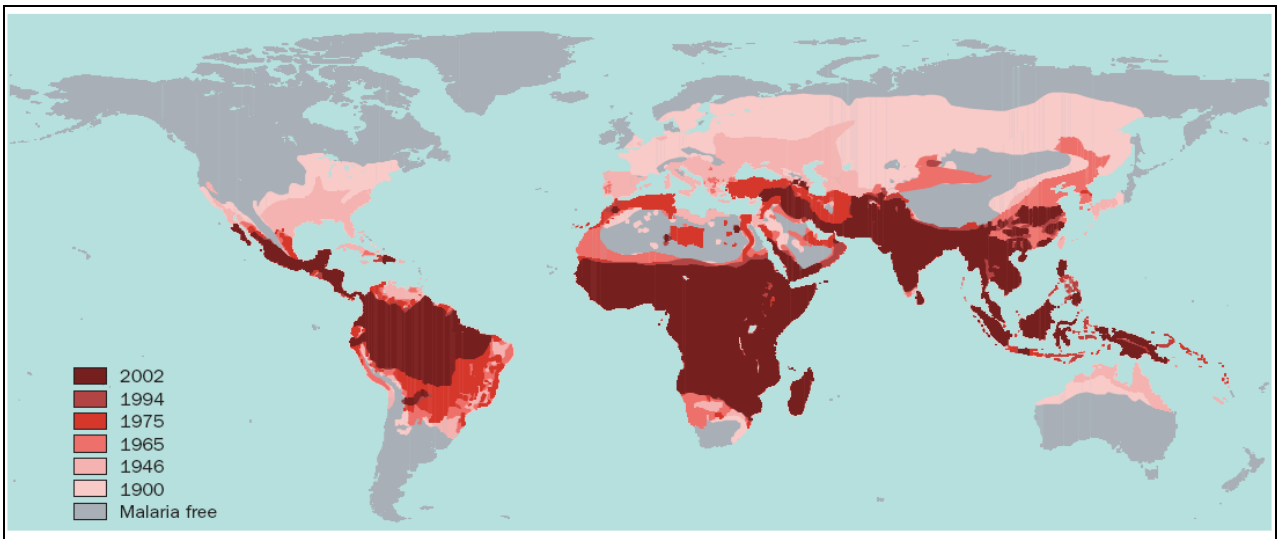
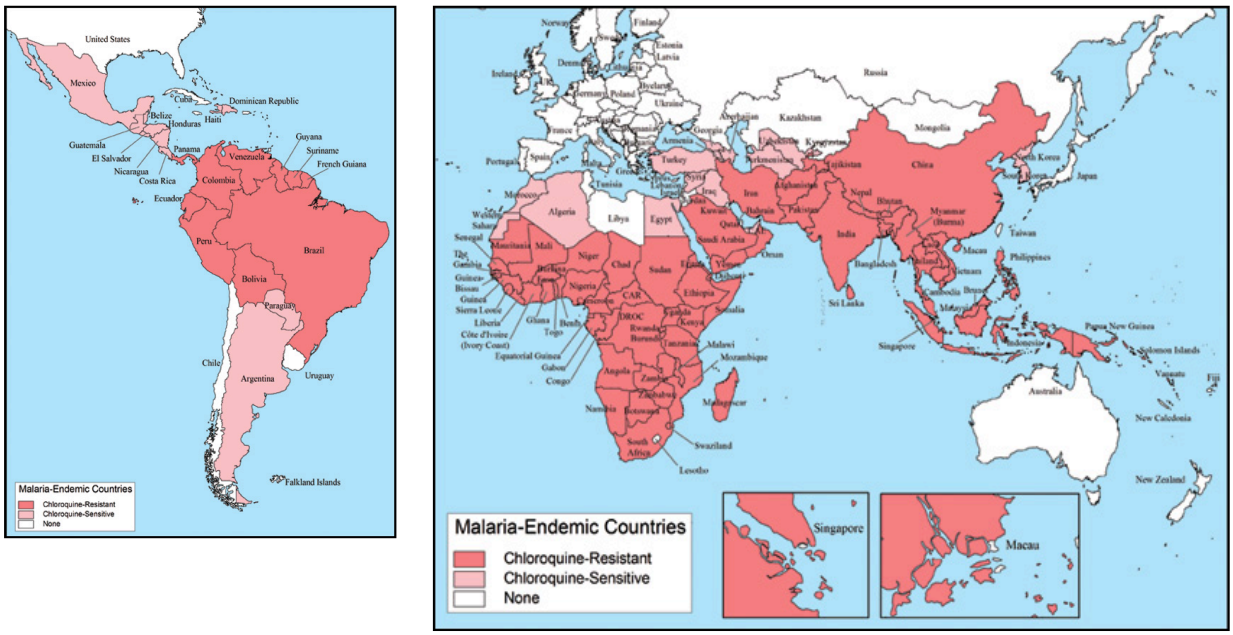


Figure 1. The global distribution of malaria since preintervention (~1900–2002). All-cause malaria distribution maps for the preintervention distribution (circa 1900)[9] and for the years 1946, 1965, 1975, 1992, 1994, and 2002[12–17] were georeferenced using ERDAS Imagine 8.5 (Leica Geosystems GIS & Mapping, Atlanta, GA, USA). Maps were then digitised on screen with MapInfo Professional 7.0 (MapInfo Corp, NY, USA). Areas of high and low risk were merged throughout to establish all-cause malaria transmission limits. The only modification of original maps was infilling areas labelled as unknown in China in the 1975 map[14] with the distribution recorded in 1965.[13] Each map was then overlaid to create a single global distribution map of malaria risk which illustrates range changes through time. Note that the 1992 distribution is excluded from the figure for clarity because it was so similar to that of 1994.

Source: Hay, S.I. &Snow, R.W. "The Malaria Atlas Project: developing global maps of malaria risk." *PLoS Med.*, **3**(12): e473. (2006).

Exhibit 4 *Chloroquine Resistance*



Source: Centers for Disease Control and Prevention, Chapter 4, 2005-2006.

Exhibit 5 *Malaria Treatment Options*

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride). * To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of *P.vivax, P.ovale and P.malariae* infections.
artemether	**Oily injection**: 80 mg/ml in 1-ml ampoule. For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection**: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Tablet**: 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
chloroquine*	**Oral liquid**: 50 mg (as phosphate or sulfate)/5 ml. **Tablet**: 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of P.vivax infection.
doxycycline*	**Capsule**: 100 mg (as hydrochloride). **Tablet (dispersible)**: 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet**: 7.5 mg; 15 mg (as diphosphate) * Only for use to achieve radical cure of P.vivax and P.ovale infections, given for 14 days.
quinine*	**Injection**: 300 mg quinine hydrochloride/ml in 2-ml ampoule. **Tablet**: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria,
Suladoxine + pyrimethamine	**Tablet:** 500 mg + 25 mg *only in combination with artesunate 50 mg.

Source: WHO Essential Medicines List, accessed June 2008.

Exhibit 6 *Global Malaria Action Plan*

Global Malaria Action Plan Targets:

1. Achieve universal coverage, as recently called for by the UN Secretary-General, for all populations at risk with locally appropriate interventions for prevention and case management by 2010 and sustain universal coverage until local field research suggests that coverage can gradually be targeted to high-risk areas and seasons only, without risk of a generalized resurgence
2. Reduce global malaria cases from 2000 levels by 50% in 2010 and by 75% in 2015
3. Reduce global malaria deaths from 2000 levels by 50% in 2010 and to near zero preventable deaths in 2015
4. Eliminate malaria in 8-10 countries by 2015 and afterwards in all countries in the pre-elimination phase today
5. In the long term, eradicate malaria worldwide by reducing the global incidence to zero through progressive elimination in countries

To achieve these targets, the GMAP outlined a three-part global strategy:

1. Control malaria to reduce the current burden and sustain control as long as necessary
2. Eliminate malaria over time country by country
3. Research new tools and approaches to support global control and elimination efforts

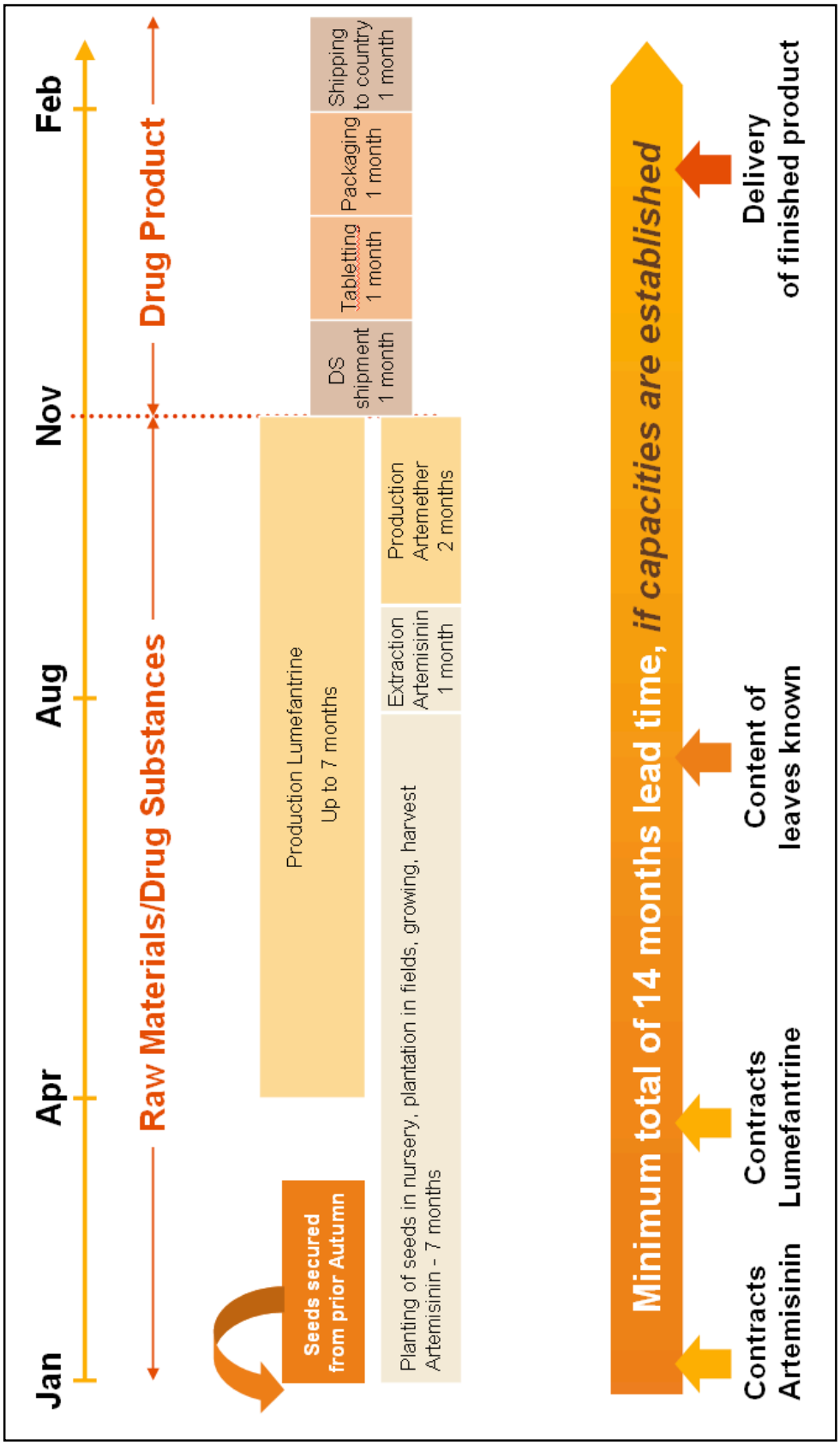
Source: The Global Malaria Action Plan, RBM, 2008.

Exhibit 7 *The* Artemisia *Plant and Cultivation*

BE affiliated farmer with *Artemisia* in the background (left) and *Artemisia annua* (right).

Sources: Advanced Bio-Extracts (left) and Farmer in Central Kenya, June 2008 (right).

Exhibit 8 *Manufacturing Timeline:* Artemisia *to Coartem®*



Source: Wells L (June 2008). Coartem®-the story so far. Global Access to Medicines Policy, Novartis International AG.

Exhibit 9 *Geographic Supply Chain of Coartem®*

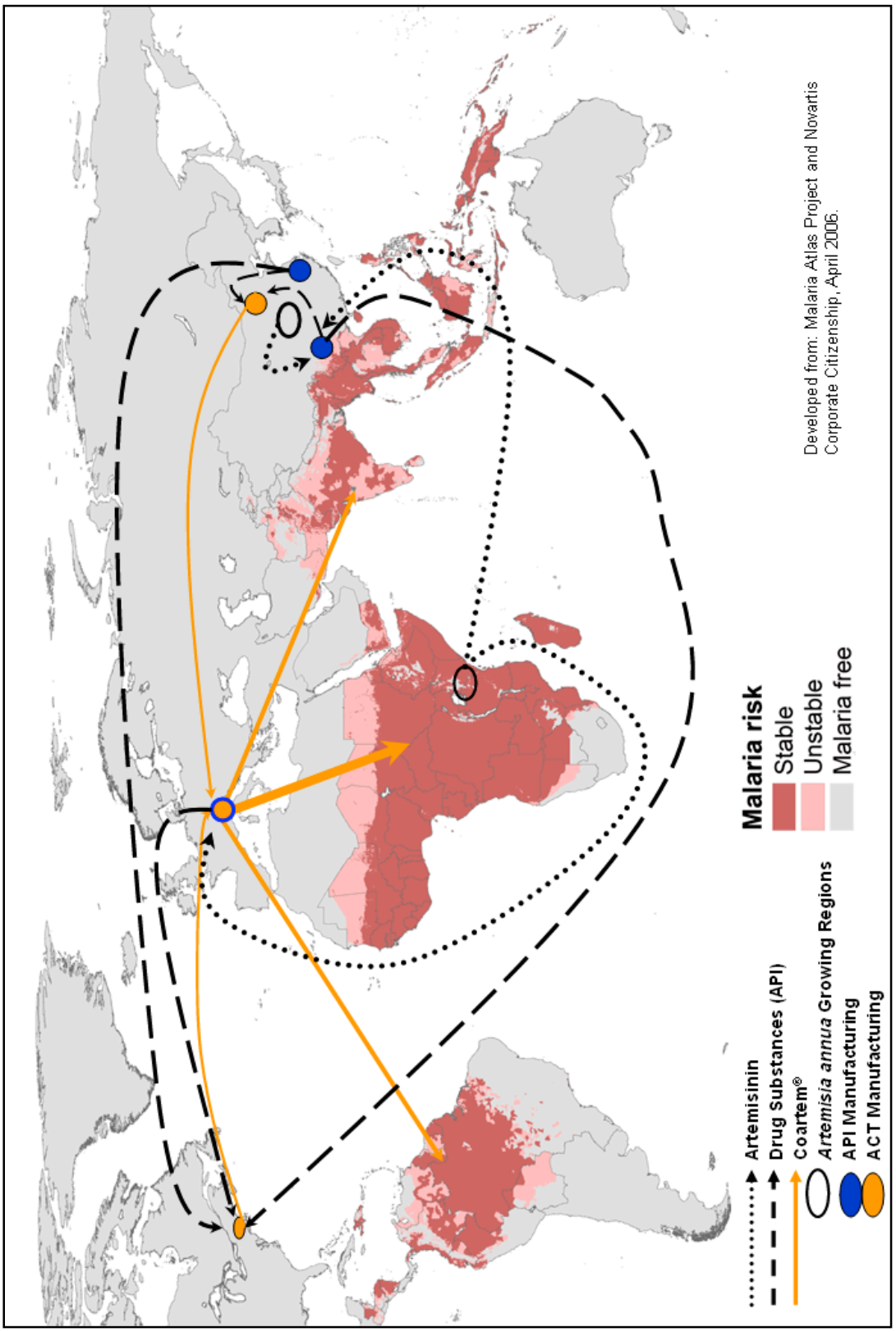
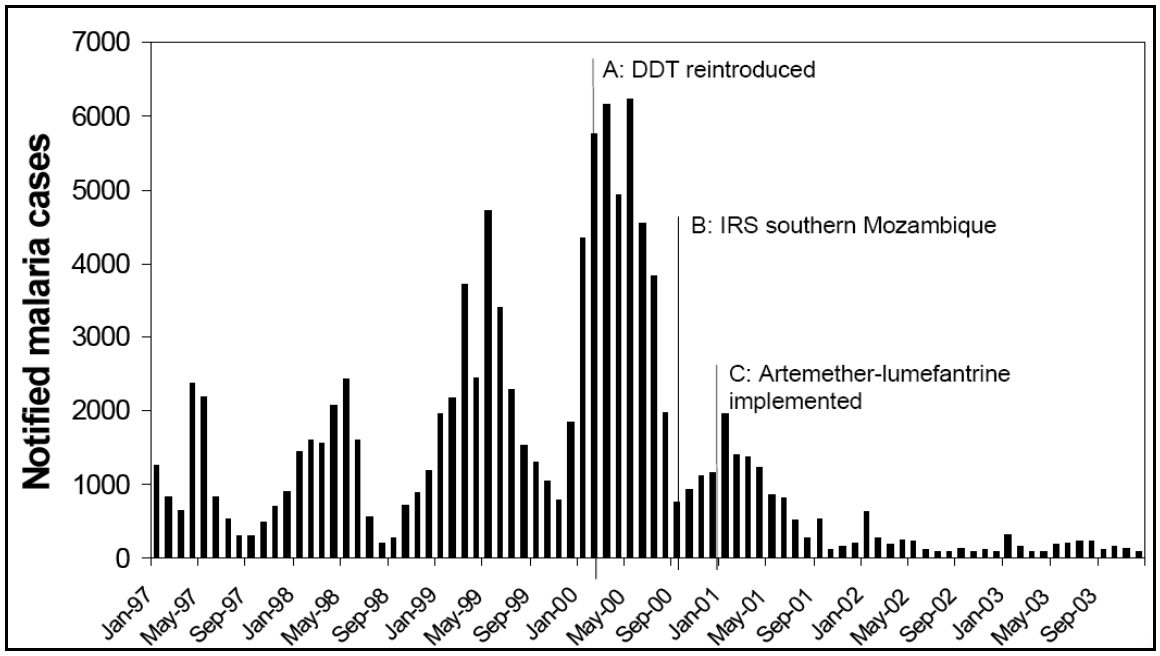


Exhibit 10 *Controlling Malaria in KwaZulu Natal, South Africa*



Source: Deloitte & Touche (2004). WHO Report for the Review of Collaborating Partner Product Pricing. South African National Department of health, Notification Data.

Exhibit 11 *Novartis Financial Highlights*

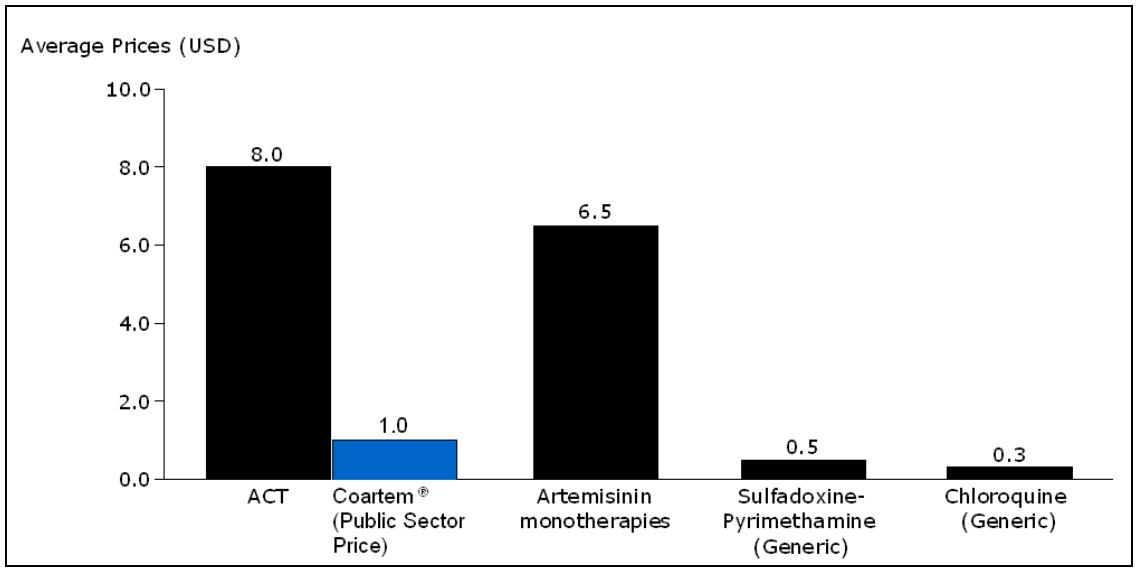
KEY FIGURES
(In USD millions, unless indicated otherwise)

	2007	2006
Total Group net sales	**39 800**	37 020
Continuing operations[1]		
- Net sales	**38 072**	34 393
- Operating income excluding environmental and restructuring charges[2]	**7 815**	7 642
- Return on net sales[2] (%)	**20.5**	22.2
- Operating income	**6 781**	7 642
- Net income	**6 540**	6 825
Net income – Discontinued operations	**5 428**	377
Net income – Total Group	**11 968**	7 202
Basic earnings per share[3]		
- Continuing operations[1]	**2.81**	2.90
- Total Group	**5.15**	3.06
R&D investments[1]	**6 430**	5 321
- As % of net sales[1]	**16.9**	15.5
Number of associates (FTE[1,4])	**98 200**	94 241

[1] Excluding Consumer Health discontinued operations
[2] Excluding in 2007 USD 590 million of Corporate environmental and USD 444 million of "Forward" initiative restructuring charges
[3] Average number of shares outstanding in 2007: 2 317.5 million (2006: 2 345.2 million)
[4] Full-time equivalent positions
[5] Dividend payment for 2007 proposed to shareholders

Source: Novartis Annual Report 2007, Page 2.

Exhibit 12 *End-user Private Sector Prices for Anti-malarials (USD)*



Note: Ranges indicate variance across countires and producting excluding outliers.

Source: Developed from Dalberg field research (Kenya, Uganda, BF. Cameroon, Observations by World Bank and Research International (Nigeria). SP and CQ dara complemented with HAI and IOM observations.

Exhibit 13 *Cost-effectiveness of ACTs*

Perspective	Cost Category	Item	Mean Discounted Cost per Patient (US$)				
			Current Recommended First-Line Treatment (SP)	Amodiaquine	Amodiaquine + Sulfadoxine-Pyrimethamine	Amodiaquine + Artesunate	Artemether-Lumefantrine
Provider/hospital	Recurrent	Drugs	0.04	0.08	0.13	0.51	0.91
		Staff salaries	3.98	3.98	3.98	3.98	3.98
		Rental of building	0.17	0.17	0.17	0.17	0.17
		Utilities	0.44	0.44	0.44	0.44	0.44
		Consumables	0.13	0.13	0.13	0.13	0.13
	Capital	Microscope	0.33	0.33	0.33	0.33	0.33
		Subtotal	5.09	5.13	5.18	5.56	5.96
Patient and family	Direct	Medication	0.14	0.14	0.14	0.14	0.14
		Hospital fees	0.01	0.01	0.01	0.01	0.01
		Transportation	1.35	1.35	1.35	1.35	1.35
		Miscellaneous	0.26	0.26	0.26	0.26	0.26
	Indirect	Time spent at Teule hospital[a]	2.03	2.03	0.64	0.41	0.30
		Time spent travelling to Teule[b]	0.15	0.15	0.05	0.03	0.02
		Time spent caring for sick child at home[c]	11.70	11.70	3.68	2.39	1.75
		Subtotal	15.64	15.64	6.13	4.59	3.83
		Total	20.73	20.77	11.31	10.15	9.79

[a]The mean time spent at Teule Hospital was 36 h.
[b]The mean time spent travelling to hospital was 3 h.
[c]The mean time spent away from normal activities at home while caring for a child with malaria was 8 d.
DOI: 10.1371/journal.pmed.0030373.t001

Measure	Perspective	Description	Amodiaquine (n = 270)[a]	Amodiaquine + Sulfadoxine-Pyrimethamine (n = 507)[a]	Amodiaquine + Artesunate (n = 515)[a]	Artemether-Lumefantrine (n = 519)[a]
Programme cost	Provider	Cost per patient	5.13	5.18	5.56	5.96
	Household	Cost per patient	15.64	6.13	4.59	3.83
	Total		5,607.90	5,734.17	5,227.25	5,081.01
Clinical outcomes		Cases averted at day 14	145	379	437	495
		Cases averted by day 28	57	181	279	382
Gross cost-effectiveness	Provider	Cost per case averted at day 14	—	5.30	5.06	4.88
		Cost per case averted at day 28	—	10.01	6.66	5.26
	Societal	Cost per case averted at day 14	—	0.53	−1.30	−1.51
		Cost per case averted at day 28	—	1.02	−1.71	−1.62
Resource savings	Provider[b]	Resource savings day 14	738.05	1,929.11	2,224.33	2,519.55
		Resource savings day 28	290.13	921.29	1,420.11	1,944.38
	Societal[c]	Resource savings day 14	3,005.85	7,856.67	9,059.01	10,261.35
		Resource savings day 28	1,181.61	3,752.13	5,783.67	7,918.86
Net costs/savings[d]	Provider	Day 14	647.05	697.15	639.07	573.69
		Day 28	1,094.97	1,704.97	1,443.29	1,148.86
	Societal	Day 14	2,602.05	−2,122.5	−3,831.76	−5,180.34
		Day 28	4,426.29	1,982.04	−556.42	−2,837.85
Net cost-effectiveness	Provider	Cost per case averted at day 14	—	0.21	−0.03	−0.21
		Cost per case averted at day 28	—	4.92	1.57	0.17
	Societal	Cost per case averted at day 14	—	−20.19	−22.03	−22.24
		Cost per case averted at day 28	—	−19.71	−22.44	−22.35

[a]n, number of patients in each category
[b]This is based on the provider cost of current treatment per patient with SP (i.e., US$5.09). See Table 1.
[c]This is based on the total cost of current treatment per patient with SP (i.e., US$20.73). See Table 1.
[d]Net costs or net savings are calculated by subtracting resource savings from programme costs.
DOI: 10.1371/journal.pmed.0030373.t002

Source: Wiseman et al. (October 2006). Cost-Effectiveness Study of Three Anti-malarial Drug Combinations in Tanzania. PLoS Medicine vol 3, no 10, e373.

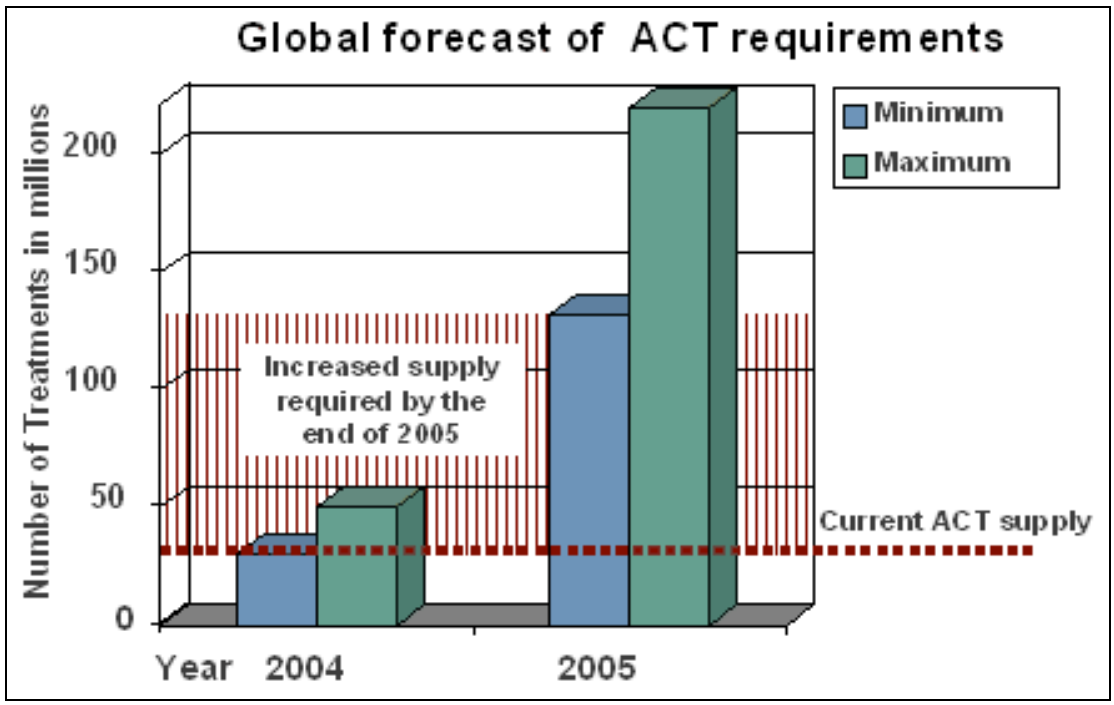
Exhibit 14 *Novartis Access-to-Medicine Projects 2007*

Project	Objective	Target region	Value (USD millions)	Patients
Malaria/WHO[1]	Provide *Coartem* at cost for public sector use	Africa, Asia, Latin America	190	64 800 000
Leprosy/WHO[2]	Eliminate leprosy by providing free medications to all patients worldwide with WHO, through 2010	Global	6	244 000
Tuberculosis[2]	Donation of fixed-dose combinations	Tanzania, Sri Lanka	3	112 000
Novartis Foundation for Sustainable Development[3]	Improve health and quality of life of poor people in developing countries through Think Tank, policy and project work	Developing countries	8	390 000
Novartis Institute for Tropical Diseases (NITD)[3]	Discover novel treatments and prevention methods for major tropical diseases; NITD discoveries to be available in poor endemic countries without profit	Developing countries	12	-
Patient Assistance Programs (PAP); excl. *Gleevec/Glivec*[2]	Assistance to patients experiencing financial hardship, without third-party insurance coverage for their medicines	US	113	106 000
Gleevec US PAP[2]	Within capability of Novartis, continue to ensure access for patients in the US who cannot afford the drug	US	56	3 000
Glivec Global PAP[2,4]	Within capability of Novartis, continue to ensure access for patients outside the US who cannot afford the drug	Global (excluding US)	534	20 000
Together Rx Access	Discount program for the uninsured	US	1	12 000
Emergency relief & other product donations	Support to humanitarian organizations	Global	14	-
Total			**937**	**65.7 million**

[1] During 2007, 64.8 million Coartem treatments reached patients based on a preliminary analysis of local distribution; Of these, 29 million treatments came from shipments completed in 2006, and 35.8 million from the total shipment of 66 million completed in 2007. The Value of the *Coartem* program in 2007 was calculated using the number of treatments shipped and the ex-factory price of *Coartem* to private-sector purchasers in malaria-endemic developing countries, minus payments to Novartis to cover costs under terms of the public-private partnership with WHO. These payments were received through WHO, UNICEF and other procurement agencies, acting on behalf of governments and other public sector institutions in developing countries eligible to receive Coartem at the "not-for-profit" price.
[2] Ex-factory price to private market
[3] Operating costs
[4] Inclusive Shared Contribution Model as described on page 77

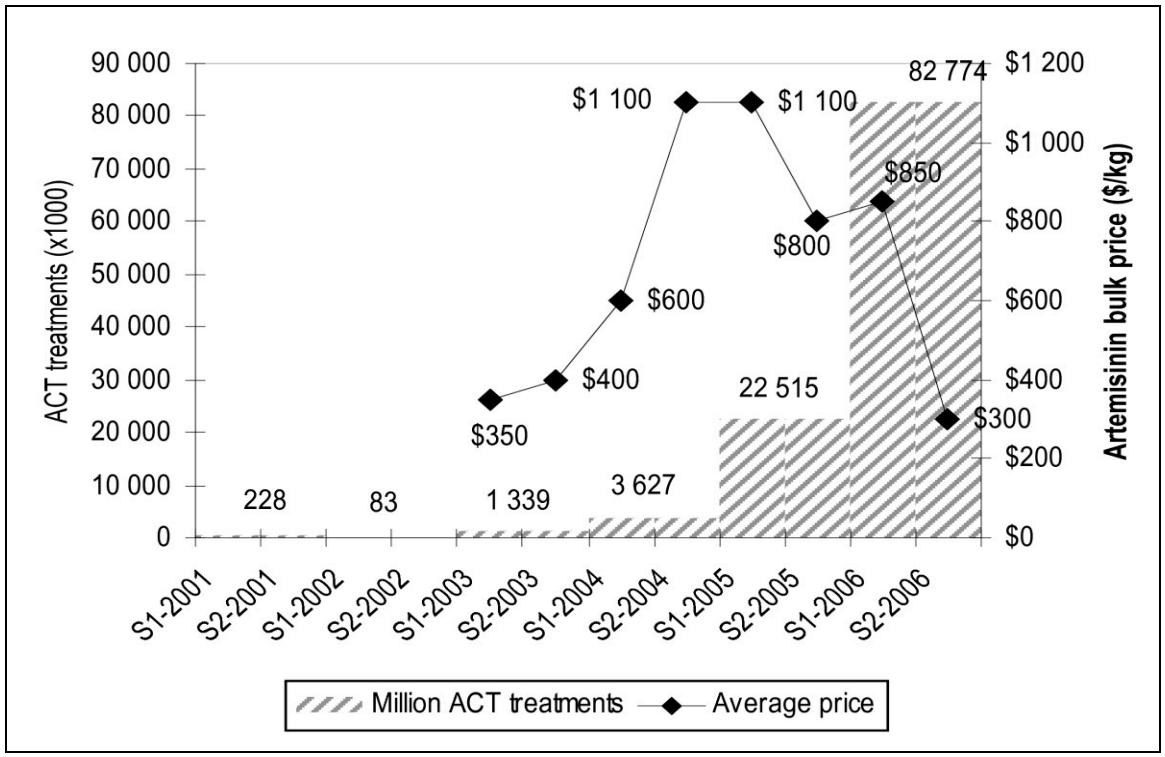
Source: Novartis Annual Report 2007, Page 76.

Exhibit 15 *WHO ACT Forecast*



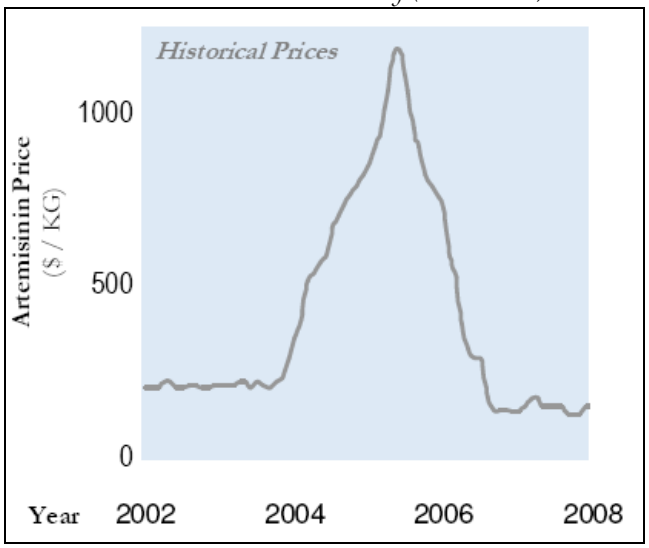
Source: WHO Facts on ACTs. 2001-2011 United Nations Decade to Roll Back Malaria.

Exhibit 16 *ACT Recorded Orders by Public Sector and Artemisinin Market Price*



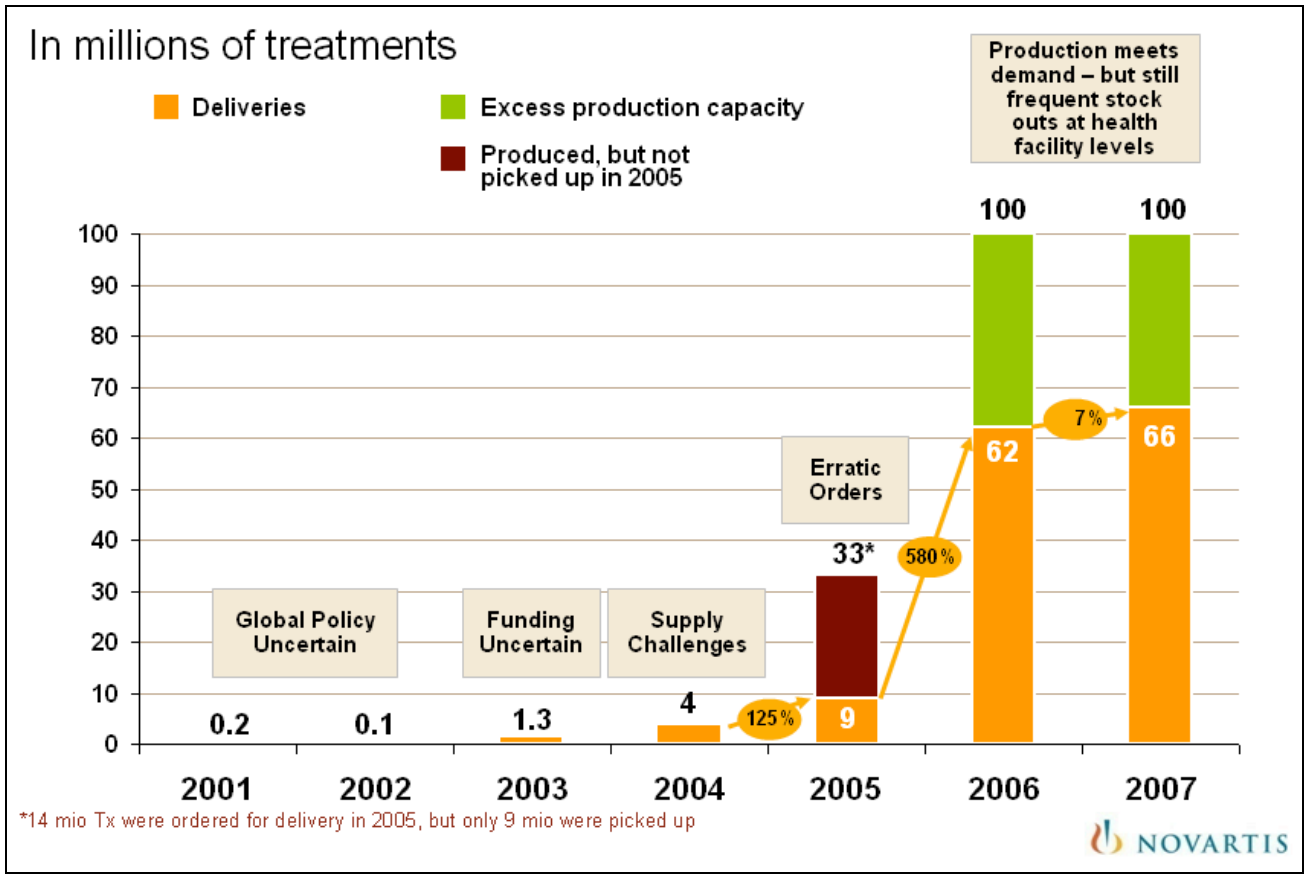
Source: Kindermans JM et al. (September 2007). Ensuring sustained ACT production and reliable artemisinin supply. Malaria Journal 6: 125.

Artemisinin Price Volatility (2002-2008)



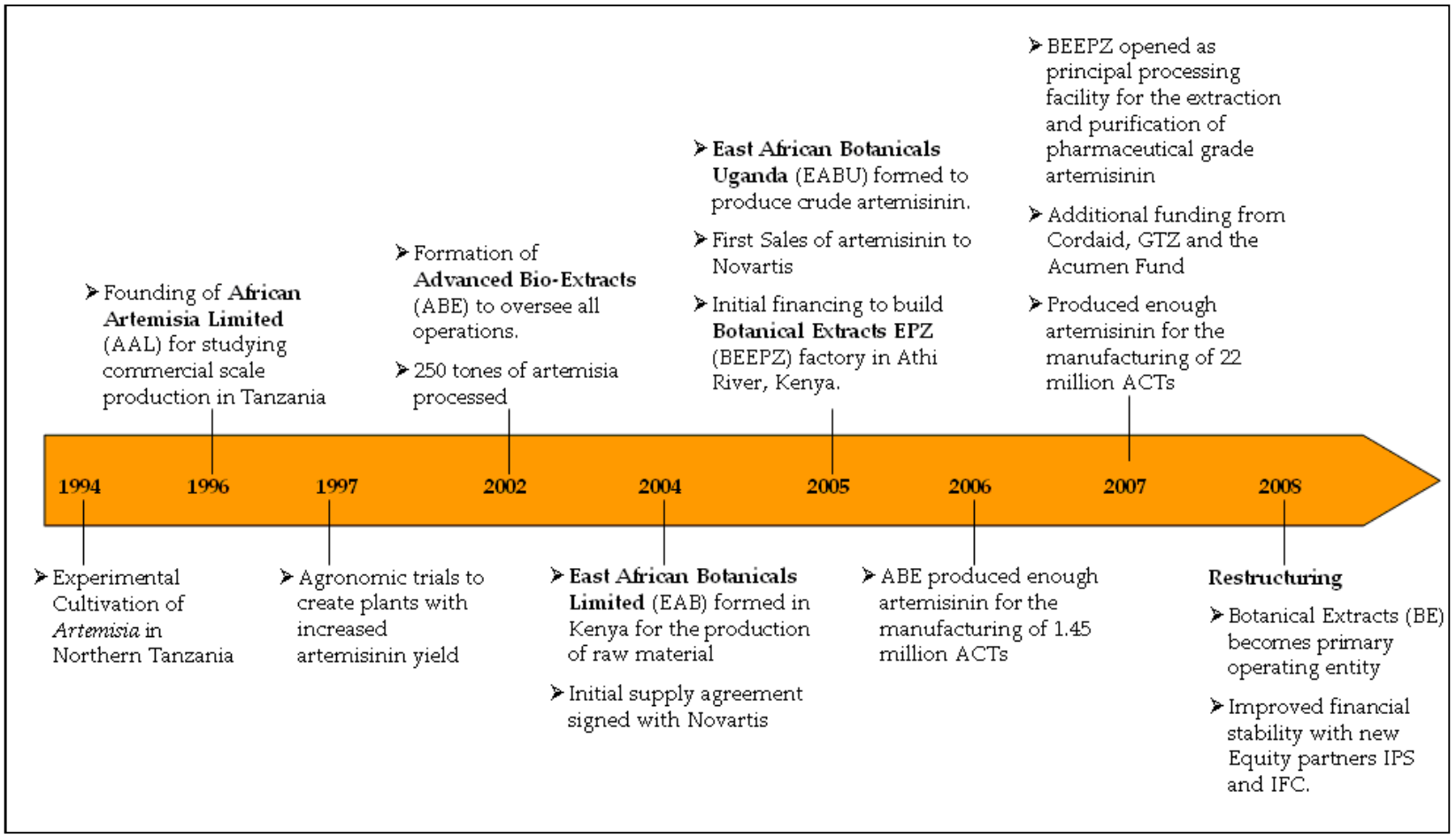
Source: CHAI Announcement on ACT Agreements for Malaria Treatment, July 2008.

Exhibit 17 *The Story of Coartem®*



Source: Wells L (June 2008). Coartem®-the story so far. Global Access to Medicines Policy, Novartis International AG.

Exhibit 18 *Timeline of Botanical Extract Activities*



Source: Developed from background section on www.abextracts.com and communication with Patrick Henfrey.

Appendix *Abbreviations*

AL	artemether lumefantrine combination (generic for Coartem®)
ACT	artemisinin-based combination therapy
BEEPZ	Botanical Extracts Export Processing Zone, Ltd.
BE	Botanical Extracts Ltd.
DDT	dichloro-diphenyl-trichloroethane
MEP	Malaria Eradication Program
RBM	Roll Back Malaria Partnership
SP	Sulfadoxine-pyrimethamine (also known as Fansidar®)
USD	United States dollar
WHO	World Health Organization

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