A new geography of pharmaceuticals : Trajectories of artemisinin-based medicines

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Chapter 5: A new geography of pharmaceuticals : Trajectories of artemisinin-based medicines (Maurice Cassier)

Research in the geopolitics of medicines has focused on the emergence of copycat capitalism in countries in the global South since the 1970s, particularly in India and Brazil (Chaudhuri, 2005; Cassier, Correa, 2003). However, in this chapter I would like to highlight the singular trajectories of artemisinin-based drugs—discovered and initially developed, industrialized, and tested in the People's Republic of China and in Vietnam—beginning in the early 1970s and 1980s. It is one of the rare, perhaps only, therapeutic classes of biomedicine to have been invented in a so-called emerging or "Third World" country, to use the vocabulary of that time. The chemist Tu Youyou of the Academy of Traditional Chinese Medicine, who was awarded the Nobel Prize for Medicine in 2015 for the discovery of artemisinin by hybridizing traditional pharmacopoeia and modern chemistry, entitled his lecture: "A gift from traditional Chinese medicine to the world."[1] What is less well known is that the most widely used treatment in the world since its inclusion on the WHO essential medicines list in 2002, artemisinin-based combination therapy (ACT), which combines artemether and lumefantrine (AL), was also invented by Chinese researchers[2]. This product was the subject of one of the first drug patents filed in China in 1990. The researchers subsequently established a partnership in 1991 with Ciba Geigy, now Novartis, to make it a global medicine. Chemist Zhou Yiqing was rewarded by the European Patent Office and the European Commission in 2009 for the invention of the first artemisinin-based fixed-dose combination therapy.[3]

The globalization of artemisinin-based medicines, i.e., the duplication of inventions, the spread of the industry, the creation of markets and uses in malaria-endemic countries, is unique in that it was not undertaken or controlled by Chinese scientific institutions and companies, but by multinationals (Novartis, Sanofi) and through the intermediary of WHO and humanitarian health organizations, especially Médecins Sans Frontières (MSF) (Balkan, Corty, 2009). The Special Programme for Research in Training in Tropical Diseases (TDR) a research group created in 1975 by WHO, the World Bank, and the United Nations Development Programme (UNDP) to accelerate the invention of new treatments for tropical diseases and compensate for the withdrawal of international laboratory R&D on these diseases, took an early interest in the Chinese researchers' work. TDR signed an initial research collaboration agreement in September 1979 with the Shanghai Institute of Materia Medica.[4] In December 1980, the Secretary General of WHO, Halfdan

[1] Tu Youyou, Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China. Nobel lecture 31 pages.
[2] AL still accounts for 75 percent of the market today (UNITAID, Malaria Medicines Landscape, 2015),
[3] "Non-European countries: Zhou Yiqing (China) for his anti-malaria drug based on a herbal agent, which has been instrumental in saving hundreds of thousands of lives" (European Inventors of the Year, 2009)
[4] TDR archives T16 -181- M2 -61, WHO Geneva.

Malher, who inspired the Alma Ata list of essential medicines and primary health policy, wrote to the Chinese Minister of Health and proposed organizing a Working Group on the Chemotherapy of Malaria (CHEMAL) seminar on artemisinin. This seminar was held in Beijing in October 1981, where it was decided that the resources for the program to develop artemisinin and its derivatives would be increased. In 1996, MSF pharmacists noted the arrival of artemisinin derivatives, presented as the result of "fortuitous analysis of traditional pharmacopeias" in the People's Republic of China (Trouiller, 1996). In 1999 and 2002, MSF published two articles of note in *JAMA* (Pecoul et al.) and *The Lancet* (Trouiller et al.) highlighting the fact that the few innovations in the field of neglected diseases (1 percent of all compounds registered between 1975 and 1999) largely arose from the development of artemisinin derivatives. The authors note that these new drugs are produced and registered in China and marketed in Southeast Asia and Africa, an unusual geography for the invention, production, and marketing of medicinal products: "Although rare, examples of registrations exclusively within developing countries do exist –e.g., artemisinin derivatives for malaria developed and manufactured in China" (*The Lancet*, June 22, 2002, p. 2188). In 1999, MSF created the Drugs for Neglected Diseases Working Group (DNDWG) which brings together experts from scientific institutions in Brazil, India, Malaysia, the Harvard School of Public Health, MSF pharmacists, and TDR members, and is committed to developing two new fixed-dose ACTs: artesunate and amodiaquine (ASAQ) in France and artesunate and mefloquine (ASMQ) in Brazil (Cassier, 2008).

This unusual geography of therapeutic innovation, initiated in China and involving many scientific institutions and firms from Southeast Asia, India, Brazil, and Africa, can be explained by a few salient points. First is the public and common appropriation of the basic components of these drugs (artemisinin and its four derivatives with therapeutic usefulness: di-hydroartemisinin, artesunate, artemether, and artemether), which were developed in China at a time when patents did not exist, so these molecules can therefore be legally copied and combined everywhere in the world. The second point concerns the public-private partnerships established through the intermediary of WHO or MSF, involving organizations from both North and South and manufacturers of both trademarked and generic drugs, to support the R&D, manufacturing, and distribution of this class of drugs intended for low- and middle-income countries, particularly in Africa. The industrial geography is widespread: WHO drew up a list of pharmaceutical companies producing artemisinin-based medicines in 2006 (41 companies); the growth in this area was such that it had to reissue the list in 2007 (83 companies, 67 of which produced monotherapies and 16 ACTs), with companies distributed across several continents: Asia (China, India, Malaysia, Pakistan,Vietnam), Europe (Belgium, Denmark, France, Germany, Italy, Switzerland), and Africa (Cameroon, DRC, Ghana, Nigeria, Tanzania). Two factors led to a decrease in this wide-ranging

production, most of it by generic companies: the reduction in monotherapy supply, as recommended by WHO and the Global Fund to Fight AIDS, Tuberculosis and Malaria;[5] and the growth in ACT supply, which gradually became the norm in subsidized markets.[6] This dispersion of industrial supply coexisted with a concentration of economic value in two multinational companies, Novartis (marketing Coartem) and Sanofi (marketing ASAQ), until the early 2010s, at which time Indian, and to a lesser extent Chinese, generic manufacturers impose their prices on the global donor market.[7]

While the artemisinin-based drug industry was globalizing, the cultivation of artemisia and the natural artemisinin extraction industry remained heavily concentrated in China and Vietnam, with a few spin-offs in East Africa and Madagascar.

In this chapter I will examine four mechanisms behind the globalization of artemisinin-based drugs. The first section will analyze TDR's intermediation to organize both upgrading Chinese factories to international standards and globalizing these new treatments through agreements with foreign firms. The second section will focus on the globalization of the most widely used combination, artemether and lumefantrine, through a dual partnership between Novartis and Chinese inventors and producers on the one hand, and between Novartis and WHO on the other. The third section will look at the alliance between the Drugs for Neglected Diseases Initiative (DND*i*) and Sanofi to invent and market ASAQ, the second most widely sold ACT after AL. Finally, the fourth section will examine the manufacture of artemisinin-based medicines in Africa, which is the main region of consumption but where production is limited and intended for local markets.

I will draw from a variety of sources: (1) the Chinese inventors' stories,[8] including their collaborations with WHO and multinational companies; (2) the archives of TDR, WHO, and Roll Back Malaria (RBM) consulted in Geneva in 2016 and 2019, including industrial agreements on R&D, industrialization, and distribution; (3) the archives of patents filed on fixed-dose combinations, particularly AL; (4) materials from a detailed survey on the invention and industrialization of the ASAQ combination, conducted in two waves in 2008–2009 and 2016–2019 among academics and start-ups who developed the fixed-dose combination (FDC), Sanofi who industrialized it, and MSF and DND*i* who oversaw this product.

[5] The Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria was created in 2002 at the urging of the United Nations to raise funds to combat these diseases. It is not a UN agency, but a non-profit foundation that works closely with WHO. Most of its funds (93 percent) come from government grants, with the remaining 7 percent from private foundations and industry.

[6] Malaria Medicines Landscape, UNITAID, 2015.

[7] Chapter 6 of this book discusses the shift from Novartis and Sanofi originator medicines to Indian generics.

[8] Tu Youyou, discoverer of artemisinin; Zhou Yiqing, inventor of the artemether/lumefantrine combination; Li Guoqiao, inventor of the dihydroartemisinin and piperazine combination; and the book published in 2013 by Zhang Jianfang, 2013.

1) The globalization of a Chinese invention: the intermediation of Tropical Diseases Research (TDR)

TDR was created by WHO in 1975 to accelerate the development of therapeutic innovations for tropical diseases, in a context of increasing resistance to existing malaria treatments and exhaustion of the proprietary model, which devotes few resources to these diseases. TDR uses its funding to establish research and industrialization partnerships between governments, academia, and industry (developing manufacturing and formulation technologies, clinical trials, bringing factories and products up to international standards, and so forth). TDR proclaims "the primacy of public interests"[9] through public-private partnerships, and focuses on accessibility to treatment in developing countries. Its board represents recipient countries as well as donors, and it offers a prominent place to countries directly affected by these endemics. In 1975, TDR set up a group dedicated to malaria chemotherapy (CHEMAL).

The TDR archives show that WHO has been funding the initial research projects in China since 1979. Concerned about the rise in treatment resistance, WHO supports the work of Chinese researchers to speed the development of technologies for two promising artemisinin derivatives: artesunate and artemether.[10] Chinese institutions have already industrialized several artemisinin-based drugs that are registered in China, so WHO's goal is to bring Chinese laboratories and factories in line with international standards. Wallace Peters, who headed the CHEMAL committee on anti-malaria drugs, points out the gap between the standards applied by China and international standards: "from the western regulatory point of view, there were big gaps in the Chinese toxicity and efficacy studies… but China wanted the drug sold and used, and was uncomfortable about TDR taking over this development work."[11]" In march 1982, TDR notes the non-respect of GMP standards: "the plant that is used to lyophilize the artesunate preparations does not conform to GMP.[12]" TDR's collaborative research agreement specifically targets the "development of a standardized formulation of artesunate and artemether" (June 1982).[13] The account published by the Chinese inventors on the WHO collaboration emphasizes the work of bringing Chinese factories up to standards (p 88–89). Between 1979 and 1986, TDR financed several collaborative research agreements at the Shanghai Institute of Materia Medica, the Beijing Institute of Materia Medica, and the Shanghai Research Institute of Pharmaceutical Industry. The funding covered the purchase of scientific equipment, the

[9] Making a Difference: 30 years of Research and Capacity Building in Tropical Diseases, WHO, 2007.
[10] This cooperation is documented in both the TDR archives at WHO and in the book edited by the Chinese inventors (op. cit.) translated by Keith Arnold, who was one of the first Western researchers to take an interest in artemisinin on behalf of the Roche Foundation.
[11] "Making a Difference," WHO, op. cit.
[12] TDR archives T 16-181-M2-83
[13] TDR archives T 16-181-M2-83.

development of new synthesis processes, and new techniques for analyzing molecules. TDR also subsidizes internships for Chinese researchers in laboratories in the United States and Europe: "Application form for research training grants for these two people will be sent to you shortly" (Scientific Working Group on Malaria Chemotherapy, December 1979); "I have been invited to visit the Netherlands by Professor BB Bremer of the Leiden University" (Shanghai Institute of Materia Medica, September 5, 1980). This same Chinese pharmacologist is pleased to be in contact with Hoffman Laroche: "Thank you for introducing me to Mr Fernex… The department of bioanalytical method of Hoffman Laroche New Jersey is very strong."[14]

Simultaneously with its research agreements with laboratories in China, TDR organizes the dissemination of work on artemisinin in laboratories in the North: "TDR helped to get researchers outside of China involved in artemisinin and get it on the research agenda" (Halfdan Mahler). TDR encouraged the Walter Reed Army Institute to grow artemisia and extract artemisinin in Mississippi. In 1986, the WHO Malaria Chemotherapy Research Group report identified two sources of raw materials for its own developments: "the acquisition of large quantities of artemisinin for conversion to arteether was facilitated by the generous gift of one kilogram of artemisinin from the government of China; other supplies were obtained from *artemisia annua* grown in Mississippi, USA."[15]

In 1986 TDR also launched its own R&D line on one of the artemisinin derivatives, arteether, which it entrusted to the Dutch firm Artecef for industrialization. WHO itself even filed a patent on this molecule, whose inventors are members of the CHEMAL research group, Arnold Brossi and Peter Buchs. The patent claims a novel synthesis of this artemisinin derivative, as well as a pharmaceutical composition comprising the product of this process and an excipient. The introduction of the patent refers to the long-standing use of artemisinin extracts in the "Republic of China," but does not reference the studies of Chinese researchers on this same derivative: "extracts of which have been used as an antimalarial preparation in the Republic of China for centuries" (EP330520, 1988). The Chinese inventors' account illustrates their irritation: "only two years later, China discovered that WHO/TDR had signed an agreement with ACF Company in Holland to develop the ether derivative" (Zhang Jianfang, p. 111).

In the early 1990s, Rhône-Poulenc signed an exclusive agreement to distribute injectable artemether in Europe and endemic regions;[16] at the same time, TDR was communicating with Kunming Pharmaceutical Factory (KPF) to carry out preclinical and clinical studies of the drug and to implement Good

[14] Archives T16-181-M2-61.

[15] "The Development of artemisinin and its derivatives." Report of the Scientific Working Group on the Chemotherapy of Malaria, Geneva, October 6–7, 1986, 30 pages.

[16] The injectable form of artemether was tested in China as early as 1978 and approved for production from 1987. Kunming Pharmaceutical Corporation still markets this formulation today under the brand name Artem.

Manufacturing Practice (GMP) standards in the Chinese plant.[17] TDR hired two pharmaceutical consulting firms, one British and the other American, to visit the Kunming plant and make recommendations. Their audits corroborate the view that while the new factory, specially built by the Chinese, and the industrial equipment meet GMP standards, efforts should be made to improve the production and quality control procedures, especially technical documentation, which must accurately track production and control testing. Kunming was quite satisfied with the assistance it received to bring its new plant up to international standards. The WHO-appointed experts were able to conduct 10-day in-depth visits to the factory and were invited back by the Chinese. However, tensions arose in 1991 when WHO learned that China was preparing to deliver 20 million vials to Myanmar before the factory was GMP-certified and without informing WHO of this plan. In 1993 WHO and Rhône-Poulenc signed an R&D agreement to speed up registration of the drug in Europe and all endemic countries and to treat severe forms of malaria in those countries. In return for transferring its preclinical and clinical data for the product, marketed under the name Paluther®, WHO required that Rhône-Poulenc offer differentiated pricing for the public sector and that it provides oversight for the company's marketing as well as the therapeutic indication for severe forms of malaria. TDR was aware that the fixed price (USD 2 per vial) was unattainable for African countries: "the African public sector can support 10 cents per treatment, so even if the product is sold at cost, there is a need for donor financial support" (November 1992). In 1994, Rhône-Poulenc complained to WHO that it was discouraging the use of artemisinin-based drugs in Africa.[18]

WHO, and TDR in particular, therefore played a key role in supporting the spin-off of Chinese inventions and making them "global" medicines. Although this process benefits from the "public good" status of the basic components of these drugs, such status also leads to a loss of control by Chinese institutions over their industrial exploitation by foreign firms on the world market: "Our mistake was not to realize that publication of our data made that information public property, and it was lost to our control and claims of ownership" (Zhang Jianfang, 2013).[19] Above I described the tension between WHO and Chinese inventors over TDR's separate development of arteether in the late 1980s. This process of disappropriation is also facilitated by the barrier of manufacturing

[17]TDR archives M20-372-5.

[18] This is reminiscent of the controversy raised by MSF about the delay in WHO recommendations for introducing artemisinin-based medicines in Africa (Balkan & Corty, 2009). Up to the early 2000s, WHO stressed the price barrier to deploying these new medicines in Africa: "The substantially higher cost of ACTs is probably the major obstacle to the implementation of this strategy, especially in sub-Saharan Africa. As a public health measure, subsidies could be justified, but assurance is needed that financial mechanisms will be sustainable" (The use of antimalarial drugs. Report from an informal consultation, WHO, 2001).

[19] In recent years, Chinese lawyers have been defending filing patents on isolated compounds from traditional Chinese medicine, which makes it possible to control the inventions and to organize royalty returns to the sources of these patents (S Xiating, 2011).

standards and clinical studies: “there are many commercial interests in this area of development outside of China… Unless the manufacturing issues can be successfully addressed, China will lose its competitive advantage to other companies outside of China who are able to manufacture certifiable products at lower cost” (TDR, September 1992). Hence the TDR-funded actions to implement GMP standards in Chinese factories. These plants have actually produced Paluther® for Rhône-Poulenc and are participating in a joint venture with Novartis to produce Coartem.

Chinese firms have so far registered 26 percent of the WHO prequalified artemisinin-based medicines; Indian firms hold prequalifications for 50 percent.[20] However, the market share of Chinese firms is limited: in 2012, the sales of Guilin, the only prequalified Chinese manufacturer, represented 1 percent of the market in terms of the value of global donors. At the same time, Indian manufacturers captured 60 percent of the global ACT market,[21] due in part to earlier WHO certification. In 2013, Guilin supplied 5.5 percent of the ASAQ market compared to Sanofi’s 90 percent (Malaria Medicines Landscape, op. cit.). However, China supplies the majority of the active ingredients for these drugs, particularly artemisinin and artemether APIs, including to India (Huang et al., 2016).

2) The globalization of Coartem: agreements between Novartis, CITIC,[22] and WHO

Three quarters of the global ACT market consists of the AL combination. Until 2008, Coartem®, produced and marketed by Novartis, accounted for 80 percent of the AL combination market, before falling to 12 percent in 2013 in the face of Indian prequalified generics. This combination is a Chinese invention, developed, clinically tested, and even patented in China in 1990. Novartis acquired the market through two main agreements: one with CITIC in 1991, without WHO intermediation, to complete the industrial and clinical developments and bring them in line with international standards; and the other with WHO in 2001, at Novartis’ request in 2000, since WHO is the required point of entry for building and even administering this market.

The inventor of Coartem, Zhou Yiqing, was one of the actors in the negotiations with Novartis, and provides us with the justifications for this cooperation: “No Chinese pharmaceutical company was capable of introducing this medicine to the rest of the world. So I went to the Ministry of Science and Technology, which introduced me to China International Trust and Investment Corporation—CITIC—the only Chinese state enterprise at the time that was authorized to deal with foreign investors. With the State’s approval and CITIC’s

[20] See List of Prequalified Medicines for Malaria, WHO, 2020.
[21] Malaria Medicines Landscape, UNITAID, 2015.
[22] China International Trust and Investment Corporation, a public company created in 1979.

help, we were introduced to Novartis."[23] Chinese researchers welcomed industrial cooperation with Novartis "because of their professionalism and eagerness to cooperate." The cooperation agreement included the re-evaluation of the therapeutic combination using international standards: "Novartis requested both parties to repeat preclinical studies, clinical trials, and a complete review of all research data. The conclusion reached was that data of our initial experiments and studies coincided with the results of the repeat studies by an international research company" (Zhang Jianfang, p. 136*).* The registration dossier for Coartem® submitted by Novartis, which is in the WHO archives, consists of an amalgamation of Chinese pre-clinical and clinical data and data produced by the multinational company.[24] Recall that the AL combination was registered in China in 1992 and produced by two national companies, Kunming Pharmaceutical Factory and later the Zhejiang Xinchang Pharmaceutical Factory (Zhang Jianfang).

The first patent on the AL combination is co-owned by China and Ciba-Geigy: "In 1991, to help our team get patents around the world, Novartis established a partnership with the Institute of Microbiology and Epidemiology and Kunming's Pharmaceutical Corporation, through Citic. Together we co-developed Coartem" (Zhou Yiqing, WHO Bulletin, 2009). The seven inventors are all Chinese researchers with Zhou Yiqing as the primary inventor, and Ciba Geigy and the Chinese Institute of Microbiology and Epidemiology as the applicants. The international extension of this patent, through 2011 covered 52 countries, 15 of which are in Africa (including Egypt, Kenya, Morocco, Nigeria, and South Africa, which all host local pharmaceutical production). It should be noted that 17 African countries where Coartem® is registered were not covered by this patent (Benin, Burkina Faso, Côte d'Ivoire, Ethiopia, Gabon, Ghana Guinea, Madagascar, Mali, Mauritania, Mozambique, Niger, Senegal, Tanzania, Togo, Zimbabwe, and Zanzibar). Generic versions could therefore be legally produced or imported into these latter countries. Ciba-Geigy strengthened its patent portfolio in the 1990s and obtained full ownership without the Chinese institutions, and in 1999 filed a patent on lumefantrine derivatives. In the 2000s, it obtained exclusive patent rights for Coartem® dispersible, developed in collaboration with the Medicines for Malaria Venture (MMV).[25] In 2014,

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[23] "Ancient Chinese anti-fever cure becomes panacea for Malaria. An interview with Zhou Yiking", Bulletin of the World Health Organization, volume 87, n° 10, October 2009. P 743-744.

[24] The same amalgamation of Chinese clinical data and Rhône Poulenc data can be found for the Paluther® registration.

[25] MMV was created in 1999 by development funding from Switzerland, Great Britain, and Germany, together with funding from the World Bank and the Rockefeller Foundation. MMV in some respects takes over from TDR for developing and industrializing new antimalarial drugs through Product Development Partnerships between academia and industry. Since 2015, MMV also manages the two ACTs invented by DND*i*, ASAQ and ASMQ.

Chinese inventors patented a new formulation of the combination: "preparation of artemether and benflumetol (or lumefantrine) compound fat emulsion for injection, and application of same for malaria treatment"[26]—that is, a sort of reappropriation of this medicine (patent coverage is however limited to China).

At the beginning of 2000, Novartis offered WHO a USD 1 pediatric Coartem® in endemic countries. The multinational company noted that very few countries had registered Coartem® at that time, and that adoption of the combination therapy would depend on the WHO's commitment: "What happened is that almost no government was interested in buying the drug. But then WHO changed the policy and we saw a change in behavior and some governments like Zambia for example placed some orders" (D. Vasella, Novartis, January 2007).[27] Furthermore, WHO refused to register Coartem® in 1999 on its list of essential drugs due to its high price (USD 4.5) compared to the anti-malarial drugs used previously. It was also a new drug for which there was little feedback on its use. At the same time WHO launched the Roll Back Malaria[28] initiative with the goal of reducing the incidence of malaria in Africa.

The agreement signed in May 2001 between WHO and Novartis aimed to complete the clinical data on the use of Coartem® and to set the price, which must not be at a profit when the drug is distributed in the public sector, and to establish the market. The agreement initially called for a Phase 4 clinical trial in three African countries to fill out data on Coartem® adherence, efficacy, and safety. The two partners agreed on co-ownership of the data from this trial, which was financed on a shared basis. WHO, via TDR, would also collaborate with Novartis to improve the drug packaging to increase patient compliance. This collaborative development work (Article 2: Collaborative development work)[29] helps justify Coartem®'s preferential price for the public sector, as public funds have been used for R&D.

This policy was discussed at a joint WHO/WTO (World Trade Organization) workshop in April 2001,[30] at the time when Pretoria's trial on South Africa's drug law was winding down.[31] Novartis participated in the workshop and presented the company's differentiated pricing and marketing strategy to develop the artemether/lumefantrine combination for two market segments: "The representative of a pharmaceutical company describes how a malaria drug, Coartem®/Riamet®, was designed from the beginning of the product's life, to be packaged, branded, registered, and priced differently for use

[26] Patent WO2014/180011A1, filed by Xi'an Libang Pharmaceutical Co., Ltd.
[27] RBM archives M50 372-3, WHO Geneva.
[28] Roll Back Malaria is a consortium for coordinating public and community health actions to combat malaria. It was created in 1999 by WHO, the World Bank, the UNDP, and UNICEF. It brings together a wide variety of partners: governments, multinationals, generic manufacturers, associations, universities, foundations, etc.
[29] Memorandum of Understanding between Novartis Pharma and WHO, May 23, 2001: M50 372-3.
[30] Report of the Workshop on Differential Pricing and Financing of Essential Medicines, WHO and WTO Secretariats, Norwegian Ministry of Foreign Affairs, World Health Council, April 8–11, 2001, 31 pages.
[31] Cassier M, 2002, Propriété industrielle et santé publique, [Industrial property and public health], *Revue Projet*, No. 270, 47–55.

in high- and low-income countries" (report cited, WHO-WTO, p. 16.). A provision in the Novartis/WHO agreement provides that WHO may perform audits of production costs to monitor the application of this price formulation. Such an audit was conducted in early 2003, and concluded that the price of USD 2.40 set by the agreement was lower than the observed production cost of USD 3.20 established by Deloitte, based on information provided by Novartis and without visiting the production plant located in China.[32]

One of the most important points of this agreement is that WHO will be in charge of constructing and administering this market: "WHO has agreed to sell and supply the product to Public sector agencies for such distribution on a not for profit basis" (Memorandum of Understanding, May 2001).[33] On the demand creation side, Article 5 of the agreement provides that WHO will review the registration of the AL combination in its list of essential medicines and its inclusion in its malaria treatment recommendations. Registrations that will promote the adoption of the new fixed-dose combination by States in endemic regions where resistance to chloroquine and sulfadoxine-pyrimethamine, the molecules used historically, are increasing. On the administration side of this market, WHO is setting up a mechanism for collecting purchase orders (Submission Form for Country Applying for Coartem®). A technical commission of five experts evaluates the procurement request forms. WHO does not advance funds for these purchases, which must be paid in advance by the requesting States. WHO also provides Novartis with demand forecasts for the next six months to plan industrial investments.

It can therefore be argued that this agreement formed and structured the market for public donors of ACTs while the Global Fund was in the process of being established (the WHO/Novartis agreement was signed in May 2001; the Global Fund was created in 2002). WHO in fact bore the cost of creating and administering this market, while attempting to avoid any marketing of the company: "WHO cannot allow the publication of material which provides a good public image for Novartis" (April 2002).[34] The WHO partnership and the creation of the Global Fund supported Novartis' commitment in a market considered to be unprofitable: "From the outset, Novartis was aware that in those regions where malaria is endemic there is a limited market in a commercial sense" (October 6, 2002).[35] Solvency, if not profitability, would be ensured by the growth of Global Fund interventions: "While we provide Coartem at cost, our efforts would be in vain without the Global Fund's financial aid allowing governments of malaria endemic countries to purchase the drug" (D. Vasella, Novartis CEO, April 2005).[36] Novartis will use its

[32] RBM archives M50-370-21.
[33] RBM archives M50-372-3.
[34] M50 372-3.
[35] M50 372-3.
[36] Novartis: New Study Finds Coartem (Artemether-Lumefantrine) is the Most Effective Malaria Treatment in Areas of High Resistance to Conventional Anti-Malarials, Novartis, April 26, 2005

partnership with WHO to promote itself as a "corporate citizen" (corporate document referring to "corporate citizenship").[37]

Novartis had yet another reason for investing in the development of Coartem®: "it opened up the possibility of a cooperative venture with a group in China, which at the time was novel and of general interest" (October 2002).[38] The geography of Coartem® production was disclosed by Novartis at a meeting with WHO in November 2004:[39] a plant owned as a joint venture between Novartis and China that produced the artemether derivative as well as the AL combination in Beijing. The plant was certified to GMP standards. Upstream of this plant, Novartis must contract with Chinese growers for the cultivation of artemisia and with extraction plants for the raw material, natural artemisinin.

This production and distribution system for Coartem® was put to the test in 2004–2005 when it became clear that the supply of the drug could not meet the growth in demand from countries that had adopted the AL combination as a first-line treatment. As early as May 2004, WHO notified Novartis: "Both the WHO forecast and the recent analysis of the Global Fund indicate a probability of product shortage in 2005, where around 40–50% of the demand will not be met by Novartis unless the production capacity for 2005 is increased" (WHO letter to Novartis, May 20, 2004).[40] WHO urged Novartis to fund artemisinin extraction plants in Africa. To meet the strong growth in demand (10 million treatments in 2004, 60 million in 2005, 120 million in 2006), Novartis decided in 2005 to invest in the construction of a large-capacity plant in the United States[41] and temporarily collaborate with a plant in Switzerland to produce the artemether derivative to complement Chinese production. Novartis proposed passing on its capacity investments in the price of Coartem®, which WHO rejected.

Faced with this treatment shortage, which may have led some States to second-guess the adoption of ACTs, several lines of criticism emerged. MSF's Access to Essential Medicines Campaign blamed the company for the delay in investing in a program that was not profitable for it: "We had been sounding the alarm about the risk of shortages for several months, but Novartis paid little attention, because in reality it is not interested in this treatment. Novartis would never have been in this situation if the drug had been profitable" (JM Kindermans, November 23, 2004).[42] A Swiss NGO, the Berne Declaration,[43] challenged the "exclusivity" of the agreement between Novartis and WHO,

[37] M 50 372–3: WHO: Clearance of documents submitted by Novartis, September 25, 2003.
[38] Yale Initiative on Public-Private Partnerships for Health, October 6, 2002, M50 372-3.
[39] Coartem Demand and Supply Planning Meeting, November 26, 2004, Novartis Pharma Basel, M50 372-3 and M2 441-84.
[40] Archives M50-370-21.
[41] WHO & Novartis meeting on Coartem, August 31, 2005.
[42] Un médicament antipaludisme qui marche mais qui manque, [An antimalarial drug that works but is in short supply], *Libération*, December 2, 2004.
[43] The Berne Declaration was founded in 1968 with the idea of establishing more equitable relations between Switzerland and developing countries.

which failed to ensure the supply of ACTs to African countries.[44] Not only did the Swiss firm fail to anticipate WHO's increased needs, but the agreement prevents the UN organization from sourcing from other producers of artemisinin-based combinations. The Berne Declaration wanted this monopoly dismantled through a two-pronged approach: WHO purchasing additional ACTs, and Novartis renouncing its patent in developing countries. In March 2005, WHO advocated opening the market to generics: "Current production levels of ACTs are insufficient to meet current needs and there is an urgent need to increase production… There are also only a limited number of producers. Generic substitution, stimulation of domestic production of quality generic medicines should not only increase production but also lead to lower prices through market competition" (WHO, 2003b, c and f).[45]

Novartis had a de jure and de facto monopoly on production of the AL combination, and thus on the only fixed-dose artemisinin-based combination therapy available at the time (Sanofi's ASAQ only came on the market in 2007). It was also the only prequalified ACT available for the global donor market. The 2001 agreement reiterated Novartis' ownership rights, via the patent co-owned with China, and did not consider the use of generics. However, this "public market under monopoly" described by Orsi and Zimmermann (2015) would open up without a patent dispute at the end of the 2005 shortage crisis. Initially, WHO began to consider opening up to generics in 2003.[46] Then Novartis, which had committed in the agreement to building a "corporate citizenship" image following the major crisis of the 2001 Pretoria trial, could not block the path to generics, even though its patents were valid until 2011. The multinational company was careful to cede its rights to China, co-owner of the patent for least developed countries (WHO/Novartis meeting November 26, 2004).[47] In 2005, the company announced a price reduction (USD 2.15), which was justified by the sharp increase in the scale of production. Finally, the 2001 agreement rightly developed Coartem® as a global public good based on the global donor market. Defending the monopoly was impossible. In 2008, Novartis still held 85 percent of the market, but by 2013 its share had dropped to 12 percent, and Indian manufacturers now have the lion's share.[48]

3) The invention and globalization of ASAQ: between humanitarian health and multinationals

In the early 2000s, the intervention of humanitarian medicine in the field of pharmaceutical R&D through the creation of the Drugs for Neglected Diseases

[44] "Les pays africains font les frais de l'accord problématique de Novartis avec l'OMS" ["African countries bear the brunt of Novartis' problematic agreement with WHO"], April 25, 2005.
[45] Malaria Control to Day, WHO, March 2005, p 26.
[46] Improving the affordability and financing of ACTs, WHO, 2003.
[47] Archives M50-372-3.
[48] Malaria Medicines Landscape, UNITAID, 2015.

Initiative (DND*i*) led to a new geography of innovation and the ACT industry (Cassier, 2008). In 2002, MSF took over the WHO project to formulate two new fixed-dose combinations: artesunate and amodiaquine, to be developed in Bordeaux, France; and artesunate and mefloquine, to be developed by the public laboratory Farmanguinhos in Brazil (Kameda, 2014).[49] My focus here is on the development and industrialization of ASAQ, which occupies about one quarter of the global donor market according to UNITAID, behind AL.

The FACT consortium[50] has entrusted development of the ASAQ formulation to the University of Bordeaux, supported by an R&D company spun off from the University, Ellipse Pharmaceuticals. It took the researchers two years to develop a stable formulation of the combination of the two components, artesunate and amodiaquine, which are difficult to hold together. Bordeaux received analytical technology developed by Mahidol University in Malaysia, which has been working on these molecules for many years: "We saw the transfer of the analytical method, for example between Malaysia and Bordeaux. This is a South-North transfer" (interview, Pascal Millet, University of Bordeaux, July 2016). The Universities of Oxford and Bordeaux assisted research centers in Senegal and Burkina Faso with ASAQ clinical trials.

Once developed, the technology was transferred free-of-charge to Sanofi for industrialization. Sanofi had also been working on a co-formulation of ASAQ, but without devoting sufficient resources and without success. In 2004, Sanofi approached the University of Bordeaux and DND*i*, and the multinational company was able to freely exploit the technology, which was not patented, and even enjoyed a period of exclusivity until the drug was prequalified by WHO (which occurred in 2008),[51] The invention, including the initial clinical trials, was therefore performed by a "non-profit R&D pharmaceutical laboratory" in the words of Yves Champey of MSF, and then industrialized by the multinational company. The latter was forced to adopt the public good model imposed by DND*i* (Bompart et al., 2011). This public good model, defended by DND*i* as a means to promote access to medicines in resource-limited countries, is discussed by academic inventors who would have liked to file a patent, if only for the purpose of controlling the technology. However, it should be emphasized that DND*i* retains ownership of the data from the technology development and clinical trials it has funded, and has the power to decide on further transfers and new production, which took place in East Africa beginning in 2011. Unlike the agreement between WHO and Novartis, the agreement between Sanofi and

[49]This Brazilian technology was later transferred to Cipla in India.

[50] The Fixed-Dose Artesunate Combination Therapies (FACT) consortium was established in 2002. Its coordinator was Jean René Kiechel, a former pharmaceutical industry executive who became project manager at DND*i*.

[51] Sanofi would market ASAQ under two brand names: one for public markets, Asaq Winthrop®, at a price fixed by the agreement (USD 1 for adults and USD 0.50 for children), and the other, Coarsucam®, for private markets, with a free price. The private market quickly closed, and Sanofi stopped production of Coarsucam®.

DND*i* embodies the strategy of technology sharing and spin-off: "DND*i* considers its products as public goods. It does not wish to profit from its new products and wants to share the knowledge it creates by transferring technologies to other researchers and manufacturers when required."[52] Here, however, DND*i* is the inventor and sets the intellectual property policy.

Sanofi decided to locate the industrial production of ASAQ in one of its subsidiaries in Morocco, a decision that had a significant impact on the country's pharmaceutical industry. Sanofi-Maphar, located in Casablanca, was already assembling the artesunate and amodiaquine combination in co-blister pack form in the early 2000s. Implementation of the fixed-dose technology developed in Bordeaux began in 2004, with the assistance of the Bordeaux inventors (Bertin Pharmaceuticals). The transfer operation was especially delicate because the technology did not originate from Sanofi's internal R&D department. The establishment of ASAQ production was accompanied by several simultaneous investments in the Casablanca plant: (1) investments to modernize equipment: ASAQ's technology involved the purchase of new machinery to produce a two-layer drug; (2) investments to create a logistics platform to export the product, which was intended for endemic countries, mainly in Africa; and (3) investments to raise the standards of the plant in order to obtain WHO prequalification. Establishing ASAQ manufacture in Morocco was part of Sanofi's strategy to extend its reach into markets it considered "emerging" and to have production close to endemic regions of sub-Saharan Africa (interview, Director of the Sanofi-Maphar plant in Casablanca, May 2016). It should be noted that the economy of this local production had limitations: (1) the Casablanca plant imported the active ingredients for amodiaquine from India and for artesunate from Italy, produced semi-synthetically by Sanofi; and (2) the boxes of ASAQ produced in Casablanca were sent to France before being shipped back to the African markets, for reasons of financial consolidation within the company: "The finished product of ASAQ was not distributed directly from Morocco; instead it was transferred to France for onward distribution: (WHO inspection, November 2016).[53]

The installation of the ASAQ production facility in Morocco had two significant local impacts. First, replicating a technology as complex as ASAQ, which involved transfer from Bordeaux to Casablanca via a German R&D company that did the pre-industrial testing, required the creation of local industrial expertise and knowledge between 2004 and 2008, until the drug was prequalified by WHO. The industrial teams in Casablanca then had to overcome a real production crisis in 2011–2012, as the Global Fund was setting up a new system of subsidized markets, the Affordable Medicine Facility-malaria (AMFm), which will be discussed in the next chapter, and which resulted in

[52] "Pragmatic and Principled: DND*i*'s Approach to IP Management," IP Handbook of best practices, Jaya Banerji and Bernard Pecoul, 2009, 7 pages.
[53] WHO Public Inspection Report, Maphar Laboratories, Morocco, 12 pages.

strong growth in demand for ASAQ. The production process had to be adapted to address recurring problems of artesunate underdosing, which generated waste and reduced yield at a time when Sanofi was the sole supplier of ASAQ in fixed-dose combinations. The production and development teams at the Moroccan plant and in the group in France, at Ambarès near Bordeaux, were mobilized for many months to stabilize the process and the product: "The 2011 crisis put us back almost a year" (interview, quality engineer, Casablanca, May 2016).

Secondly, obtaining WHO prequalification for ASAQ, a condition for marketing the product on global donor markets, required extensive internal documentation of production and quality control operations, in close collaboration with Sanofi's central services in Paris. This work of coding and recording data led to changes in the plant's industrial culture, according to the statements by Sanofi managers in Paris and Casablanca. Obtaining ASAQ prequalification by the Casablanca plant also helped to further progress pharmaceutical regulation in Morocco: the country established a bioequivalence center in 2016, and the bioequivalence standard for generic drugs is promoted by law.

Sanofi enjoyed a de facto monopoly on the market for the fixed-dose combination of artesunate and amodiaquine until 2013: "In 2012, Sanofi accounted for approximately 98% of ASAQ volumes procured. Between June and November 2012, six more FDC ASAQs became prequalified from two manufacturers (Ipca Laboratories Ltd and Guilin), however, these still represent very small portions of the market" (Malaria Medicines Landscape, UNITAID, 2015). Sanofi was protected by the temporary exclusivity clause granted to it by DND*i* until 2008, as well as by the late publication of the formulation developed in Bordeaux (in 2011). Indian manufacturers were able to copy the technology from several sources: by reverse engineering the combinations that had been marketed since 2007 or by referring to the 2011 publication of the technology in the *Malaria Journal*. Moreover, they benefited from an incidental disclosure of the industrial process during a training session given by WHO, according to Sanofi's malaria manager (interview, Paris, February 2016). In any case, competition from Indian and Chinese generics became very strong from 2014 onwards: production at the Casablanca plant in 2015 was half of what it was in 2013, falling from 100 million treatments in 2013 to 50 million in 2015 (Cassier, 2016). In 2017, Sanofi sold the majority of Maphar's shares in Casablanca to Eurapharma, a long-standing pharmaceutical distribution group in Africa, a subsidiary of CFAO.[54] This can be viewed as a strategy of increased exports to African markets as well as a withdrawal by Sanofi in the face of low margins compared to its high-profit therapeutic areas (cancer and diabetes).

[54] This society is also discussed in chapters 1 and 2 of this book.

4) Making artemisinin-based medicines in Africa? DND*i* transfers ASAQ technology to Tanzania

In the early 2000s, several local producers of artemisinin-based drugs emerged in Africa, in the form of monotherapies, free combinations or co-blister packed combinations. The lists of producers drawn up by WHO in 2006 and 2007, aimed at encouraging manufacturers to turn away from monotherapies to produce combinations, show local generics production in Cameroon, Ghana (3 firms), Nigeria, the Republic of Congo and Tanzania. Chinese companies also established firms that produced ACTs (in Côte d'Ivoire, for example, to produce AL). African producers appear to face several barriers: (1) a technological barrier, particularly in mastering the technology of the artesunate and amodiaquine fixed-dose combination;[55] (2) the barrier of product certification standards: no African firms had thus far obtained WHO prequalification, which limited their products to local markets and prevents them from reaching global donor markets;[56] and (3) competition from subsidized products distributed on private markets through financing mechanisms such as the AMFm in the early 2010s had the effect of crowding out local firms, if only temporarily (Pourraz, 2019). However, local production for this therapeutic class intended for local and regional markets does exist (see Chapter 6).

I wish to focus here on the singular trajectory of the ASAQ technology that DND*i* decided to transfer to a laboratory in Tanzania, Zenufa. As soon as Sanofi's production was installed and certified by WHO in 2009, DND*i* embarked on a process of technology transfer to another producer in Africa. The foundation's goals were to ensure an open market, to distribute production as close as possible to the endemic regions, and to secure supplies. In 2009–2011, DND*i* commissioned a study to evaluate the production capacities of several laboratories in Africa. After considering an agreement with a Nigerian firm, initially of interest to Sanofi, DND*i* opted for a firm from the Democratic Republic of Congo based in Tanzania, the Zenufa Group.[57] Sanofi was henceforth excluded from the transfer process and the managers of the Casablanca plant now identify Zenufa as a potential new competitor. Potential, because the Tanzanian plant only started the WHO prequalification process in July 2016 and is still not on the list of prequalified combinations. This transfer operation is no less remarkable: (1) the DND*i* Foundation has scrupulously followed its policy of non-exclusive exploitation of its invention and

[55] See the ASAQ crisis that occurred in Ghana in 2004–2005, which is well documented in J Pourraz's thesis, 2019.

[56] "Kenya is also a country who produces Artemisia and artemisinin, but due to the stringent WHO prequalification standards is precluded from local manufacturer of prequalified ACTs," Health Minister, Artemisinin Conference, Nairobi, January 14–16, 2013. However, three Kenyan-based manufacturers have registered eight prequalified ARVs.

[57] Zenufa is introduced in "Pharmaceutical Manufacturing Decline in Tanzania: How Possible is a Turnaround to Growth ?", Tibandebage P et al., 2016.

encouraging local production in Africa; (2) although the technology has not been patented, DNDi that conducted the R&D does own and control the technological and clinical data for the development work, which it transmitted to Zenufa to file the ASAQ registration files; (3) it was the inventors of the technology in 2002 and 2003 in Bordeaux who carried out the technology transfer operations in Tanzania. They visited Zenufa no less than 11 times to teach the technology to the operators, supervise the purchase and installation of equipment, and conduct tests on the first batches: "We had to do a lot of work on Good Manufacturing Practices (GMP) and on our quality reference materials, both for technology and especially for documentation; everything about documentation, traceability, we helped them quite a lot with that" (Bertin, 2016); (4) more than a mere transfer of technology, this was a true industrial re-creation of the plant, including the purchase of new equipment, the introduction of two-layer technology, training of technicians and operators, implementation of production data documentation, and so forth, in a context of a high turnover of technicians, often Indian, who are in charge of management; and (5) in October 2016, a few months after the ASAQ prequalification file was submitted, the Zenufa group was bought out by Catalyst, an investment fund with a strong presence in East Africa, adding uncertainty to the project. If WHO accepts Zenufa's ASAQ prequalification dossier, it would be the first factory in Tanzania to obtain this international standard.[58]

5) Conclusion

The geography of artemisinin-based drug innovation and industry is uniquely distributed; originally developed in China, it was subsequently globalized through WHO, humanitarian medicine, and the multinational pharmaceutical companies Novartis and Sanofi. Dissemination was encouraged by the public and common good status of the basic molecules, which were legal to duplicate and combine. This resulted in the dispersion of manufacturing companies and a multiplicity of products, which WHO attempted to rationalize in the early 2000s to eliminate monotherapies that were potential sources of drug resistance, recommending the manufacture of combinations, increasingly at fixed doses. Patent claims on the first fixed-dose combination of artemether and lumefantrine, in China in 1990 and then internationally through co-ownership between Ciba Geigy and China in 1991, did not prevent the market from opening in 2005, when Novartis production capacity proved inadequate. Exclusive rights could not stand in the way of generics once these medicines had been constructed as global public goods. More generally, the market monopolies

[58] On the African continent, seven laboratories have registered 17 medicines prequalified by WHO (including Maphar in Morocco for three formulations of ASAQ). The other laboratories are located in Egypt, Kenya, and South Africa.

of Novartis and Sanofi fell victim to price competition from India's large, certified generic manufacturers.

Although Chinese inventors lost control of their inventions because they had not been patented and because of the standards barrier that separated them from world markets, Chinese researchers and industrialists continued to play an important role: part of Novartis' Coartem® production was located in Beijing; Chinese factories account for a predominant share of the production and exportation of active ingredients (85 percent of the world market, mainly with artemisinin and artemether APIs)[59] ; 85% to 90% of the extraction capacity of natural artemisinin is located in China.[60] China defended the economy of natural artemisinin against the market for semi-synthetic artemisinin developed by the Bill and Melinda Gates Foundation and Sanofi, which sold its plant; Chinese researchers continued to develop new ACTs such as dihydroartemisinin-piperaquine; prequalified Chinese products represent one quarter of WHO-certified products; and the market share of Chinese finished pharmaceutical products, which was very limited in the early 2010s, is trending upwards (Huang et al., 2016). While most drugs in this therapeutic class are used on the African continent, modest local production there remains disconnected from international markets. The technology transfer organized by DND*i* in Tanzania illustrates the possibilities of raising the industrial standards of a factory in Africa for a very modest transfer cost, and the 2019–2021 Sino-African cooperation plan includes the transfer of pharmaceutical technology.

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[59] India and North America are the main importers of Chinese artemisinin-derived APIs (Huang, and al.2016).
[60] Malaria Medicines Landscape, UNITAID, 2015.

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