The Market for Artemisinin-Based Combination Therapies and the New Era of "*Market Makers*"

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Introduction

The pharmaceutical market is not tailored to cater to the needs of patients who are located in the economically disadvantaged Southern countries, particularly in Sub-Saharan Africa. The market for medicines against global scourges such as HIV/AIDS, tuberculosis, and malaria would have not existed if left alone to market forces.

International organizations are working in numerous ways to increase the access to quality-assured medicines at affordable prices in the global South and have acquired the role of "market makers" who not only convert the need for medicines into real demand but also shape the institutional environment for market functioning by setting up the rules of exchange for market functioning. In this regard, this study sheds light on the role of international organizations in the creation and functioning of the market for artemisinin-based combination therapies (ACTs) that constitute the therapeutic backbone of malaria control programs. The study relies on multiple methodologies. First, we undertook an in-depth review of the scientific literature and reports concerning the deployment and scale-up of ACTs as the first-line of treatment against *falciparum* malaria in endemic countries. Second, we analyzed the prequalification status of artemisinin-based products registered by five Indian firms – Ajanta, Cipla, Ipca, Macleods, and Strides – In Mali as of December 2014. Lastly, the study also draws from a case-study of Synriam – a new antimalarial medicine.

Creating the demand : legitimization and financing of ACTs

Chinese researchers had discovered and extracted artemisinin from the plant *Artemisia annua* (sweet wormwood) in 1971 and soon synthesized other derivatives such as artesunate and artemether as potent antimalarials . However, their use was mainly confined to Southeast Asia. It would take almost three decades for them to receive global recognition and acceptance as the gold standard treatment against *falciparum* malaria after being recommended by the World Health Organization (WHO).

The 1990s saw a reemergence of malaria with mortality count of over a million (Krogstad, 1996; Malakooti, Biomndo, & Shanks, 1998; Murray *et al.*, 2012; Nchinda, 1998). Classic treatments like quinine, chloroquine, proguanil, and mefloquine were already ineffective due to the rise of parasitic resistance . At the end of the 1990s, WHO organized informal consultations and debates about the role and use of artemisinin and its derivatives which were the only group of molecules still highly effective against the malaria parasite. For a short span, WHO endorsed the use of artemisinin monotherapies for the treatment of severe malaria and as the treatment of choice for uncomplicated malaria in regions of resistance (WHO, 1998). However, there was growing concern that using these molecules as monotherapies may lead to a quicker emergence of resistance rendering them useless. Researchers suggested using artemisinin derivatives in combination with other parasitic drugs with antimalarial activity, i.e., the use of artemisinin-based combination therapies (ACTs), to delay the onset of resistance (Bloland, 2001; Bloland, Ettling, & Meek, 2000; White, 1999).

In 2001, under the growing pressure from researchers and international organizations such as the Médecins Sans Frontières (MSF), WHO recommended the use of ACTs in countries where resistance to classic treatments had already emerged. Later in 2006, it issued the first malaria treatment guidelines recommending ACTs as the first-line of treatment against *falciparum* malaria in all endemic countries (WHO, 2006). These recommendations were well received by the international community, and global efforts were directed to support the introduction, implementation, and scale-up of ACTs. Indeed, WHO recommendations have played a pivotal in the construction of the ACT market. As the single largest health entity built on the universal membership of the sovereign member states of the United Nations (UN), its mandate in setting the global health policy and governance remains decisive. By developing evidence-based guidelines of treatment standards for specific diseases, it acts as an ex-officio prescriber designating legitimate medicines that should be purchased by the national health authorities. As countries adhere to these guidelines, there is a growth in the demand for the specified medicines. However, most malaria-endemic countries also happen to be the most resource-constrained and a largescale switch to a comparatively more expensive ACT regimen would not have been possible without the presence of new international financing mechanisms.

In 2003, MSF launched “ACT Now” campaign urging international donors to support African countries in implementing WHO recommendations. In 2004, the newly created Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund) switched its financial

support towards the procurement of ACTs replacing classic treatment to qualified countries (Kindermans, Pilloy, Olliaro, & Gomes, 2007)[1]. Further financial support came from the establishment of the President's Malaria Initiative (PMI) in 2005 – a bilateral funding agency backed by the US government. The synergetic effect of WHO recommendations and arrival of new funding mechanisms resulted in the rapid assimilation of ACTs by countries in their national treatment guidelines. By 2011, 79 countries had adopted ACTs as the first-line treatment (WHO, 2012) and public sector procurement of ACTs increased from 11 million treatments in 2005 to a peak of 259 million treatments in 2013 (WHO, 2014).

Market stabilization using supply-side interventions

Quality assurance

Assuring the quality of medicines is essential to avoid the risks of toxicity and to guarantee therapeutic effectiveness. Typically, national and regional authorities are responsible for quality certification of medicines, and as such, they play a decisive role in the construction and organization of pharmaceutical market by providing concepts previously unknown to buyers (Montalban, Smith, & Gorry, 2012). Meanwhile, during the HIV crisis, no international authority existed to assure the quality of generics antiretrovirals (ARVs) and most developing countries lacked the necessary technical capability. As such, pharmaceutical quality was a major concern for international procurement agencies (Hoen, Hogerzeil, Quick, & Sillo, 2014; Lantenois & Coriat, 2014).

WHO addressed this problem early on by establishing the prequalification of medicines program in 2001 to guide UN agencies and other international organizations procuring ARVs for supply to developing countries. The program was soon extended to malaria (and tuberculosis) medicines.[2] The program made WHO an international technical prescriber whose role in determining the rules of trade became decisive. Indeed, the WHO prequalification has become the minimum standard of quality for medicine procurements carried out by major agencies like the Global Fund and the PMI. That is to say that only those manufacturers who have a WHO prequalified product can supply to these organizations. By July2017, 11 firms supplied 38 WHO prequalified products belonging to 6 types of ACTs Artemether-Lumefantrine (AL), Artesunate-Amodiaquine (ASAQ), Artesunate-Mefloquine (ASMQ), Artesunate-Sulfadoxine-Pyrimethamine (ASSP), Dihydroartemisinin-Piperaquine (DHA-PPQ) and Artesunate-Pyronaridine.

1 Burundi (2003), Gabon (2003), Ivory Coast (2003), Benin (2004), Cameroon (2004), Ghana (2004), Kenya (2004), Burkina Faso (2005), and Gambia (2005) were among the first countries to incorporate ACTs in their national malaria treatment guidelines.

2 At present the prequalification program covers eight therapeutic areas.

Negotiation with manufacturers

In 2001, while WHO recommended the use of ACTs in regions of resistance to classic treatments, there was also a question of maintaining a reliable supply of ACTs. In the same year, WHO and Novartis signed a memorandum of understanding where Novartis agreed to supply Coartem (AL)[3] at "cost-price" to national authorities in developing countries and the WHO agreed to provide twelve-months rolling quarterly forecasts for expected orders. Demand forecasts allowed the WHO to anticipate a new and unpredictable market while giving Novartis a four-month lead time to supply the orders (WHO, 2011). Soon, Novartis extended the offer to other public-funded procurement agencies.

So, even if there were no patents on the individual molecules used in ACTs, the initial public market formed under the quasi-monopoly of Novartis and the price ranged from $0.9 - $2.40 depending on the age/weight of the patient. This price was nearly double the price of ACTs such as ASAQ and ASSP which were available as co-blisters (two separate tablets packaged together). The ASAQ combination was available for $1.30 per adult treatment and the ASSP combination for $1.20 (Snow, Eckert, & Teklehaimanot, 2003). Even more so, ACTs were nearly 20 times more expensive compared to conventional chloroquine, which ranged between $0.10 and $0.15 in 2001 (MSF, 2003).

Two critical factors can be cited for this. First, Novartis was then the only firm with an ACT (AL) approved by a Stringent Regulatory Authority (Swissmedic in 1999).[4] Second, in 2001, the ACT market was still in its infancy as it was not used as a standard of treatment in most malaria-endemic countries. So, it lacked generic competition. In 2005, the quasi-monopoly of Novartis was challenged by the agreements signed between the Global Fund and Indian generic companies Ajanta Pharma (Ajanta) and Cipla Ltd. (Cipla) to produce AL. Novartis reacted with the first price-cut in 2006 (WHO, 2011). This was also in response to the prospective arrival of a fixed-dose combination (FDC) of ASAQ due to a public-private partnership between institutional actors and Sanofi-Aventis (Sanofi). Further, 2006 WHO recommendation fastened the incorporation of ACTs in national treatment guidelines by countries leading to consolidation of demand which created incentives for generic manufacturers to enter the ACT market following a low-cost, high volume business model.

In 2006, the WHO also issued a strong recommendation to stop the use of oral artemisinin-based monotherapies. Several pharmaceutical companies including India firms like Cipla and Ipca were among the first to show their support to the WHO call. WHO also carried out several technical briefings with selected manufacturers who accepted the Code for Artemisinin Marketing Practice (CAMP). The code required the participants to manufacture and market medicines in line with the WHO guidelines for the treatment of malaria and observe WHO or Stringent Regulatory Authority (SRA) approved GMP practices. The WHO also provided technical assistance to manufacturers who were interested in the WHO prequalification program. From the WHO's point of view, the aim was not only to

3 For more on the development of Coartem (also of Chinese origin) and the politics of "cost price" see (Orsi & Zimmerman, 2015).

4 In 2002, AL was included in the WHO essential medicines list and in 2004 Coartem became the first ACT to get a WHO prequalification and remained the only prequalified product until 2007.

eliminate classic treatments like chloroquine but also to avoid the deployment of artemisinin-based monotherapies in malaria-endemic regions, to thwart the rapid development of resistance to this active ingredient.

Securing the market for raw artemisinin

While the donor-driven market of ACTs was still taking its shape, international organizations were faced with yet another challenge of securing and stabilizing the supply of raw artemisinin which is extracted from the plant *Artemisia annua*. Since the announcement of the WHO recommendations to use ACT as the first-line treatment, the cultivation of *Artemisia annua* was trapped in a cycle of boom and bust leading to an extremely volatile market for artemisinin. The increased demand after the WHO recommendations skyrocketed the price of artemisinin at $1100/kg in 2005 (Kindermans, Pilloy, Olliaro, & Gomes, 2007). This led to massive investment in the cultivation of *Artemisia annua* resulting in an oversupply and prices were down to less than $200/kg in 2007 (Orsi & Zimmerman, 2015). This forced many extractors out of the market and led farmers to plant alternative crops. This fluctuation of prices combined with the long cycle of 14 months from planting the crop to the finished ACT product necessitated advance planning and storage of stock (Shretta & Yadav, 2012). It was believed that market forces alone would not invest in the expansion of artemisinin supply needed to meet future demands.

In November 2008, the Medicines for Malaria Venture (MMV) and the WHO convened an 'Artemisinin Forum' in Guilin, China to discuss the ways to scale-up the production of artemisinin and to ensure the supply in case of shortage (Unitaid, 2013). It was decided to put in place a temporary non-market corrective intervention to create equilibrium between supply and demand and to generate market intelligence for better communication and organization of supply-chain. The forum led to the creation of Assured Artemisinin Supply System (A2S2) in mid-2009 to address the forecasted artemisinin shortages. The project was financed by the UNITAID and received guidance from the WHO, the Roll Back Malaria Partnership, and MSF among others. A2S2 had two central functions. First, it provided a pre-finance facility to artemisinin extractors selected by eligible ACT manufacturers, i.e., approved for procurement by the Global Fund, UNICEF, and WHO. Second, it collected and disseminated market intelligence on the actual artemisinin supply situation to increase market transparency and responsiveness.[5] In March 2012, the UNITAID Executive Board decided to close down the A2S2. Nevertheless, despite the challenges the project had a positive impact on artemisinin marketplace and provided valuable lessons for future work. Most importantly, the case of A2S2 shows the willingness and extent of international organizations to stabilize the market.

Catalyzing R&D to develop new antimalarials

A crucial shortcoming of the ACT market in the early phase of scale-up was the lack of availability of fixed-dose combinations (FDCs; partner drugs in the same tablet) adapted to specific populations. AL was the only ACT available in FDC and other ACTs like ASAQ,

5 "Independent Final Review of the A2S2" can be accessed at: https://unitaid.eu/assets/End-of-project-evaluation-Assured-artemisinin-supply-system.pdf

ASSP and ASMQ were only available as co-blisters (partner drugs as separate tablets but packed together). FDCs are better than co-blister packs for treatment adherence by patients and for delaying parasitic resistance against the drug. Further, Artemisinin and its derivatives were the outcome of military research and were adapted to the adult populations while young children accounted for nearly 80 percent of malaria-related mortality (Carneiro *et al.*, 2010; Hay *et al.*, 2010).

International organizations like the Drugs for Neglected Diseases Initiative (DNDi) and Medicines for Malaria Venture (MMV) proactively worked to solve these problems by guiding research and development of new ACT formulations through public-private partnerships. Some noteworthy examples are:

- ASAQ-FDC was developed by the Fixed-Dose Artesunate Combination Therapies (FACT) partners and Sanofi under the aegis of DNDi (Pécoul, Sevcsik, Amuasi, Diap, & Kiechel, 2008). The product was launched in 2007 at a cost price of less than $1 per adult treatment and $0.5 per child treatment in the public sector.[6]

- DNDi partnered with the Brazilian government-owned pharmaceutical company Farmanguinhos/Fiocruz to develop ASMQ-FDC, and the product was first registered in Brazil in 2008 (Wells, Diap, & Kiechel, 2013). DNDi facilitated an agreement between the Brazilian company and Cipla for a south-south technology transfer to scale-up ASMQ-FDC in Asian and African countries (DNDi, 2012).

- MMV joined hands with Novartis in 2003 to develop dispersible-AL tablets suited to young children (launched 2009) (Abdulla & Sagara, 2009; Hamed & Grueninger, 2012). In fact, MMV currently maintains a dynamic portfolio of 47 projects including six already in the market (MMV, 2017).

Influencing the operational strategy of firms

In this last section, we cite two examples to show how the operating strategies of firms are both guided and limited by the rules put in place by international organizations.

WHO-prequalified Indian manufacturers of AL in Mali[7]

All five Indian manufacturers – Ajanta, Cipla, Ipca, Macleods, and Strides – who have one or more WHO prequalified AL product were present in Mali in 2014. However, they had registered both prequalified and not-prequalified products (oral suspensions, injections, and novel formulations of higher strengths) (table 1). While this raises concerns about quality assurance from the international authority, it also indicates that the growth of the ACT market has influenced these firms to innovate to penetrate the private market.

6 The drug was initially marketed under the brand name Coarsucam®, with free pricing in the private sector.

7 Findings based on the analysis of Malian product registration data (version: December 2014) and interviews conducted with public and private sector actors in Mali.

There are no patents on the active pharmaceutical ingredients used in ACTs, and Indian firms have used their R&D capabilities in re-formulating pharmaceutical drugs to develop novel dosage forms adapted to the need of target populations. Indeed, over 70% of malaria mortality is still concentrated in children less than five years of age (WHO, 2016). It is difficult for small children to swallow a tablet. We find that three firms (Ajanta, Cipla, and Macleods) have oral suspensions targeting small children with malaria (table 1). We also notice that Ajanta[8], Ipca, and Strides have registered one or more AL dosage forms with higher strengths ("40 mg + 240 mg", "60 mg + 360 mg" or "80 mg + 480 mg") mainly to target adult patients. The advantage of using higher strength is that it reduces the number of pills a patient has to take to treat malaria and can promote adherence to treatment in adults.

Further, we also observe that all five firms use the same brand name for prequalified and not-prequalified AL formulations (table 1). To clarify this point, firms are using the same brand name for products which are approved by a rigorous regulatory authority and those which are not. This behavior indicates the firm strategy to gain legitimacy. Indeed, researchers have argued that firms not only need to conform to regulatory norms of the host country, but they also need to be consistent with the established cognitive structures in the society (Dunning & Lundan, 2008; Kostova & Zaheer, 1999; Laufs & Schwens, 2014).

A long way for Synriam™: a new Antimalarial from Ranbaxy[9,10]

Synriam is an FDC antimalarial that combines faster-acting arterolane maleate (also known as OZ277 or RBx-11160) and longer acting piperaquine phosphate (piperaquine). It was first approved by the Drug Controller General of India (DCGI) in 2011 for treating acute, uncomplicated *P. falciparum* malaria in patients from 12 to 65 years of age. Synriam offers an improved "three days-three tablets" treatment regimen (Patil, Katare, Baig, & Doifode, 2014; Valecha *et al.*, 2012). The drug is also unique in the way it was developed. One of its components, arterolane, is the outcome of PDP-funded research by Medicines for Malaria Venture (MMV) (Vennerstrom *et al.*, 2004). For the further development of the molecule, MMV partnered with a Southern firm (Ranbaxy) from India. However, unsatisfied with the results of the early clinical trial, MMV left the partnership but not before giving Ranbaxy exclusive intellectual property rights (IPR) to continue further product development. After MMV left, another partnership was formed between the government of India and Ranbaxy to complete the clinical phase.

The results of the trials were positive (Valecha *et al.*, 2012) and it got approval from the Drug Controller General of India in 2011 (Patil *et al.*, 2014). Synriam was launched in India in April 2012, and by 2015, Ranbaxy had already managed to launch the product in 9 Sub-Saharan countries. However, WHO has still not made general recommendations regarding the use of Synriam citing insufficient data (WHO, 2015). As Synriam lacks recom-

8 Ajanta got a WHO prequalification for all three dosage forms in April 2017.

9 Now Sunpharma

10 Findings based on the case study of Synriam.

mendation from the WHO, it is still not included in national treatment guidelines of endemic countries and not procured by donor agencies like the Global Fund or PMI. This shows that even if Ranbaxy had a new antimalarial product, its option was limited to targeting the private sector without the legitimacy and approval from international agencies.

Conclusion

We show that market of ACTs would not have been possible without myriad market shaping interventions from international organizations. They have achieved and leveraged their dominant position to stimulate all dimensions of the pharmaceutical value curve leading to a competitive and affordable ACT market. They are acting as intermediaries between states and firms, shaping their action simultaneously. This is especially true for the public sector where firms need to conform not only to national regulations but also to the rules set by international agencies. Further, while initially, the pharmaceutical industry had been reluctant to invest in malaria research, we observe several firms collaborating with international agencies like the MMV towards new antimalarial medicines adapted to patient needs.

Table 1: Product Portfolio of WHO Prequalified Indian Manufacturers for Artemether-Lumefantrine (AL) in Mali (December 2014)

SN	Firm	Brand Name/ INN	Form	Strength	Pack-Size	WHO Ref.
1	Ajanta	Artefan	Tablet	20 mg + 120 mg	24 Tablets	MA052
2	Ajanta	Artefan	Tablet	40 mg + 240 mg	12 Tablets	MA128*
3	Ajanta	Artefan	Tablet	80 mg + 480 mg	6 Tablets	MA130*
4	Ajanta	Artefan Dispersible	Tablet	20 mg + 120 mg	6 Tablets	MA092
5	Ajanta	Artefan	Suspension	180 mg + 1080 mg	Bottle - 60 ml	No
6	Cipla	Lumartem	Tablet	20 mg + 120 mg	24 Tablets	MA064
7	Cipla	Lumartem	Suspension	180 mg + 1080 mg	Bottle - 60 ml	No
8	Ipca	Laritem	Tablet	20 mg + 120 mg	6 Tablets	MA062
9	Ipca	Laritem	Tablet	40 mg + 240 mg	12 Tablets	No
10	Ipca	Laritem	Tablet	40 mg + 240 mg	6 Tablets	No
11	Ipca	Laritem	Tablet	80 mg + 480 mg	6 Tablets	No
12	Ipca	Larither	Injection	40 mg /ml	Bottle - 1 ml	No
13	Ipca	Larither	Injection	80 mg/ml	Bottle - 1 ml	No
14	Ipca	Artemether Lumefantrine	Tablet	20 mg + 120 mg	12 Tablets	MA062
15	Ipca	Artemether Lumefantrine	Tablet	20 mg + 120 mg	18 Tablets	MA062
16	Ipca	Artemether Lumefantrine	Tablet	20 mg + 120 mg	6 Tablets	MA062
17	Macleod	Lumiter	Tablet	20 mg + 120 mg	24 Tablets	MA091
18	Macleods	Lumiter	Suspension	180 mg + 1080 mg	Bottle - 60 ml	No
19	Strides	Combiart	Tablet	20 mg + 120 mg	24 Tablets	MA088
20	Strides	Combiart	Tablet	80 mg + 480 mg	6 Tablets	No

** Products were only approved on April 21, 2017.*

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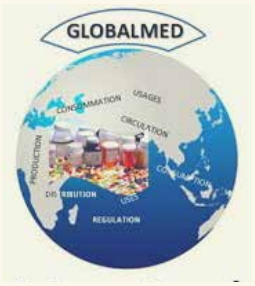
OUIDAH, BENIN

Regulations, Markets, Health

QUESTIONING CURRENT STAKES OF PHARMACEUTICALS IN AFRICA

from March 26 to 29, 2018



OUIDAH, BÉNIN

Régulations, Marchés, Santé

INTERROGER LES ENJEUX ACTUELS DU MÉDICAMENT EN AFRIQUE

du 26 au 29 mars 2018

ACTES | PROCEEDINGS

Baxerres C., Marquis C. (coord.)
(on-line, déc.2018)

Actes électroniques, hal-01988227, Décembre 2018
Electronic Proceedings, hal-01988227, 2018, December

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