Between humanitarian medicine and pharmaceutical capitalism — the singular trajectory of artesunate-amodiaquine for treating malaria (1999)

Maurice Cassier
Paris, September 2016

Artesunate-amodiaquine, currently available mainly in the form of a fixed-dose combination therapy, is one of the most sold and used ACTs (accounting for roughly 25% of the ACT market in 2013, although far behind the arthemeter-lumefantrine combination that had three-quarters of the market in that year)[1]. It is commercialized mainly in Africa, especially on the large donor markets for the subsidized public and private sectors (Global Fund, AMFm). The economy of this molecule is unusual, as it has been based since 2004 on a partnership between MSF-DNDI and the multinational Sanofi that produces it at its Casablanca factory in Morocco. It has also benefited from an agreement on a fixed price and zero profitability for public markets (based on the "no profit, no loss" principle). In this paper I present the main singularities of the history and economy of this medicine, that is: its invention in France by the FACT, an international consortium set up in 2002

[1] This relative share is expected to remain stable until 2018 (UNITAID, 2016).

by MSF; its appropriation (the technology was not patented); its transfer and industrialization in Morocco by Sanofi; its adaptation to donor markets — Sanofi's ASAQ has been pre-qualified by the WHO since 2008 —; the recent upsurge of competition from Indian generics producers, which is rapidly shrinking Sanofi's market share and production; MSF-DNDI's policy of technology transfer to another pharmaceutical laboratory in Africa, in Tanzania, which has just submitted its pre-qualification application to the WHO; and, finally, the development of a new technology to produce a synthetic raw material to replace or complete the natural raw material offer, within a partnership between Bill Gates, MMV and Sanori.

I was able to interview people at Sanofi and the innovative firms that had developed ASAQ because this medicine fits into a particular segment of pharmaceutical capitalism that is expected not to yield profits — or very few —, unlike the cancer or diabetes medicines also sold by Sanofi.

1) A collective and humanitarian invention

The idea of associating the two molecules artesunate and amodiaquine in a free or a fixed form predated MSF's project set up in the early 2000s. Artesunate was developed in China in the 1980s but was not patented, and amodiaquine was patented in 1949 by Parke Davis but has fallen into the public domain. Their combination is therefore subject to no intellectual property restrictions. A WHO report disclosed in 1998 identified the evaluation of artemisinine-based combinations, including artesunate and amodiaquine, as an R&D priority. In April 2001 the WHO recommendations on "antimalarial drug combination therapy" reported therapeutic evaluation trials on the free combination of artesunate and amodiaquine in several African countries. The idea of combining the two molecules in a single tablet was not new when MSF and the DNDI set up an international research consortium in the early 2000s. This research collective, based on the work of the WHO's Tropical Diseases Research and the neglected diseases movement under the impetus of MSF since the mid-1990s, financed R&D at Bordeaux University and one of its spin-offs, the start-up Ellipse Pharmaceuticals. While the idea of the combination was not new, the technology invented to combine the two molecules, which usually deteriorate when they are mixed, was

indeed new. After devising and testing several solutions at the university, Ellipse Pharmaceuticals developed an original technology to obtain a bi-layer tablet with a high level of stability over time. This invention overtook esearchers at Sanofi who were working in parallel on the same combination. We can call it a collective and humanitarian invention insofar as: it was coordinated by MSF, which had become an R&D entrepreneur by founding the DNDI; it produced a sharing of technologies within an international consortium, the FACT; and it was put into the public domain to be copied freely. This consortium of universities and R&D start-ups was financed by public and philanthropic funds. It carried out both the industrial development and the clinical trials, and Sanofi recovered all of these data free of charge. As in the case of many therapeutic innovations for tropical diseases today, the invention took place outside of the industrial research context.

2) Appropriation of the combination

Accounts of the invention of ASAQ, published by MSF-DNDI and by Sanofi in the *Malaria Journal*, all emphasize the fact that the ASAQ formulation technology developed in Bordeaux was not patented; it is thus qualified as a "public good". The Bordeaux researchers however do not all agree with this public good policy adopted by MSF and DNDI in the wake of the Campaign for Essential Medicines that MSF launched in 1999 and the 2001 Pretoria trial. While some think that this solution facilitates the copying and dissemination of the invention and its production, others tend to think that the DNDI would have been in a better position to control the industrialization of ASAQ if it had patented it. Yet, even though the DNDI does not have a patent, it does have the data on the invention of ASAQ, which is kept confidential, and owns the exploitation licences on the invention. The non-profit foundation has granted exploitation licenses on the technology twice: to Sanofi in 2004, and more recently to the firm Zenufa in Tanzania. However, insofar as there is no patent, Indian laboratories are free to copy the technology and to commercialize it. According to the inventors in Bordeaux, this is easy to do. Another noteworthy fact is that the copying of the technology was made possible by the WHO's unexpected disclosure of the industrial data

supplied by Sanofi for the ASAQ pre-qualification (Sanofi interview, February 2016). Copying has therefore been facilitated via several routes: the publication; the pre-qualification file put online for a while; reverse engineering of the product, which is licit; and voluntary licences and technology transfers distributed and controlled by MSF-DNDI.

3) Industrialization by Sanofi: the creation of local knowledge in Morocco

Sanofi thus acquired a technology that had not been developed in-house. At the same time, the firm had to learn this technology and adapt it to its Moroccan factory. It also had to comply with WHO standards and to overcome the many difficulties of producing a fixed-dose combination, which took several years. Learning the technology took sustained interaction with the inventors in Bordeaux and the German sub-contractors who had produced the first pre-industrial batches and who were supervising production in Morocco. The first inventors in Bordeaux provided the technical and clinical data in the pre-qualification that Sanofi filed at the WHO in 2007. Then, in 2011-2012, the team at the Casablanca factory faced a production crisis just

as the AMFm demand for ASAQ was being established. It had to adapt the production process to solve recurrent problems of under-dosage of artesunate which were difficult to explain and decreased the efficacy at a time when Sanofi was the only supplier of ASAQ in a fixed-dose combination. The production and development teams at the Moroccan factory and in France devoted many months to stabilizing the process and the product, adapting the machines and flow of materials and adjusting the production parameters: “the 2011 crisis hit us between 2011 and 2012” (quality control engineer). Improvements to the industrial process and product-measurement methods attest to the local creation of industrial knowledge that was essential to productivity and quality. Although Sanofi benefited from the invention freely, its industrial application did have specific costs.

4) “Investments of form”, of control and of documentation, to ensure that this production complied with WHO standards

The ASAQ produced in Morocco complies with the certification standards defined by the WHO in the early 2000s for the generic markets for Aids,

tuberculosis and malaria medicines (that is, WHO pre-qualification). While the pre-qualification system is used primarily by generics — especially Indian — producers, Sanofi and the DNDI applied for this certification for a new brand medicine, ASAQ Winthrop, with a view to accessing the large international donor markets. The Bordeaux inventors contributed their technical and clinical data, and Sanofi added its own industrial and clinical data to put together a pre-qualification file. The Maphar factory is today still the only Moroccan factory to have WHO prequalification. This certification did not require heavy industrial investments, but it did need quality procedures to be strengthened, production and quality-control data to be collected, production incidents to be documented and signalled to the WHO, and all changes in the production process to be recorded and communicated Once the technology and the products had been stabilized, it was necessary to guarantee the procedures for recording production data, for solving technical problems, and for documenting industrial events. Obtaining the pre-qualification required many interactions between the various departments of the Sanofi group and the Casablanca factory. Moreover, the renewal of certification every three years, with a visit to the industrial site by WHO

inspectors, is a source of tension for the industrial organization.

5-Sanofi's de facto monopoly and the competition of generics producers

Sanofi's bi-layer tablet was put on the market in 2008 when the group was granted WHO pre-qualification. Until 2012 and even up to 2013, Sanofi had a de facto monopoly on the ASAQ fixed-dose combination market (but no de jure monopoly). In 2012 and 2013, under the impetus of AMFm's procurement programme, the Casablanca factory's production rose steeply. For the past two years it has been confronted with competition from low-cost Indian producers and has halved its output (from 100M courses of treatment in 2013 to 40-50M in 2016). As Sanofi cannot compete with these manufacturers' low prices, it is putting its marketing emphasis on quality — although Indian and Chinese producers are also pre-qualified now — , on the stability of its tablets, and on the user support services that it offers. It has for instance highlighted the recent difficulties of one of its rivals, IPCA, which had WHO certification withdrawn from one of its products.

6- Sanofi’s marketing around the notion of “local production”: realities and limits

Sanofi’s marketing department has been playing the “local production” card in Africa near malaria-stricken areas. The group has firmly established its production in a country that has developed an industrial base since the 1950s and ‘60s. We have seen that the teams at the Casablanca factory developed local industrial knowledge to overcome production crises and to optimize its production. At the same, the ASAQ produced in Casablanca arrives in France by boat before being shipped back to African countries, and the revenue from ASAQ is consolidated at the corporate level in France and not by the local pharmaceutical company.

7- The DNDI’s policy of technology transfer to Tanzania

MSF and the DNDI have always supported the spread of ASAQ production in Africa, to the areas concerned by malaria. This strategy was first adopted in collaboration with Sanofi, in Nigeria, and then independently of the multinational, in

Tanzania. The DNDI commissioned an evaluation of African laboratories in 2009-2010, before choosing the Zenufa group in Tanzania. Technology transfer started in 2011 and is still ongoing, and a WHO pre-qualification application has just been filed. It has necessitated specific industrial investments to produce the bi-layer tablet, as well as many interactions between the technical teams working on the transfer. Sanofi Morocco, which has been excluded, sees this as additional competition. It hopes to have some extra time to maintain its own production in Morocco before Zenufa obtains WHO certification and fully launches production in Tanzania.