# PARTNERSHIP FOR THE DEVELOPMENT OF ANTIMALARIAL COMBINATION THERAPY IN BRAZIL: **LESSONS FOR INNOVATION IN NEGLECTED DISEASES**

— Final Report —

DNDi
Drugs for Neglected Diseases *initiative*
*Iniciativa* Medicamentos para Enfermedades Olvidadas
*Iniciativa* Medicamentos para Doenças Negligenciadas

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## ILLUSTRATIONS



## ACRONYMS

| | |
|---|---|
| **ACT** | Artesmisinin- based combination therapy |
| **AQ** | Amodiaquine |
| **AS** | Artesunate |
| **ASMQ FDC** | Artesunate-Mefloquine Fixed-Dose Combination |
| **Anvisa** | Health Surveillance Agency (Brazil) |
| **GMP** | Good Manufacturing Practices |
| **S&T** | Science and Technology |
| **CAME/MSF** | Doctors Without Borders Campaign for Access to Essential Medicines |
| **Conass** | National Council of State Health Secretaries (Brazil) |
| **Conasems** | National Council of City Health Secretaries |
| **FACT** | Fixed-Dosed Artesunate Combination Therapy Consortium |
| **DHA** | Dihydroartemisinin |
| **DNDi** | Drugs for Neglected Diseases initiative |
| **FDC** | Fixed-dose combination |
| **IAVI** | International AIDS Vaccine Innitiative |
| **API** | Active pharmaceutical ingredient |
| **LEM** | List of Essential Medicines |
| **MMV** | Medicines for Malaria Venture |
| **MoU** | Memorandum of Understanding |
| **MQ** | Mefloquine |
| **MSF** | Médecins Sans Frontières/ Doctors Without Borders |
| **WHO** | World Health Organization |
| **PAHO** | Pan-American Health Organization |
| **R&D** | Research and Development |
| **PDP** | Partnership for the Development of Product |
| **PNCM** | National Malaria Control Program (Brazil) |
| **PPQ** | Piperaquine |
| **PQ-WHO** | WHO List of Prequalified Medicinal Products |
| **Ravreda** | Amazon Network for the Surveillance of Antimalarial Drug Resistance |
| **RH** | Human Resources |
| **SP** | Sulfadoxine-pyrimethamine |

## INTRODUCTION

About 3.3 billion people – half of the world's population – are at risk of developing malaria in the 106 countries where this disease is endemic. In the World Malaria Report 20121, the World Health Organization (WHO) estimated 219 million cases of malaria in 2010 worldwide; 91% of those are related to Plasmodium falciparum.

Despite being preventable and treatable, malaria killed some 660,000 people in 2010, 86% children under the age of 5 years[2]. According to the 2010 WHO guidelines for the treatment of malaria[2], the estimated number of malaria cases per year in Latin America was 1.3 million, 35% of them due to P. falciparum; mortality was estimated at 1,800 deaths a year, 29% of which being children under the age of 5 years.

Early diagnosis and effective treatment are essential in the efforts to control and eventually eliminate the disease. Currently, the best available treatment for P. falciparum malaria is artemisinin-based combination therapy (ACT), preferably in fixed-dose combination (FDC)[3].

In 2002, the Doctors Without Borders (MSF) established the FACT (Fixed-Dose Artesunate Combination Therapy) consortium, to develop combined therapy (FDC) for the treatment of malaria. The 2001 World Health Organization (WHO) strategy[4] to delay the development of antimalarial drug resistance indicated the fixed-dose combination of Artesunate (AS) + Mefloquine (MQ) as the best option for Latin America and Asia.

In Brazil, a partnership with the public laboratory Farmanguinhos, of the Oswaldo Cruz Foundation (Fiocruz), was established within the scope of the FACT project aiming at the development of ASMQ FDC5 therapy.

The consortium was a global example of success, with partnerships established in five continents, addressing formulation, clinical trials, control, manufacturing, recording and access, so that new artemisinin-based combined therapy (ACT) for the treatment of malaria caused by P. falciparum, the most lethal of the parasites that cause the disease, could be developed[6].

In the clinical stages, the epidemiological and drug-development expertise of research institutions, and public and private pharmaceutical laboratories of different countries, such as Brazil, India, France, Malaysia, Thailand and United Kingdom were combined.

ASMQ FDC was developed, consisting of one or two tablets taken in single dose for 3 days, in a 2-in-1 combination that ensures the two drugs are taken at the same time, in the proper dosage: a simple treatment suitable for children and adults[5,7].

One of the main features of this medication is its 3 year shelf-life, which, along with ASAQ, is the longest of any of the combined therapy options against malaria.

Two studies that examined the development of ASMQ in greater depth have been identified in the literature[6,8]. The first[8] focuses the development of a model that is oriented towards the health needs of developing countries, while the second[6] analyses the collaborative approach of international partners as a potential strategy for the development of medications for neglected tropical diseases.

One of the gaps of this investigation was how the different access-to-medication dimensions were considered throughout the medication-development process, and which access-related hurdles and barriers were encountered.

## STUDY RATIONALE/ RELEVANCE

The history of the ASMQ FDC development illustrates the potential of public-private partnerships, as well as the challenges, for the development of products for neglected diseases. The combined experience and resources of research institutes, the national malaria control program, industry and non-for-profit organizations may be decisive components for the effective control of this neglected disease.

Notwithstanding the successful development of a first-line treatment, a number of knowledge gaps about the process remain to be addressed, such as the strength of the relationships, and the efficacy and efficiency of this public-private partnership.

From the perspective of a joint effort in health-related Science and Technology (S&T), it is necessary to assess the progression of knowledge in terms of technological innovation and good practice in the pharmaceutical sector. This is necessary not only to enable the acceptance of such knowledge by partners, but also to enable its replication, through the dissemination of the knowledge and experience accumulated, in order to build capacity locally.

At this stage, when the outcome of the consortium is known, it is time to conduct a critical and constructive assessment, in order to draw conclusions and understand the lessons learned from this experience. This is a story that had not been documented in its entirety, but it has been compiled from the memories and perceptions of each of the players involved.

## STUDY QUESTIONS

- What were the main accomplishments, barriers and facilitators, considering the core access elements found in the Frost & Reich model9?
- Has the ASMQ project reflected the dimensions – advocacy, capacity building, and delivery – of DNDi's mission?

## GOAL

### Overall

Analyze the ASMQ development process in terms of the access-to-medication dimensions.

### Specific

- Map and describe the development stages of the partnership up to the registration of ASMQ in Brazil and in the first foreign market outside Brazil;
- Map and analyze the progression of the ASMQ development project between 2002 and 2014 according to the access-to-medication dimensions – architecture, availability, affordability and adoption, and their sub-dimensions.

# THEORETICAL AND METHODOLOGICAL REFERENCE FRAMEWORK

## Overview of malaria in Brazil and worldwide

Here we present an overview of the malaria landscape worldwide and in Brazil in particular, in the period under examination. *P. falciparum* malaria is responsible for high mortality, and is a target of the *ACT*s.

Estimates indicate that there were 227 million cases of malaria worldwide in 2000, with continuous transmission in 106 countries; five countries had over one million cases: Afghanistan, Bangladesh, Brazil, Cambodia, and Papua New Guinea[3].

International initiatives aimed at reducing malaria incidence and mortality rates that started in the turn of the millennium led to significant results, with most countries experiencing a marked reduction in incidence (figure 1).

Worthy of note is the fact that of the 106 countries with continuous transmission of malaria in 2000, 64 are close to reaching the incidence reversion target established in the Millennium Development Goals (MDG). Of these 64 countries, 55 have a good chance of reaching the targets set by the World Health Assembly and the RBM program, which established an incidence reduction rate of 75% of malaria cases by 2015.

In 2013, there were 198 million estimated cases of malaria (95%CI: 124 to 283 million), and 584,000 deaths worldwide (95%CI: 367,000 to 755,000). Most cases (about 82%) occurred in Africa (figure 2), as well as 90% of deaths due to malaria globally; pregnant women and children under the age of five are the main victims.[3]

Almost half of the world's population is at risk of being infected with malaria, with a higher concentration in poorer countries; estimates indicate there are 3.3 billion people at risk in 97 countries and territories, with 1.2 billion at high risk (>1 case of malaria per 1000 inhabitants every year).

In Brazil, most cases of malaria (about 99%) occur in the Brazilian states that comprise the Legal Amazon (Acre, Amapá, Amazonas, the Eastern areas of Maranhão and Mato Grosso, Pará, Rondônia, Roraima and Tocantins), where socioeconomic and environmental conditions favour the proliferation of the mosquito; 57 (7.1%) of the 807 cities in the states of the Amazon region are accountable for 80% of the total number of cases[10]. Malaria *vivax* is accountable for the highest morbidity (around 84% of the recorded cases)[10], and malaria *falciparum* for the highest mortality.

The highest number of cases, 637,470, in the Brazilian Legal Amazon in the 1960-2009 period occurred in 1999. In 2000 the Brazilian government started to implement the Plan for the Intensification of Malaria Control Actions in high-risk areas, with a focus on early diagnosis and treatment.

The incidence rose again between 2003 and 2005, reaching figures close to those of 1999. Factors that account for this increase include climatic changes; migration with disorganized occupation of the outskirts of major cities in the Legal Amazon, as a result of agrarian reform and deforestation projects; poor development and management of the actions recommended by the National Malaria Control Program (PNCM) in the cities; and an increase in the mosquito-vector population. The Ministry of Health subsequently started a multi-sector mobilization to coordinate population migration, and established priorities regarding surveillance, prevention and control. As a result, the number of cases started to decrease from 2006 onward. In 2007, 456,000 cases were recorded. In 2008, there was an additional drop of 31%, and the number of cases recorded (314,420) was comparable to those of 1983. In the Legal Amazon, the Annual Parasite Incidence (number of cases/ thousand people) dropped from 31.9 in 1999 to 12.8 in 2008. In 2009, some 306,000 cases were recorded in Brazil (figure 3)[10].

.

**Figure 1. Number of countries with decreases (or increases) in reported case incidence rates 2000–2013, by WHO region.**

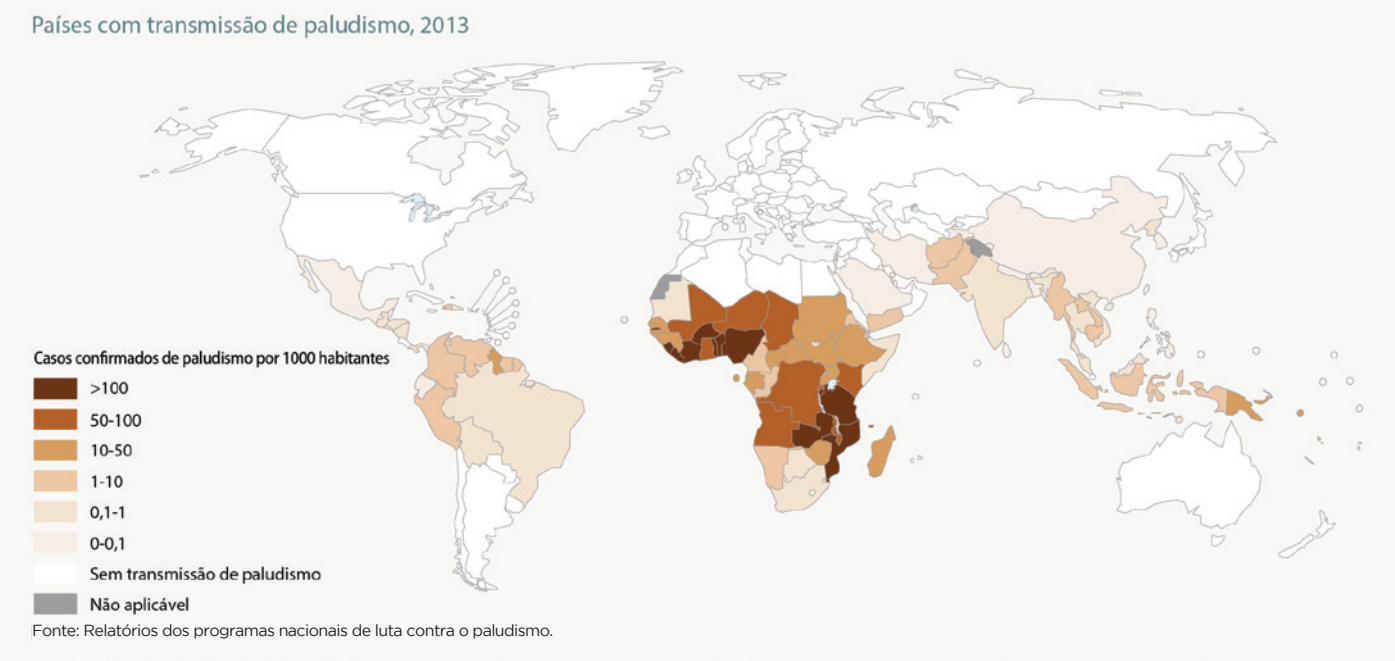

Source: The Malaria Report, WHO, 2014[3]

The PNCM believes that strengthening local management capabilities by constantly expanding the diagnosis and treatment network has contributed to reducing the number of cases from 2006 onwards. Despite a decrease in the overall incidence rates of the disease, the rates for women and for children under the age of 10 are increasing (from 34.9% of the cases in 2003 to 38.6% in 2008 for women; from 22% in 2003 to 25.2% in 2008 for children), due to environmental factors, such as the proximity of homes to mosquito breeding sites.

The predominance of *P. vivax* incidence is a recent phenomenon (starting in the 1990s), and is due mainly to the PNCM efforts towards early diagnosis and treatment.

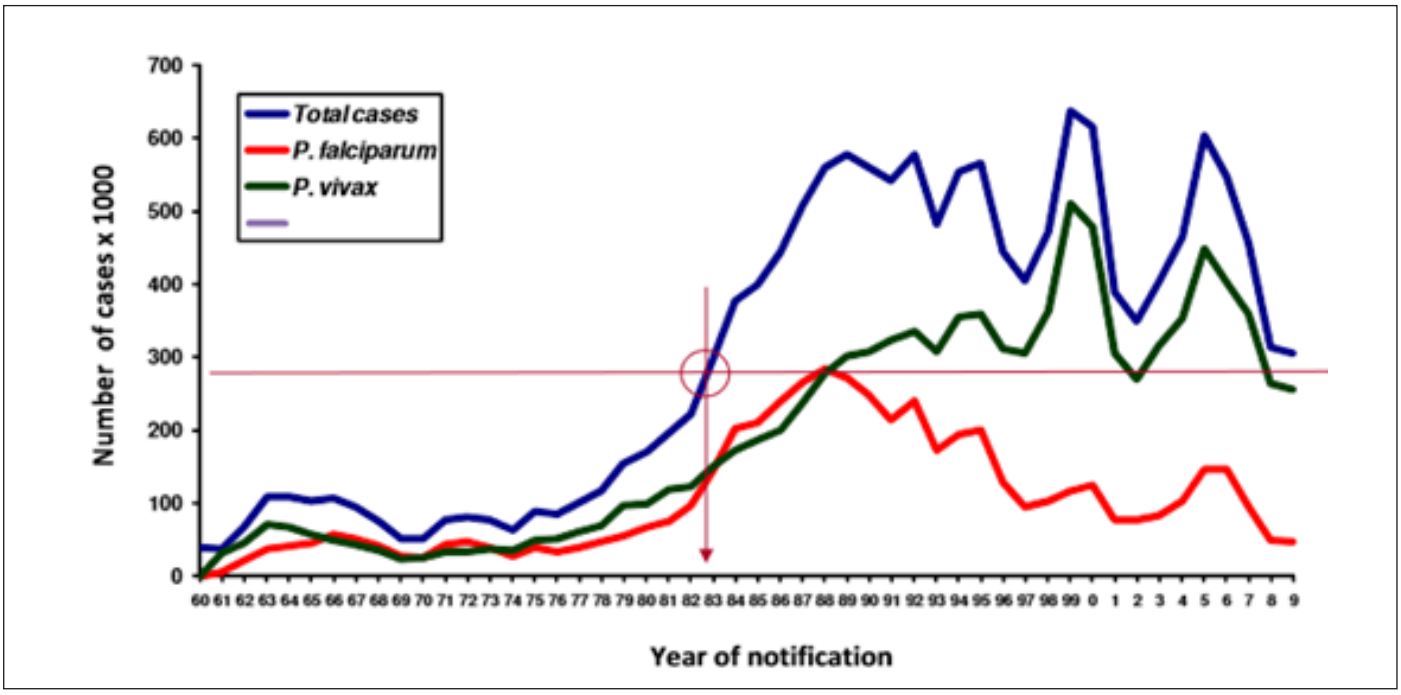
As *P. falciparum* only appears in the blood 8 or 10 days after infection, early diagnosis and proper treatment of *P. falciparum* malaria cases may prevent the transmission of the parasite more effectively than the *P. vivax* malaria cases, where the gametocytes circulate in the blood within three days of the infection.

**Figure 2. Countries with on-going transmission of malaria, 2013**




Source: Report of national programs against paludisme, apud The Malaria Report, WHO, 2014[3]

**Figure 3. Number of malaria cases recorded annually, between 1960 & 2009, in the Brazilian Amazonian region, according to plasmodium species.**




Source: Oliveira-Ferreira et al., 201010

## How *ACT* came to be indicated for the treatment of malaria: the international context

The use of artemisinin-derived compounds (artemether and artesunate) for the treatment of malaria, extracted from a plant used in Chinese medicine, dates back to the 1960s and 1970s, in Asia, in the north of Vietnam[11].

Early signs of resistance to the recommended treatments of the time were identified by MSF in the 1980s, which prompted communication with research institutions and the university in Thailand to find a solution. Early in 1990, the first clinical trials with artemisinine derivatives in combination with other antimalarial drugs were conducted, mainly at the Burmese border.[11]

As a result, from 1994, patients cared for by MSF could receive a treatment for uncomplicated malaria based on the association of artesunate and mefloquine, once a day, for three days[12]. Three years later, this organization also adopted injectable artemether. Since 1996-97, combinations that included artemisinin derivatives have been used as first-line therapy in refugee camps in Thailand.

In African countries, the malaria treatment adopted by MSF was that recommended for national protocols by WHO. In general, the therapeutic schemes included sulfadoxine - pyrimethamine (SP).[11] Series of studies were conducted to assess different therapeutic schemes that combined artesunate with different compounds (SP, chloroquine, amodiaquine) by a consortium of investigators coordinated by WHO/ TDR in collaboration with different partners, including MSF/Epicentre, the University of Antwerp, the Wellcome Trust, and others.

The first time combination medication that included artemisinine (*ACT*) derivatives, namely AS+SP, was used by a government was in 1999, in Kenya, after fatal epidemic outbreaks in different areas of that country in 1998. This was an important precedent that prompted other countries to also adopt this therapy, such as Burundi (2001), Sudan (2002) and Ethiopia (2004).[11]

In order to contribute to changing national protocols towards the adoption of *ACT*s, MSF and Epicentre, in collaboration with the Ministries of Health of the countries involved, conducted 43 clinical trials in 18 countries (8 in Asia and 35 in Africa) between 2000 and 2004. These studies represented 25% of the studies conducted[11]. In 1998, WHO published a joint CTD/DMP/TDR report addressing an informal consultation on "the use of artemisinin and its derivatives as anti-malarial drugs", with different experts making statements and presenting an overview of the existing evidence concerning the use of *ACT*s[13].

Early in the 2000s, a series of changes took place worldwide concerning the use of *ACT* as an antimalarial agent. The reason for this was that in 2001 the World Health Organization published a report of the Technical Consultation held on April 4 and 5 on "Antimalarial Drug Combination Therapy"[14], and recommended, for the first time, that *ACT* be included among the therapeutic options. The recommended combinations were: artesunate + amodiaquine, artesunate + SP, artesunate + mefloquine and artemether+lumefantrine[15]. This report indicates that the basic criteria regarding therapeutic options, in addition to effectiveness and safety, should include quality assurance, availability, affordability, and acceptability by the population at risk, so that the main therapeutic goals for this disease could be reached[14]:

- Assurance of fast and lasting cure;
- Prevention of the progression of uncomplicated malaria to severe disease and death;
- Reduction of the clinical episodes of malaria, and reduction of malaria-related anaemia in populations that live in areas of high transmission of malaria;
- Lessening the consequences of malaria-related placental and maternal infection through chemoprophylaxis or intermittent preventive treatment during pregnancy;
- Delay the development and spread of antimalarial drug resistance.

Prior to these options, only the artemether+lumefantrine combination was available as a fixed-dose combination (FDC) (brands Coartem® and Riamet®), manufactured by Novartis Pharma AG[14]. Also in 2001, WHO signed a Memorandum of Understanding (MoU) with this company, establishing access to Coartem® at cost price for a term of ten years (2001 to 2011), , so that WHO could make it available to the governments of developing countries where malaria is endemic.[15]

According to the MoU, WHO would be in charge of providing quarterly estimates of the need for the treatment, and assessing, with the use of external audits, the "cost price" of the treatment made available. The two organizations were also committed to conduct clinical trials that would collect data on treatment to be used in children weighing less than 10kg, and initiatives to improve treatment compliance[15].

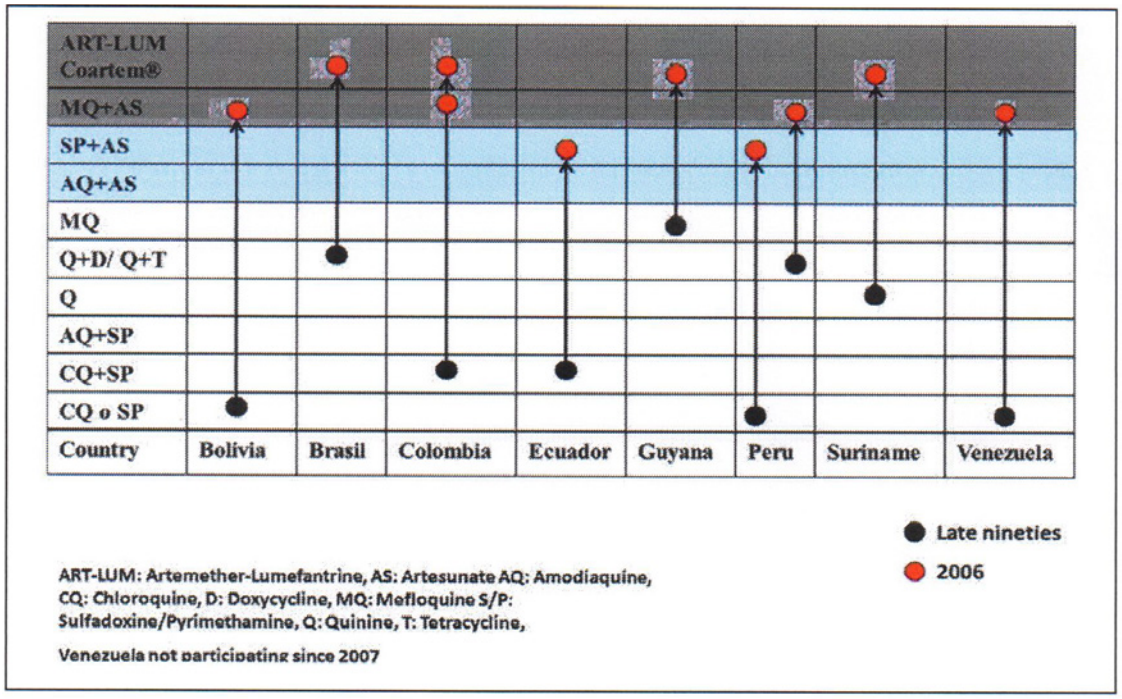
This change in the treatment of malaria, with the adoption of *ACT*s, is a result of the global acknowledgement of malaria as

being epidemic, and the development of important initiatives that played a major role in expanding access to treatment.
One such initiative is the Roll Back Malaria (RBM)[16] partnership, including WHO, UNICEF, PNUD and the World Bank, whose purpose is to provide a coordinated response to the disease. Another example is the explicit reference to the disease as one of the eight millennium development goals (MDG); goal 6 stated "Combat HIV/ AIDS, malaria and other diseases", and its targets included "Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases" and "Have halted by 2015 the incidence of malaria and tuberculosis".[17] The Global Fund Against HIV/ AIDS, Tuberculosis and Malaria (henceforth called the Global Fund), established in 2002, has become a major donor and treatment procurer for countries. In 2004, it stated that it would only fund projects that adopted *ACT*[11]. In 2006, UNITAID (the International Drug Purchase Facility) was created to implement innovative solutions to scale up actions for the prevention, treatment and diagnosis of HIV/ AIDS, malaria and tuberculosis.[18] With the use of strategies that disrupted pharmaceutical market dynamics, UNITAID has contributed to the expansion of access to antimalarial drugs in many developing countries.
In 2003, the Doctors Without Borders Campaign for Access to Essential Medicines (CAME/ MSF) advocated for the expansion of the use of *ACT* in Africa, based on a recent WHO recommendation. Under the name "ACT NOW to get malaria treatment that works to Africa", the campaign provided detailed information on the evidence for resistance to antimalarial drugs that were in use at the time, such as chloroquine and SP, and presented a rationale for their replacement[16].

In Latin America, in 2001, the Amazon Network for the Surveillance of Antimalarial Drug Resistance (*Red Amazónica de Vigilancia de la Resistencia a los Antimaláricos* - RAVREDA) was established under the coordination of the Pan-American Health Organization (PAHO) (Ravreda Official Presentation[20]). The Amazon region accounts for most (90%) malaria cases in the Americas.
Ravreda's initial goals were to assess resistance to the treatment being used so far, and to consider the adoption of *ACT* and guide changes in treatment protocols, (Ravreda Official Presentation[20]). Between 2001 and 2004, dozens of sentinel centers were established throughout the region, and in the 2003 to 2006 period, 62 studies to assess therapeutic efficacy for *P. Falciparum* malaria were conducted in eight countries in the Americas (Bolivia, Brazil, Colombia, Ecuador, Guiana, Peru, Suriname, and Venezuela). From the efficacy results ascertained by Ravreda's studies, the countries of the region adopted four *ACT*-use possibilities: AS+AQ, AS+MQ, A+L and AS+SP (Figure 4).

Even though efforts to adopt *ACT* by the different countries were based on evidence of resistance to the antimalarial drugs previously used and advocacy for the substitution of single-drug therapy, it was known that other challenges were also present. Among these, concerns about securing a regular supply[11]. Moreover, *ACT*s were more expensive than the previously available therapies[11,19]. For example, in 2003 the cost of treating an adult with monotherapy with either chloroquine or SP was 0.10 USD, whereas the cost of therapy that included artesunate and amodiaquine was 1.50 USD.
It was acknowledged that the lack of *ACT* fixed-dose combinations could hamper compliance in Africa[14] and that their development could address this[11].

**Figure 4. Changes in antimalarial policies in Amazonian countries, 2001–2006.**




Source: Ravreda, 2006

## Product development partnerships (PDPs) for neglected diseases

The World Trade Organization agreement on intellectual property rights – the TRIPS Agreement – came into effect in 1995 and gave rise to a number of questions about the implications of this international system on access to new technologies. Patent protection of medicines allowed companies that owned these patents to charge high prices, thus making access unfeasible in many countries. The main rationale for this system is the assumption that the price of treatment should cover the research and development (R&D) costs. This means that the patent protection system establishes an innovation system for the pharmaceutical industry by linking R&D costs to the final price of the product[21].

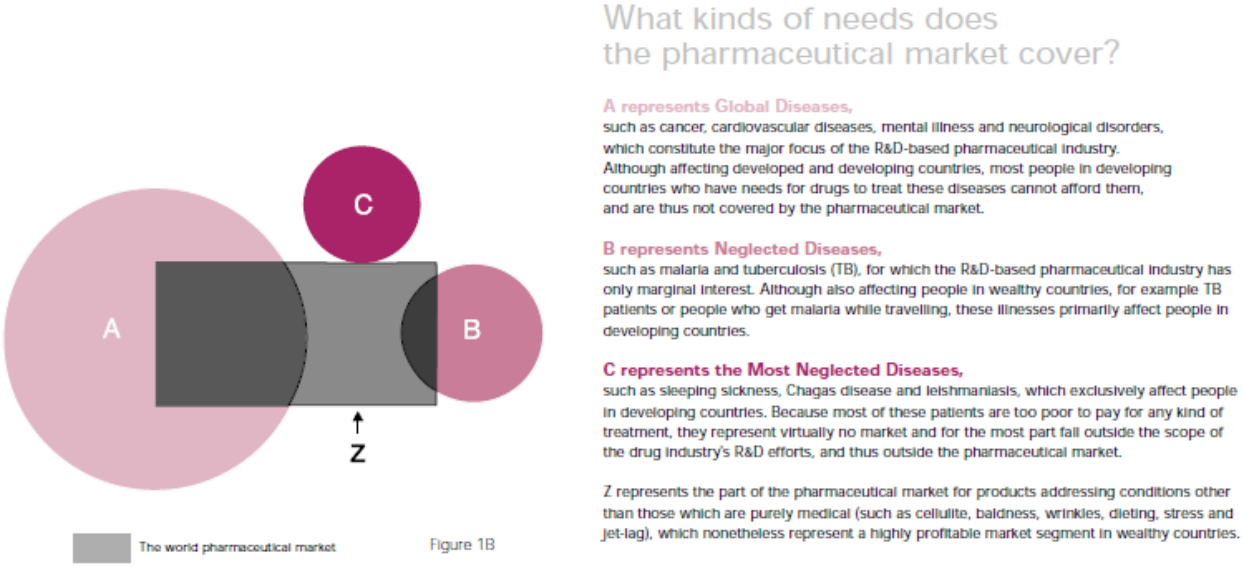
In 2001, the Doctors Without Borders Campaign for Access to Essential Medicines and the Drugs for Neglected Diseases Working Group (DND working group) published a study mapping the R&D efforts on the so-called neglected tropical diseases, and made a very clear diagnosis: very little or no R&D effort was being made by the pharmaceutical companies on these diseases. The document, entitled "Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases" (Medécins Sans Frontières – MSF, 2001)[22] made evident that innovation in the pharmaceutical industry was oriented by the potential of the market, and left a major gap for the health needs of developing countries (Figure 5).

The lack of innovation for the so-called neglected diseases was also acknowledged and set as a priority for member countries of the World Health Organization. In 2003, the World Health Assembly passed Resolution WHA 56.27[23], establishing a commission to seek to rebalance intellectual property rights, innovation and public health. After two years of work, the Commission published the CIPIH9 report in 2006. One of the diagnoses was that the intellectual property system established by the TRIPS Agreement stimulated innovation efforts towards diseases that affected mainly developing countries (the so-called type III diseases).

In the last ten years, one of the R&D responses to gaps in some of the health needs of developing countries has been the establishment of Product Development Partnerships (PDPs). In general, PDPs involve mostly non-profit organizations that manage a portfolio of projects, whether at drug discovery stages or in development for use in specific diseases. The PDP brings together different organizations, public and private, to implement projects. Some examples of PDPs include the International AIDS Vaccine Initiative (IAVI) for the development of an HIV vaccine, the Medicines for Malaria Venture (MMV), the TB Alliance (medications for tuberculosis), and DND*i*[24] itself. Of note is the fact that the initials PDP in this setting are not the same as the initials used in Brazil for the framework of the pharmaceutical industry policy for an arrangement that includes international and domestic public and private pharmaceutical laboratories for local manufacture of drugs (Partnership for Productive Development) used by the Brazil's Public Health System (SUS)[a]. The concept of PDP used in this project, differs from the one in effect in Brazil, and relates to an international concept for specific organizations.

The Drugs for Neglected Diseases initiative (DND*i*) was established in 2003, and is currently developing projects for the following diseases: sleeping sickness (African trypanosomiasis), Chagas disease, leishmaniasis, filariasis, and HIV in children. DND*i* Latin America is DND*i*'s regional arm, and is registered in Brazil as a Civil Society Organization of Public Interest (OSCIP)[b].

**Figure 5. Pharmaceutical market and coverage of diseases for which there are existing treatment.**




Source: MSF e DND Working Group, 2001. Fatal Imbalance: the R&D crises for drug for neglected diseases.

## Access to treatment

Access to treatment is essential for health outcomes. It is a core component of access to health. In the case of neglected diseases, all of which are infectious, this means the difference between life, and death or disability.

Access to treatment is a complex issue that involves a number of factors; product availability and affordability remain the fundamental elements in ensuring access. However, understanding the concept of access is essential, and includes the real possibility of a timely use of a service or product where and by whoever needs them[25].

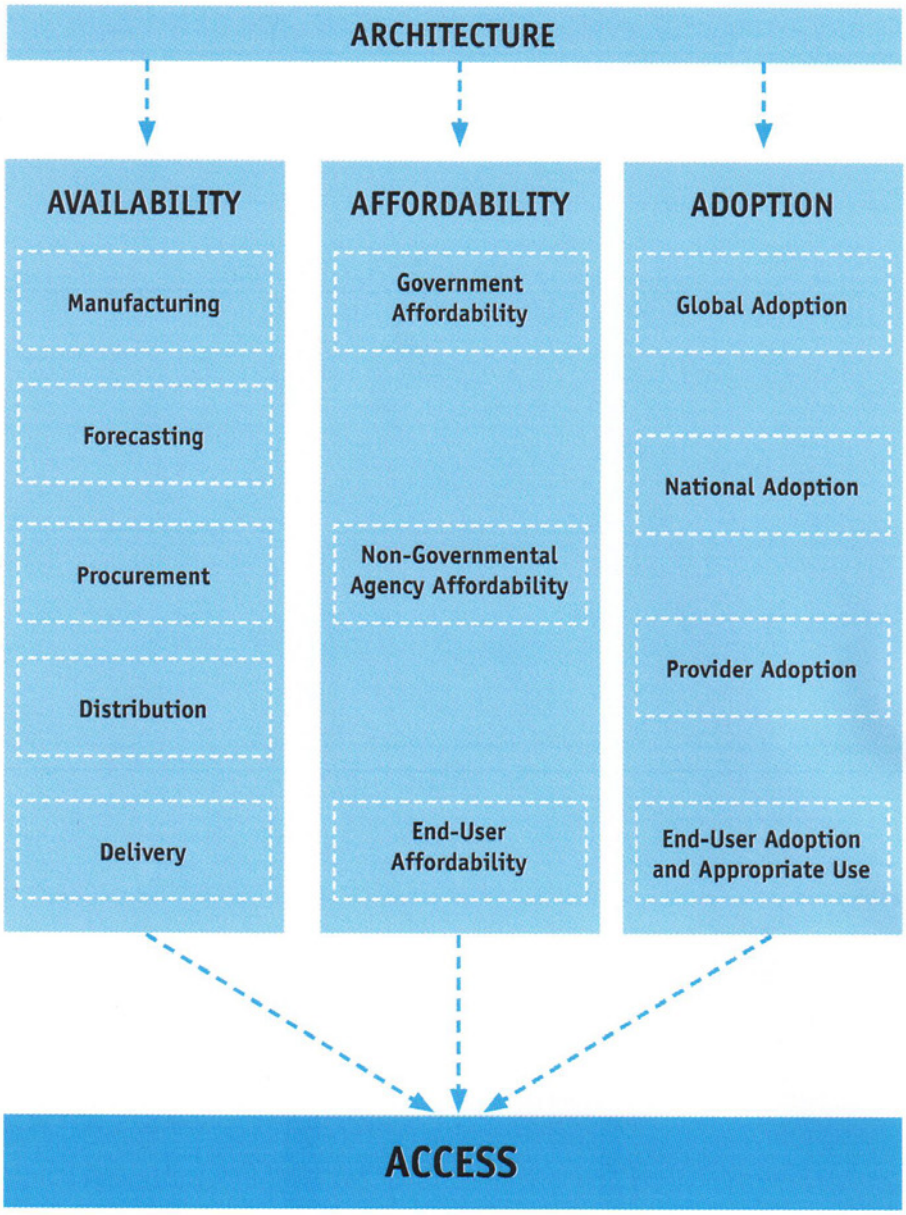
Frost and Reich[9] focused on access in terms of specific health technologies, including medicines. They justify their effort to propose a specific theoretical model by the big gap between a product being in the market and its being used by the target population, with a chance of effectively solving the problem for which that technology was created, particularly among those who are more vulnerable. They also acknowledge that the low price may be part of the problem. They point out that, in addition to technical issues, access involves social values, economic interests and political processes. The mechanisms of access should also protect users from improper use and from treatments of inferior quality.[26]

Their theoretical access model[9] considers availability, affordability and adoption, as dimensions coordinated by an overall architecture (figure 6). The definitions proposed by the authors for the access activities addressed in the model are presented in table 1.

Bigdeli *et al.*[27] performed a search and analysis of existing theoretical models on access to medication, and developed a proposition informed by a comprehensive understanding health systems and complex adaptive systems. Even though, according to this perspective, the theoretical model considers the elements of access for different health system levels, the core dimensions of availability, acceptability, affordability and geographic accessibility remain for each level of health care provision.[26,27]

a http://www.brasil.gov.br/saude/2014/08/ministerio-da-saude-cria-regulacao-para-producao-de-medicamentos
b http://www.dndial.org/

**Figure 6. Access-to-medication model**




Source: Frost & Reich, 2008[18]

Chart 1. Definition of access activities

| ACCESS ACTIVITIES | DESCRIPTION |
|---|---|
| **Architecture** | Organizational and relational structures established with the purpose of coordinating and managing availability, accessibility and adoption-related activities |
| **Availability** | Involves the logistics of production, procurement, transportation, storage, distribution and delivery of a new health technology, to ensure it gets to the hands (or mouths) of the final user. |
| **Output** | Transformation of raw material into finished products for use of sale. |
| **Planning** | Estimation of the amount of a product that must be purchased, and at what price. |
| **Procurement** | Process to obtain health technologies from public or private providers, including all decisions related to specific amounts, prices paid, and the quality of the health technologies received. |
| **Distribution** | Technology-transfer process through public or private or public-private channels. |
| **Provision** | Point of the supply chain in which the technology is physically transferred to the final user through public or private channels. |
| **Affordability** | Implies the assurance that health technologies and related services are not too expensive for the people who need them. |
| **Affordability by governments and NGOs** | Ability of procuring departments of national governments in developing countries and NGOs to procure technology . |
| **Affordability for the end user** | Possibility for the end user to purchase the technology. |
| **Adoption** | Involves acceptance, thus creating a demand for new health technology from global organizations, government players, suppliers and distributors, prescribers and individual patients. |
| **Global adoption** | Acceptance of the technology by international organizations (WHO, UNICEF, UNAIDS, UNFPA) and technical experts. |
| **National adoption** | Acceptance of the technology by policy makers at the ministries of developing countries, with political engagement, regulatory approval and adoption of treatment protocols. |
| **Adoption by the provider and prescriber** | Acceptance of the technology by the provider, proper prescription. |
| **Adoption by the end user and proper use** | Acceptance of the technology by the patient or consumer, including its proper use. |

Source: Frost & Reich, 2008[18]

## Health evaluation

Evaluation can be defined as a value judgement based on valid and socially legitimate scientific information, and involves quality, significance and effectiveness as core and inter-related issues[28,29].

Negotiations between evaluators and players, particularly those being evaluated, involved participative evaluation[12], use-focused evaluation[13], and the usefulness of the evaluation[14]; these aspects characterize the current evaluation approach.

The evaluation, showing to what degree and why interventions are effective in low and middle-income countries, is particularly important. These are the settings where vulnerable populations with poor resources are concentrated, making a determination of the effectiveness and efficiency of the technology more relevant and urgent. Moreover, there are a number of peculiarities in these settings that make it harder to "import" evidence from high-income countries[30].

The questions to ask for the evaluation depend on the stage of evolution of the intervention or program: planning, development or full operation. Therefore, if the intervention is fully operational, it is reasonable to ask about the results that were obtained and their magnitude, the main internal and external strengths and weaknesses. These aspects are relevant for the improvement of the intervention itself, and for learning and applying them to similar situations in the future.

The importance of theory-based evaluation has been strongly advocated[31]. Even though it is not a panacea, there are many reports of its usefulness in guiding evaluations with a better understanding of how different elements work together in a given situation, in order to best define the design and explain the findings[13].

In order to ensure the core pillars of the quality of an evaluation – feasibility, usefulness, property and validity – the CDC has proposed basic stages that are summarized in table 2.

**Chart 2. Main evaluation stages and matching goals**

| EVALUATION STAGES | MAIN PURPOSES |
|---|---|
| **Involving the players** | To increase understanding and acceptance of the value of the information; to involve people early on in order to encourage support for the evaluation; to increase the reliability of the evaluation; to make roles and responsibilities clear; to help to protect people; to lessen real or perceived conflicts of interest; to help increase the chances that the evaluation will be useful, and, therefore, that the results will be used. |
| **Describing the intervention** | To elucidate the purposes of the program, its development stage, the activities performed, the ability to achieve the expected results, and the development setting. |
| **Establishing the design of the evaluation** | To define the method and operational procedures that are feasible and capable of responding to an evaluation question |
| **Obtaining reliable evidence** | To ensure the application of the method as planned, including compliance with ethical care, to ensure the quality of research procedures, to ensure the necessary logistics, to implement correction measures in case of unforeseen events. |
| **Justifying the conclusions** | To analyze and interpret the collected data, in order to respond to questions posed by the evaluators. |
| **Sharing the lessons learned** | To disseminate and discuss the findings in different languages and types of communication, in order to reach the set of relevant players. This stage tends to make the interpretation of the findings richer. |

Elaborado com base em CDC[28]

## METHOD

The selected approach was the ASMQ development case study, as it allowed a more in-depth understanding of the phenomena involved[32]. A qualitative approach was used since the focus was on rationale, not on quantification[33].

Despite the aforementioned[27] limitations of the Frost & Reich[23] model, the decision was made to adopt it, since a similar method had already been used in similar situations for access-promotion initiatives that ranged from the R&D of specific technologies to adoption by the final user. This theoretical model[9] has shown to be useful in mapping the path from the identification of the needs to provision to the final user. Semi-structured interviews were conducted (Appendix I, p.69) with the players involved in the different ASMQ development stages from all partner institutions. In addition, the documents provided by the interviewees were analyzed.

The workshop that took place at Fiocruz on 10 June 2015 was fundamental for the feedback and validation of the findings. The inputs made at the discussion were included in this report, particularly regarding data analysis. In addition to the interviewees and research team, experts in evaluation, policy analysis, and pharmaceutical care were also invited and participated in the discussion. The workshop agenda, list of participants and specific report are presented in appendices 3 (p. 73), 4 (p. 75) and 5 (p. 77). At least one scientific article is expected to be prepared for submission to an international journal.

The snowball sampling technique was employed to identify the interviewees[34,35]; DND*i* did the initial identification.

The interviewees were identified according to their institutional affiliation (table 3), and their role in the ASMQ development project (table 4). Their names were omitted because their role in the process was deemed to be more important.

**Chart 3. Institutional affiliation of the interviewees.**

| Institution | Code |
|---|---|
| DNDi | **A** |
| Farmanguinhos | **B** |
| Fiocruz (excl Far) | **C** |
| International agnecies (PAHO;WHO;UNITAID) | **D** |
| CIPLA | **E** |
| Ministry of Health Brazil/ Brazilian Government | **F** |
| MSF | **G** |

Between January and April 2015, 25 interviews were conducted[a]; most were face-to-face, six were via skype, and two sent their responses in writing. Face-to-face and Skype interviews lasted between 30 and 60 minutes, and were conducted by one or two members of the National School of Public Health, Brazil (ENSP) (list of interviewees in the Appendix 5, p. 87). The interviews were transcribed and their content analyzed according to the logic model method. This is the preferred method when the aims of an investigation are pre-established, rather than becoming evident in the course of the investigation, as this allows for the time for analysis to be shortened[36]. Stages include the definition of the logical model, acquaintance with the field material, findings indexation, mapping and interpretation. For this study, the access-to-medication dimensions (table 1) oriented the analysis of the categories, so that elements related to strengths and weaknesses of each one of them could be identified.

Considering that this study focused primarily the supply-side, and that affordability is a consumer-related aspect (demand-side), the aspects of this dimension are addressed in the reports on availability and adoption.

The report about the findings combined elements from the problem-solution and the analytical approaches: the former shows how the elements affect the policy or interventions; the latter organizes the findings according to the logical model[34]. Therefore, the analytical model also included the SWOT (strengths, weaknesses, opportunities, and threats) matrix[37].

All interviewees were asked to sign an informed consent form stating their agreement with the investigation, the recording of the interview, the quoting of their statement, and their being identified by name in the text of the study[2].

The project was submitted to the ENSP/ Fiocruz Ethics in Research Committee, and approved in December 2014 under record number 924.687.

**Chart 4. Role of the interviewees in the ASMQ development model.**

| ROLE IN THE PROJECT PER INSTITUTION | DESCRIPTION | CODE |
|---|---|---|
| **Decision maker** | Role in defining the agenda; little control in establishing alternatives and in the outcome | DM |
| **Developer/ operational** | Role in the implementation of the development process (up to registration) | IO |
| **Developer/ adoption** | Role in the implementation of the development process (after registration), particularly those outside the DNDi-Far partnership | IA |

## Method limitations

The case under study included a number of partners of different nationalities and settings throughout the development process. Moreover, the interviewees had different degrees of interaction with the interviewers. Therefore, it is possible that some players felt more comfortable than others in pointing out negative aspects or weaknesses identified in the course of the process, which might have influenced the analysis of the partners' different perspectives.

This means that those players who felt more at ease to criticize will influence the analysis of a given institution to a greater degree than other players. The perceptions about the role played by the different partner institutions may be biased due to cultural factors that affect the players' comfort in presenting their views on the development of the project.

The evaluation involves players internal and external to the core issue, with different degrees of interaction between themselves and with other interviewees during their professional career. This may influence, in an unpredictable way, their responses at the time of the interview.

a One questionnaire was answered jointly by two people.

b Interviewees who authorized their names be disclosed in the study (in alphabetical order of family name): Jorge Bermudez; Núbia Boechat; Jean-Herve Bradol; Aparna Chaphalkar; Eduardo Costa; Érico Daemon; André Daher; Graciela Diap; Hayne Felipe; Nora Giron; Luciana Gonçalves; Sweety Jimmy; Jean-René Kiechel; Laura Krech; José Ladislau; Michel Lotrowska; Izanelda Magalhães; Jorge Mendonça; Carlos Morel; Eloan Pinheiro; Isabela Ribeiro; Eric Stobbaerts; Pedro Tauil; and Shirley Trajano.

## RESULTS AND DISCUSSION – ASMQ IN AN ACCESS FRAMEWORK

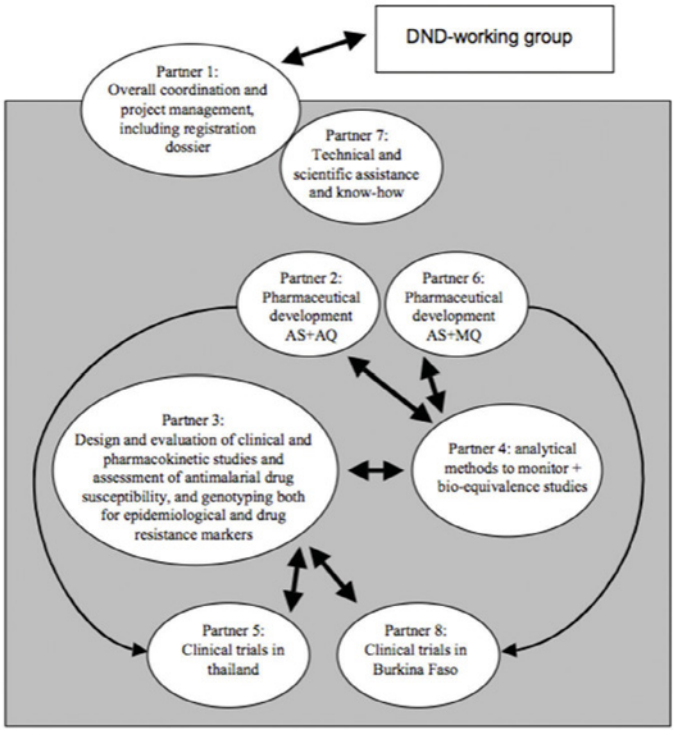
### Architecture

Architecture implies the organization network that is involved in the access to a specific technology. It relates to the coordination and connection of the activities of the logic model elements (availability, affordability and adoption)[9]. The first step is deciding to introduce a given technology, which implies considering its safety and effectiveness, both specific and in comparison to others, and the initial demand estimate[9].
In this investigation, it was possible to separate the architecture into at least three stages of the project: (a) Decision to conduct the FACT Project (2001-2002); (b) development process up to when registration was obtained (2002-2008); and (c) implementation of post-registration access strategies (2008-2014).

#### *DECISION TO CONDUCT THE FACT (FIXED-DOSE ARTESUNATE COMBINATION THERAPY) PROJECT AND THE ESTABLISHMENT OF THE PARTNERSHIP (2001-2002)*

The MSF Campaign for Access to Essential Medicines, launched in 1992[22], was the arm of this organization that led the project for the development of fixed-dose combinations that include artesunate.
Since MSF is an organization of health practitioners with medical experience, even though the concept of developing new treatments was not included in MSF's core social mission, the idea of developing a fixed-dose combination formula was adopted as an additional strategy in their efforts to tackle malaria in the settings where the organization operated, particularly in Africa. There was a need for "simple, affordable, easy-to-manage tools" (G-DM-1).
Initial funding for the development of Artesunate based Combination Therapy was granted by the European Commission, and called "Fixed-dose Artesunate-based combinations for the treatment of uncomplicated malaria" (known by the initials FACT) (G-DM-1; A-DM-2; EU Agreement[II]). The project started in July 2002, with an initial 3-year term (until July 2005), but it was extended until July 2006 (4-year term). The initial grant given by the European Commission was $1,163,873 euros (EU Agreement[II]).
The consortium was initially coordinated by the MSF, which passed it on to DND*i* after its creation (G-DM-1; EU Agreement[II]).
The FACT project included the development of two FDC: Artesunate + Mefloquine (ASMQ), and Artesunate + Amodiaquine (ASAQ); the partners for the pharmaceutical development were Farmanguinhos (for the former) and the University of Bordeaux for the latter (Figure 7).
The development of the FACT Project was within the Drugs for Neglected Diseases (DND) Working Group framework (B-DM- 1; A-DM-2; B-DM-2; C-DM-1; C-DM-2), established after a meeting organized by the MSF, WHO and Rockfeller Foundation in 1999, where a number of players from different areas gathered to "discuss how to encourage the development and ensure availability of medication for neglected diseases"[22]. DND*i* was created in 2003 as part of this framework.

Figure 7. FACT Consortium chart



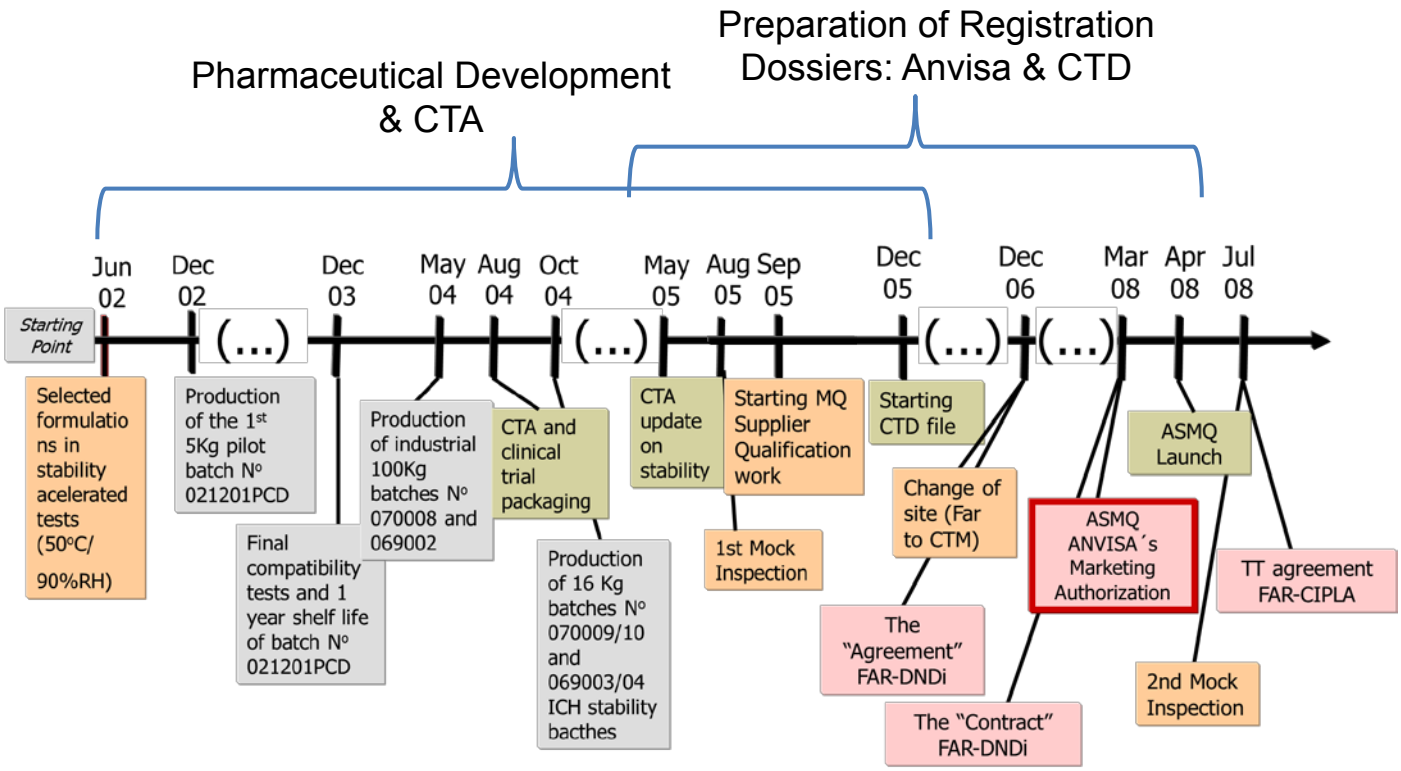

Source: European Commission Agreement.

Captions: Partner 1 and coordinator (scientific, administrative and financial) - Foundation Médecins Sans Frontières (MSF), France; Partner 2- TROPIVAL, Université de Bordeaux 2 (UB), France; Partner 3- Centre for Tropical Medicine, University of Oxford (UO), UK; Partner 4 - Centre for drug research, University Sains Malaysia (USM), Malaysia; Partner 5 - Faculty of Tropical Medicine, Mahidol University (MU), Thailand; Partner 6 - Instituto de Tecnologia em Fármacos, Far-Manguinhos (FM), Brazil; Partner 7 and co-Scientific Coordinator - Tropical Disease Research--WHO (TDR), Switzerland; Partner 8 - Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso

#### *PROJECT DEVELOPMENT AND RELATIONSHIP WITH PARTNERS (2002-2008)*

The stages of development of ASMQ by Farmanguinhos up to its registration are presented in Figure 8.
In the strategy development outline, the components of the agreement to be financed by the European Union ranged from the definition of the new formulation and production scale-up, to the development of safety, efficacy and bioavailability data, the conduct of clinical trials, the assessment of stability, and the registration of the new formulations.[II] The agreement lacked a plan for the provision of access to these treatments once the certification was granted.
MSF was the first coordinator of the project and had collaborations with the following partners: Université Victor Segalen (Bordeaux II), France; Wellcome Trust-Mahidol, Thailand; University of Oxford, UK; University Sains, Malaysia; Mahidol University, Thailand; Farmanguinhos/ Fiocruz, Brazil; World Health Organization; Centre National de Recherche et de Formation sur le Paludisme (EU AgreementII). In January 2005, the MSF passed the FACT Project coordination to the newly created Drugs for Neglected Diseases initiative (DND*i*) (amendment to the EU Agreement[II]). TDR/ WHO was the technical coordinator at the early stage of the project.

Figure 8. AMSQ development stages up to registration (2002-2008)




The connection between the MSF and Farmanguinhos/ Fiocruz was established first because of the local public manufacturing of non-patented antiretroviral drugs (ARV) (A-DM-1; A-DM-2; B-DM-2). In 2001, MSF tried to purchase the ARV manufactured by Farmanguinhos for its projects in South Africa.

During the DND Working Group activities, players from Farmanguinhos were active in activities such as the assessment of the technological stages of developing countries, output capabilities in Latin America, and neglected diseases in these countries (B-DM-2).

> *I am not sure if this project started in 2002. In fact, this project originates from that DNDi workgroup, [...]it started in 1999, when Doctors Without Borders received the Nobel Peace Prize and decided to allocate it towards the development of a technology development arm. So, when this was done, they established a group [...] We started to get together, to do a type of assessment, not only of the manufacturing capabilities of Latin America but also of what the priorities should be, as many diseases were neglected and this group had the idea of studying all neglected diseases, which they were, what their status was, what the manufacturing capacity in these countries was like". [B-DM-2]*

With the approval of the FACT Project, Farmanguinhos became involved in the project, and provided the technical team for the development of the formulation. This team had worked previously in ARV development (B-DM-1). There were few research groups willing to invest in the development of FDC for malaria (A-IO-1).

The DND*i*-Farmanguinhos partnership was promising, due to the high compliance of the project with the ideology of the organizations and partners involved (A-DM-2; A-IO-1). The project was ideologically oriented: its backdrop was the fight against monopolies and the patent system, as financial incentives were insufficient to ensure the development of treatments for neglected diseases (A-DM-2).

The project was a priority for DND*i* (A-DM-1; A-DM-2; A-IO-1; A-IO-2; A-IO-3), particularly in the beginning (A- DM-1; A-IO-2; A-IO-3). It was the project that drove the organization, even before the development of the ASAQ FDC or other combinations for Africa (A-DM-1). In fact, the project not only preceded, but was a catalyst for the creation of DND*i*. At first, it received a lot of attention, a plenty of resources and the support of the Farmanguinhos board of the time, which opened doors for the project to be developed (A-DM-1).

One of the partners of the FACT project development, which came through Farmanguinhos, the Oswaldo Cruz Foundation, later became one of DND*i*'s founding partners, with a seat on the Board of the organization (A-DM-1; A-DM-2; C-DM-1; C-DM-1; B-DM-2; B-IO-1).

And yet, a number of interviewees (C-DM-1, B-DM-1, A-IO-1, B-DM-4; B-IO-1) mentioned oscillations in the rating of the project's priority by Farmanguinhos over time, depending on the executive board, as there were also other projects to be considered. One of the reasons is the organizational culture that targeted Brazilian needs (C-DM-1).

> *"Fiocruz was selected because it was a founding member, for having Farmanguinhos and people capable of getting things done." [C-DM-1]*

Even though there is no consensus among the interviewees about why the project priorities varied throughout the development of the product in Farmanguinhos, it was mentioned that a group of researchers had the project as a priority throughout its development. (C-DM-2).

> *It was a project developed more by people than by organizations. [ADM-2; B-IO-2]*

When asked whether the goals and roles were clear, most of the interviewees (13) agreed, but mentioned problems throughout the development process, such as the interactions with a broad array of international partners with different organizational cultures, internal changes in the teams (particularly in Farmanguinhos), the adoption of new working processes, and different understandings of the stages by the different operational teams.

There were communications mechanisms in place, such as periodic meetings of the partners involved, and follow-up at Farmanguinhos by DND*i*'s board. However, mention was made that decision-making responsibilities of the project as a whole were not clear.

During the product development process, there was some tension around the patenting of the product, the excessive time gap between product development and supply (B-DM-2, B-IO-3, A-DM-2), and the variations in the project priority rating by Farmanguinhos.

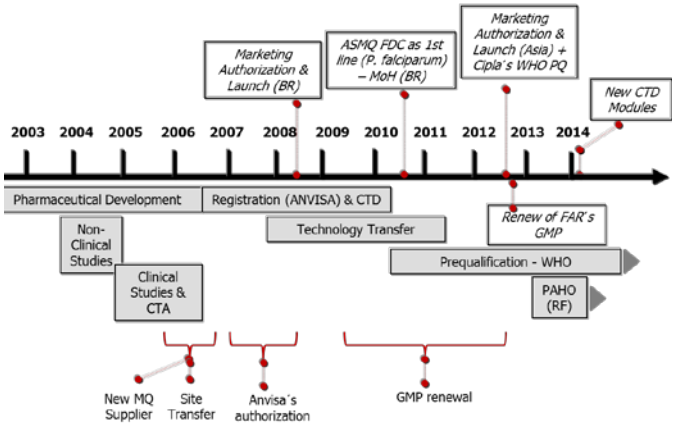
One of the product development stages also included an intervention study in the state of Acre[38] between 2006 and 2008, with 23,845 patients. The study design and implementation were done through a collaboration between DND*i*, Farmanguinhos/ Fiocruz, PNCM and the state government of Acre, and it was deemed fruitful, as the roles of the partners were clear and there was no tension (F-IA- 1, F-IA-2, F-DM-2). This study was within RAVREDA's scope.

However, as mentioned in the face-to-face workshop, the relationship between DND*i*, Farmanguinhos/ Fiocruz and the PNCM was not so consistent or as intense in the period after the study (A-IO-2). As discussed in the section "Adoption", it is likely that the weakening of the collaboration might have affected decisions on the adoption of the ASMQ FDC starting in 2012, in Brazil.

## *POST- REGISTRATION PERIOD*

The main stages after registration up until the completion of the study are related to the entry of the product into the market – adoption (Figure 9).

**Figure 9. ASMQ Project stages after registration (2008-2014)**




Caption: BR= Brazil; ASMQ= Artesunate + Mefloquine; FDC= Fixed Dose Combination; WHO= World Health Organization; GMP = Good Manufacturing Practice; PQ = Pre-qualification; FAR= Farmanguinhos; CTD=Common Technical Dossier; PAHO = Pan-American Health Organization; ANVISA= Brazilian Health Surveillance Agency

The stages after the granting of certification by ANVISA included the technology transfer to the company Cipla (to supply Asia), the incorporation of ASMQ FDC into the treatment protocol established by the Ministry of Health in 2010, the initiation of the WHO pre-qualification process and inclusion of the product in the procurement list of PAHO (Figure 9). Some specific aspects will be addressed in depth in the following sections.

At this stage of the project, the causes of tension identified were Farmanguinhos' lack of experience in export and international regulatory matters, the DND*i*- Farmanguinhos agreement renegotiation, the negotiation and implementation of the technology transfer agreement with Cipla (A-IO-2, A-IO-3, A-IO- 4, B-DM-3, B-DM-4, B-IO-2,C-DM-1), and Cipla's supplying of Venezuela in 2014, instead of Farmanguinhos.

Of note is the fact that most interviewees were favorable to forming new partnerships, as long as caution was taken, such as more cross-sectionalization, more extensive preparatory negotiations, clearer agreements, and better investigation of the consumer market for the technology developed.

Finally, mention should be made about the disagreement on the project success marker that evolved during its development. When the project was considered complete, what essential access actions had not been completed or even foreseen - use? Exports? Good manufacturing practices? (A-DM-1).

*In the public health system [...] in this particular product-development case, "and now let's use it" was never the logic of the public sector. The thing should be there, there should be a supplier, and only then is it implemented. And in this case, we were not motivated to implement. You cannot do that without economic analysis, you see? This was something done with good intentions but little economic consistency. [B-DM-1]*

## Availability

### *2002 2008 PERIOD*

The ASMQ FDC development process faced difficulties that led the treatment to be available after the point when it was originally planned. Difficulties included the lack of regulatory framework in Brazil and its evolvement during the development process, requiring constant changes in the work of the teams involved (B-IO-1, B-IO-3). It was a lot of effort to reconcile ANVISA's domestic requirements, still under development, with international requirements, and to deal with a consulting company specialized in regulatory matters (B-IO-3). After six years of development, and in close contact with ANVISA, the request for the certificate was filed; the registration process was expected to last six months. That agency, however, was being restructured at the time; employees were changed or reassigned to different sectors, giving rise to new requirements and approaches, and it took one year and eight months for the certificate to be granted. This was an unexpected delay (B-IO-2, B-IO-3).

Another factor that contributed to the delay in ASMQ availability was the interruption in the supply of the raw material, mefloquine, during the development process (Figure 8, p. 25). When the project began, it was decided there would be only one mefloquine supplier, and one industrial production process according to the characteristics of the raw material. Even though that seemed to be the best decision at the time, it had challenging implications for the development of the medication (A-IO-2).

On one hand, these choices were based on the possibility of ensuring simple production processes that would enable technology transfer to other developing countries (B-IO-2), but they affected the implementation of the project and contributed to the delay in availability.

The supplier halted API production without previous communication to Farmanguinhos or DND*i*. This was considered one of the main factors why the development of this project took so long (about one year behind schedule), considering that it was already in the stage of being submitted to ANVISA for registration (B-IO-1, B-IO-2, B-IO-3, A-IO-2, B-IO-4, A-IO-3, A-IO-4). Due to the interruption in supply, Farmanguinhos had to redo many of the process development stages with the new API supplier, which required major technical, regulatory and logistical efforts, such as searching for new suppliers and clearing customs. That increased costs and compromised productivity.

The final factor that contributed to the delayed availability of ASMQ was the moving of Farmanguinhos' manufacturing facility in the middle of the product development process. This required manufacturing adaptations, and it took more than six months for the transfer and validation of the facility (A-IO-4). In addition, production-process problems related to infrastructure, supply chain and labour outsourcing at Farmanguinhos were also mentioned (B-DM-3, B-IO-2, C-DM-2).

Fiocruz representatives highlighted that this project was a multicentric and multidisciplinary experience for Farmanguinhos, who had learned to deal with terms, partnerships, international requirements, and political and social involvements (B-DM- 3). The laboratory was placed into an international arena because of its development capabilities as well as its manufacturing capacity (B-DM-4), tackling a worldwide health problem (C-DM-1), and making a product for a poverty-related disease that is accountable for the deaths of millions of people (C-DM-2).

### *2008-2014 PERIOD*

Table 5 (p. 36) presents the purchases and acquisitions, in terms of number of treatments and type of supplier, for ASMQ FDC in the 2008 to 2015 post-registration period. In total, 1,369,171 treatments were acquired, 70.4% from Farmanguinhos and 29.6% from Cipla.

Some challenges were faced in ensuring timely availability for those who need the medication.

The first is related to API availability, particularly mefloquine. This is considered a challenge for access sustainability, since it is imported at high cost (B-DM-3, B-IO-3, A-DM-2).

In addition to supply difficulties, the price of mefloquine is considered high, which may compromise the competition of ASMQ with other *ACT*s in the global market (B- IO-3, B-DM-3, A-DM-2, C-DM-1).

*API supply [...]is a serious challenge. As it is supplied by companies that seek profit, and there is not much competition, I am forced to pay the price, and therefore cannot reduce the final price of the medication, since I can't reduce this cost. Because it is a solid oral drug, the main fixed cost is the active component, the raw material, so it has a lot of impact on the cost [...]Because we import artesunate and mefloquine, our final price is, so to speak, non-competitive compared to Cipla's and to artesunate plus amodiaquine [...]A safe, quality medication, with no problem whatsoever. But the thing is when we present the price to the Pan American Health Organization, and the countries check the therapeutic system possibilities. Then, we may end up losing, because we cannot negotiate a lower price when procuring the API. [B-DM-3]*

The need to develop the domestic pharmaceutical industry, which is still not capable of making this raw material, was mentioned as an important factor in the sustainability of manufacturing this medication in Brazil, which, today, is highly dependent on international producers (B-IO-3, A-DM-2, B-IO-4, B-DM-3, B-DM-2). It was also mentioned that if ASMQ FDC were to be placed in a large-scale production line in Brazil, perhaps a counterbalance system with pharmaceutical companies could be put in place, which would be an opportunity to increase availability of the treatment in the country. (B-DM-3).

The Farmanguinhos manufacturing facility is planned for large-scale output for the domestic market, which is not suitable for the production of ASMQ for the Americas, with its irregular demand and low volume; this is not an attractive market. The output of big volumes leads to big inventories, therefore production is not desirable (BDM-3, BIO-3, BDM-1, BIO-2). Despite raw material availability and costs being highlighted as part of the challenges for sustainable access to ASMQ FDC, during the face-to-face workshop, the final cost of the treatment was mentioned by many players as an access barrier in Brazil. For the Ministry of Health's representatives, the cost of treatment for malaria was never a determining factor in the choice of the therapy. The irregular demand for ASMQ, given malaria outbreak occurrence patterns, makes it difficult to plan production. Farmanguinhos need to plan in advance the manufacturing of ASMQ FDC, and the lack of a clear demand, particularly from the Ministry of Health, compromises this process (B-DM-3, C-DM-2, B-IO-2, A-IO-4, B-DM-1, A-DM-1).

The needs of the Brazilian Public Health System (SUS) drive production, thus for ASMQ FDC manufacture there is a need for clear and constant demands by the Ministry of Health and by other Latin American countries (B-DM-3, C-DM-1, C-DM-2, B-IO-2, B-IO-1). Because of a lack of national and regional definitions, there is an excess of medication that ends up being donated, as the cases of Venezuela and Bolivia illustrate (B-IO-2, B-IO-3, B-DM-3).

It was also mentioned that part of the inventory was donated because the Ministry of Health did not take the lots that were made to complete process accreditation and to meet WHO's pre-qualification documentation requirements (B- IO-2).

> *First, to ensure the procurement of raw material, the active pharmaceutical input, in a quantity that is enough to meet the demand. Second, it is difficult to have an annual procurement plan according to the demand, and not be able to respond to emergency situations, and many a time that has happened in Brazil [...] Farmanguinhos, because of budgetary difficulties, with cuts in its budget and even a decrease in the orders from the Ministry of Health, cannot afford to manufacture and stock, waiting for an order to come. It has to plan the production according to an annual demand estimate [...]If there are no orders, it cannot produce and have an inventory. [C-DM-2]*

> *[It is important] to make operational the donations that some South American countries have asked us for, like, if I am not mistaken, Peru, Bolivia and Venezuela. We have made [donations], as we no longer have the distribution line from the Ministry of Health [...] The Ministry purchases, it has a strategic stock, but for two years now it has not placed an order; it focuses on acute cases, and does not propose ASMQ as a chronic treatment [...] Financial management is always a problem in the public service, the lack of resources, uncertainties about orders by the Ministry. The important aspect for us is the demand versus production, [...] we produced much more than the demand by the Ministry, particularly for pediatric formulation. Thus, it was common that we had stock. WE even made donations, but that should not be necessarily the way [...] The right thing would be to meet the demand with the right amount. [B-DM-3]*

Table 1 shows that after 2012 there were not significant purchases of ASMQ FDC by the Ministry of Health. In 2013, there was no purchase, and in 2014 they bought very little (21,000 tablets).

**Table 1. ASMQ FDC procurement by the Ministry of Health, in blister packs manufactured by Farmanguinhos. Brazil, 2009-2014**

| MEDICATION: ARTESUNATE+ MEFLOQUINE | 2009 | 2010 | 2011 | 2012 | 2014 |
|---|---|---|---|---|---|
| **100+220MG W/03 - BLISTER** | 31.590 | 4.830 | 5.030 | 20.560 | 1.000 |
| **100+220MG W/06 - BLISTER** | 126.420 | 34.800 | 31.590 | 36.180 | 1.500 |
| **25+55MG W/03 - BLISTER** | 18.000 | 30.000 | 23.020 | 20.230 | 1.000 |
| **25+55MG W/06 - BLISTER** | 36.000 | 72.000 | 23.370 | 19.720 | 1.000 |
| **TOTAL AMOUNT** | 212.010 | 141.630 | 83.010 | 96.690 | 4.500 |

Source: Ministry of Health, 2015

In addition to the issues related to uncertain demand, another challenge Farmanguinhos had to face was supplying other countries. One way to do that is through joint strategic purchases made by international organizations, such as PAHO's Strategic Fund for Latin America and Caribbean countries.

One of the difficulties for Farmanguinhos in supplying the medication via PAHO was the reaccreditation, by ANVISA, of Good Manufacturing Practice (GMP), which was only completed in 2012 (A-IO-4, A-DM-1). Therefore, this laboratory only became a PAHO supplier in 2013.

Another initiative to expand the possibilities for supplying other countries in the world is related to WHO's pre-qualification process, which Farmanguinhos started in 2010 (figure 9). Cipla, after the technology transfer, could pre-qualify its product at WHO in 2012.

Farmanguinhos' pre-qualification effort at WHO, currently at its final stage, and also its pre-qualification at PAHO, in 2013, were considered strengths for the global acquisition of the treatment, despite its temporary suspension, depending on pre-qualification by WHO. These initiatives would increase the chances of marketing the product internationally, expanding the availability of the treatment (B-IO-4, B-DM-3, B-IO-3).

There were also other challenges for global availability. Purchase demands that became donations, e.g. to Venezuela in 2013, were also ascribed to export difficulties by Farmanguinhos, that had no experience in this, and was unable to meet purchase orders in a timely manner and in the requested amounts (A-DM-1, C-DM-1, B-IO-1, B-IO-2, D-IA-1). Donation was the mechanism that allowed meeting the international demand more quickly (B-DM-3).

Another challenge for the availability of the product is the different import regulations of Latin America countries, and the lack of registration in these countries makes it more difficult to make the product available (D-IA-1). It is also important to share knowledge about the product in Latin America among organizations, decision makers and users (D-IA-1).

> *It will be very good if we are accredited [by WHO], not only for us, that can grow a lot technically, but for the people, not only of Brazil, but of all South America, wherever malaria is present, that is gratifying for us [...] We hope we can produce more than what we do today, that we can meet a larger demand than we do today. [B-IO-4]*

In terms of distribution, technology transfer to the Indian laboratory Cipla was considered a positive initiative, as it made it possible to have the treatment available to large populations throughout the world, and it was also a successful South-South endeavor, from a public to a private organization (A-DM-1, B-DM-3, B-IO-1, B-IA-1).

On the other hand, most of the interviewees saw the technology transfer process as permeated with tension. Among the reasons for tension, was having a private company selected to receive the technology (B- DM-1, B-DM-4), and the perception of some Farmanguinhos people that this transfer was imposed by DND*i* (A-DM-2, B-DM-1, B-DM-3, B-DM-4).

DND*i* representatives and some of the interviewees from Farmanguinhos understood that one of the project principles was to ensure product availability from more than one manufacturer, as originally established in the agreement with the European Commission (A-IO-2; A-DM-2). In addition, as the continuity of the project at Farmanguinhos was uncertain, technology transfer was considered a way to ensure its sustainability (A-IO-2).

According to a Farmanguinhos representative, in addition to the selection of the partner the technology would be transferred to, some consideration clauses by the partner established in the technology transfer agreement were never effectively enforced (B-DM-1). Among these, are the payment of compensation (3%) to Farmanguinhos of the sales made by the technology recipient to private markets of countries where malaria is endemic, and the technology transfer of the API mefloquine to Farmanguinhos (B-DM-1, Technical Agreement Fiocruz-Cipla-DND*i*[IV]).

The technology transfer agreement also established that the treatment would be made available in the Latin America region by Farmanguinhos, and in Asia by Cipla. Each manufacturer could supply the other's area upon consent[IV]. The fact that Cipla supplied most of Venezuela's needs in 2013, even though it was Farmanguinhos that was in charge of Latin America, was mentioned as one of the project's problems, and was ascribed to poor organization and communication between the partners (A-DM-1, B-IO-3).

On the other hand, in order to supply the order from Venezuela in 2013, Farmanguinhos would have had to import the raw material for manufacturing the entire order, and that would have taken time (B-IO-2). Cipla, then, provided the amount Farmanguinhos did not have in stock. This episode reinforces the need for a minimum manufacturing amount by Farmanguinhos for the sustainability of the medication (A-DM-1). This example also shows the importance of having two manufacturers to ensure timely availability of the treatment.

Finally, a cross-sectional factor that was reinforced during the workshop relates to changes in the malaria landscape in Brazil and worldwide (see the section 'Overview of Malaria in Brazil and worldwide', p.8), in terms of epidemiology, policy, R&D, and available products. The variations in ASMQ FDC demand are also associated with a significant decrease in the number of *P. falciparum* malaria cases. For example, the number of *P. falciparum* malaria cases registered in 2000 in Brazil, Bolivia, Colombia, Peru and Venezuela was 211,991, while in 2013 there were 80,469 cases. In addition, it is important to consider that in the beginning of the ASMQ FDC development process, there was only one combination available in the market [AL (Coartem®)]. However, at the time ASMQ FDC was launched, there were other *ACT* FDC available, including DND*i*'s ASAQ; this was released in 2007 and more than 400 million ASAQ tablets have been distributed. It should therefore be acknowledged that when ASMQ FDC was released, there were at least two FDC therapeutic alternatives –A+L and ASAQ – which are competing treatments for the same indication. This factor may explain the decrease in and irregularity of ASMQ demand over time, particularly since international therapeutic guidelines are not clear about the criteria for selecting the best FDC treatment for malaria for different epidemiological scenarios (resistance, target-population, etc.)

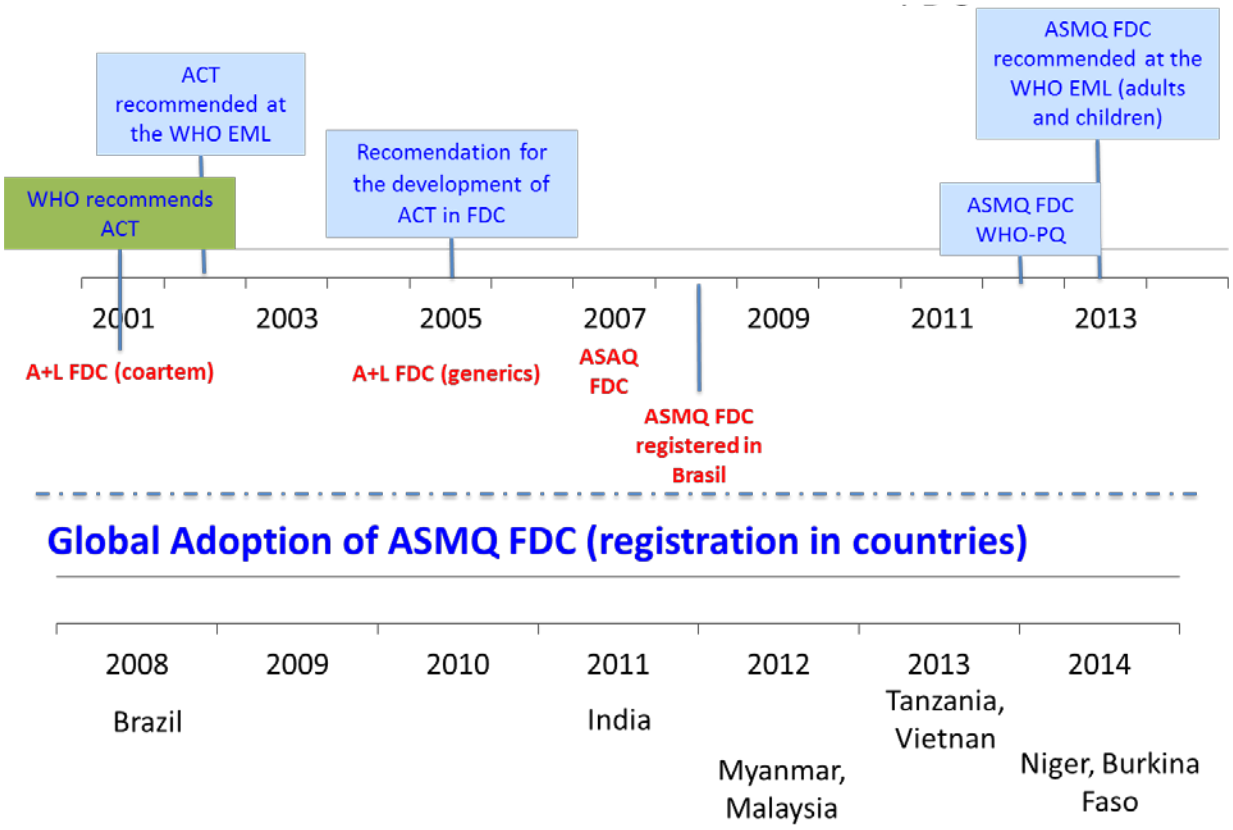
**Chart 5. Procurement of treatment according to country and supplier between 2008 & 2015.**

| COUNTRY | TREATMENT PROCURED 2008-2012 | TREATMENT PROCURED 2013 | TREATMENT PROCURED 2014 | TREATMENT PROCURED 2015 |
|---|---|---|---|---|
| BRAZIL | 260,000 including clinical trial and donations (Farmanguinhos) | | | |
| | 533,340 procured by the Ministry of Health* (Farmanguinhos) | | 4.500 procured by the Ministry of Health* (Farmanguinhos) | |
| INDIA | 77 patients 2007-2008 for clinical trial (Farmanguinhos) 23,000 (Cipla) | 5.000 (Cipla) | No sales | No sales |
| CAMBODIA | 45 patients in 2010 for clinical trial (Farmanguinhos) Donation of 30,000 treatments (Farmanguinhos) | | | 480 treatments for clinical trial (Cipla) |
| THAILAND-MYANMAR | 169 patients in 2008-2009 for clinical trial (Farmanguinhos) | | | 2.500 for clinical trial (Cipla) |
| VENEZUELA | | 3.660 (Farmanguinhos) 378.610 (Cipla) | | 160.050 (Farmanguinhos) |
| BOLIVIA | | 1.700 donation (Farmanguinhos) | | |
| NIGERIA | 540 treatments (Cipla) | | | |
| TOTAL | 817.171 | 388.970 | 4.500 | 163.030 |
| TOTAL FOR THE PERIOD | 1.373.671 (72% supplies by Farmanguinhos e 28% by Cipla) | | | |

* Data collected in accordance with the Information Access Act, Brazil

## Adoption

Figure 10. ASMQ FDC release schedule.



## *GLOBAL ADOPTION*

Figure 10 shows the timeline for ASMQ FDC release compared with other *ACT* FDC, and the countries where the product has been registered.

Many interviewees reinforced the fact that the development of ASMQ FDC took place in an international setting that favored the use of *ACT* for the treatment of malaria (D-AI-1; D-AI-2; A-IO-3; G-DM-1), particularly because of the WHO 2001 recommendations.

It is worth mentioning that in 2005, WHO recommended the development and adoption of an FDC medication for the treatment of uncomplicated *P. falciparum* malaria[39]. The second edition of the Malaria Treatment Protocol[40], published in 2010, kept the recommendation for the use of *ACT* to treat uncomplicated *P. falciparum* malaria, and suggested one of the following options: artemether + lumefantrine (AL; Coartem®), artesunate + amodiaquine (ASAQ), artesunate + mefloquine (ASMQ), artesunate + sulfadoxine – pyrimethamine (ASSP) and dihydroartemisinin + piperaquine (DHA+PPQ), the latter being included in this last edition.

WHO's 2010 protocol[40] makes no clear distinction between the different *ACT*s and states that the best treatment for each setting should take into account the efficacy of the drug to be associated with the artemisinin derivative. The resistance profile of this drug may also compromise the effectiveness of the association. It is also acknowledged that the availability of *ACT* in fixed-dose combinations is preferable to the use of single drugs or drugs presented in co-blister packs.

ASMQ FDC is listed as one of the *ACT*-based therapeutic alternatives for the treatment of uncomplicated *P. falciparum* malaria, and its adoption should take into account the mefloquine-resistance profile in different settings.

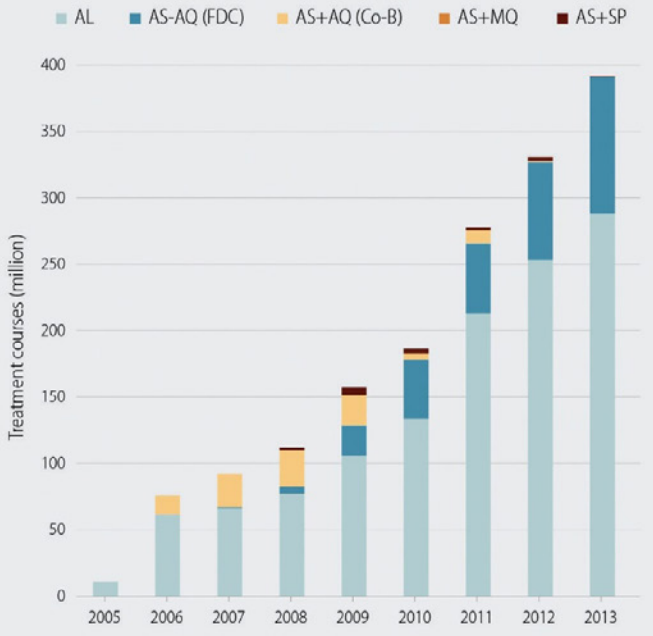
Another indicator for global adoption is the WHO Model List of Essential Medicines (EML). *ACT*s were included in the EML in 2002[41]. In that year, the 12th edition included the artemether + lumefantrine combination among the therapeutic options for adults. Artemisinin derivatives artemether and artesunate, as monotherapy, were recommended for adults in 2003[42].

The AL FDC has been included in the EML since 2002[41-48], whereas ASAQ was first listed in 2011 (17th Edition), and ASMQ in 2013 (18th Edition). AL FDC has been included as a therapy for children, in the WHO Model List of Essential Medicines for children (EMLc), since its first edition in 2007[49-53], whereas ASAQ and ASMQ were incorporated in 2011 and 2013 respectively[51-53]. ASMQ FDC was included in the WHO Model List of Essential Medicines because of a request made by DND*i* in 2012[v].

The World Malaria Report[3] mentions the rising global adoption of *ACT*, which went from 11 million courses of treatment in 2005 to 392 million in 2013 in a market highly dominated by AL (Figure 11).

**Figure 11. Incorporation of *ACT*s, 2005-2013**

**Figure 6.3** ACT deliveries from manufacturers to the public and private sectors, by drug and presentation, 2005–2013

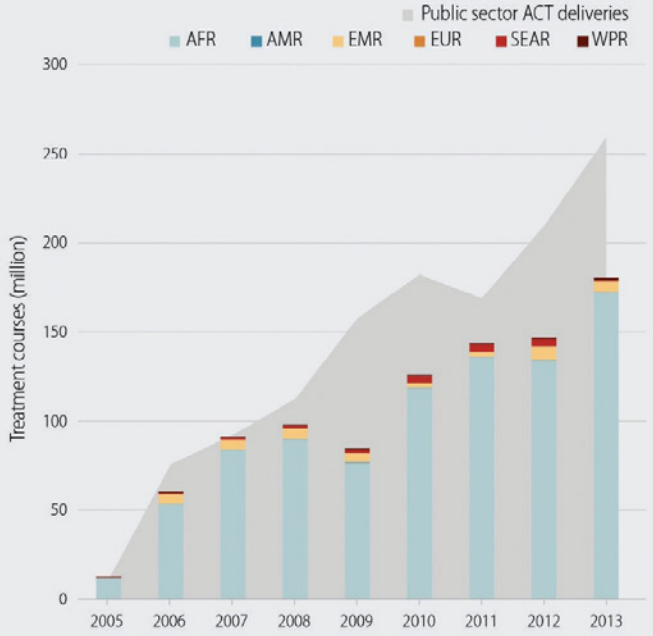



ACT, artemisinin-based combination therapy; AL, artemether-lumefantrine; AMFm, Affordable Medicine Facility–malaria; AQ, amodiaquine; AS, artesunate; Co-B, co-blister; FDC, fixed-dose combination; MQ, mefloquine; SP, sulfadoxine-pyrimethamine

***Source:*** *ACT deliveries (2005–2013*), data provided by eight companies eligible for procurement by WHO/UNICEF.*

**2005–2009 data reflects public sector only; 2010– 2013 data includes public sector plus AMFm (public and private sectors).*

**Figure 6.4** Number of ACT treatment courses distributed by NMCPs, by WHO region, and ACT treatment courses delivered to the public sector, 2005–2013




ACT, artemisinin-based combination therapy; AFR, African Region; AMFm, Affordable Medicine Facility–malaria; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; NMCP, national malaria control programme; SEAR, South-East Asia Region; WPR, Western Pacific Region

***Source:*** *NMCP data and ACT deliveries (2005–2013*), data provided by eight companies eligible for procurement by WHO/UNICEF.*

**2005–2009 data reflects public sector only; 2010– 2013 data includes public sector plus AMFm (public and private sectors).*

Source: WHO, 2014

The clinical trials conducted to date are the final part of the efforts for global and national adoption of the treatment. Between 1992 and 2011, 91 open, randomized clinical trials examining the use of AS and MQ, either as monotherapy or in fixed-dose combinations, were conducted in 22 countries[vi]. ASMQ FDC was included in clinical trials conducted in Thailand, Myanmar and Brazil. In Latin America, ten clinical trials were conducted in five countries (Peru, Bolivia, Ecuador, Colombia and Brazil) (table 6).

Of note is the fact that the clinical trials conducted in Latin American countries had a PCR-adjusted cure rate of 100%, with efficacy ranging between 80 and 100%. The only trial that included ASMQ FDC in the region, conducted in Brazil, showed efficacy >90% (Table 7).

**Chart 6. Clinical trials that included ASMQ, 1992 to 2011.**

| CONTINENT | COUNTRIES | NUMBER OF TRIALS | NUMBER OF PATIENTS | TOTAL PATIENTS PER CONTINENT | YEAR OF TIRIAL | YEAR OF PUBLICATION |
|---|---|---|---|---|---|---|
| Southeast Asia | Thailand, ASMQ FDC N=275 | 31 | 7.627 | 9.337 | 1992-2011 | 1995-2012 |
| | Myanmar, ASMQ FDC N=169 | 4 | 1.467 | | 1998-2009 | 2004-2010 |
| | India | 3 | 122 | | 2001-2008 | 2006-2012 |
| | Bangladesh | 1 | 121 | | 2003 | 2005 |
| Western Pacific | Cambodia | 19 | 1.419 | 2.294 | 2001-2008 | 2006-2012 |
| | Laos | 4 | 368 | | 2002-2007 | 2004-2010 |
| | Vietnam | 3 | 507 | | 1997-2008 | 2004-2012 |
| Latin America | Peru | 5 | 598 | 24.766 | 2000-2006 | 2003-2011 |
| | Bolivia | 1 | 70 | | 2001 | 2004 |
| | Ecuador | 1 | 100 | | Nao disponível | 2003 |
| | Colombia | 2 | 153 | | 2006-2008 | 2010-2012 |
| | Brazil, ASMQ FDC N=23.845 | 1 | 23.845 | | 2006-2008 | 2012 |
| Africa | Senegal | 2 | 299 | 1.968 | 2003-2008 | 2007-2010 |
| | Mali | 1 | 232 | | 2004-2005 | 2008 |
| | Gabon | 2 | 92 | | 2005-2006 | 2007-2010 |
| | Nigeria | 3 | 619 | | 1994-2008 | 1998-2009 |
| | Sudan | 2 | 68 | | 2000-2003 | 2003-2005 |
| | Cameroon | 2 | 274 | | 2006-2009 | 2010 |
| | Kenya | 1 | 129 | | 2004 | 2006 |
| | Ivory Coast | 1 | 75 | | 2007 | 2011 |
| | Cameroon, Benin & Ivory Coast | 1 | 104 | | 2001 | 2002 |
| | Burkina Faso, Tanzania & Ivory Coast | 1 | 76 | | 2007-2008 | 2012 |
| | 22 countries | 91 trials | 38.315 patients | | From 1992 to 2011 | From 1995-2012 |

Source: DNDi, 2012. Report submitted for the inclusion of ASMQ FDC in WHO's List of Essential Medicines[v]

**Chart 7. Studies conducted in Latin America that included AS+MQ.**

| YEAR/COUNTRY | AUTHOR | YEAR OF THE TRIAL | DRUGS | NUMBER AND AGE OF PATIENTS TREATED WITH AS+MQ | AS+MQ PCR-ADJUSTED CURE RATE |
|---|---|---|---|---|---|
| 2003[119] Peru Iquitos | Pillai DR | 2000 | AS+MQ (AS: 4 mg/kg/d for 3 days and MQ single dose 15mg/kg, (Manufacturer non specified) and MQ | N=51 5-50 | 100% |
| 2007[55] Peru Iquitos | Grande T | 2003-2005 | AS (Guilin) +MQ (Hoffman La-Roche) daily, during 3 days. (AS: 4mg/kg/d and MQ dose 8mg/kg/d and DHA-PQ) | INN 260 5-60 | 99,6% |
| 2012[47] Colombia Tumaco | Carrasquilla G | 2007-2008 | AS+MQ (Mepha) (AS: 4 mg/kg/d for 3 days and MQ dose 15mg/ kg on D2 and 10 mg/kg on D3) vs. AL | N=53 12-65 | 100% |
| **TRIALS IN LATIN AMERICA NON-ADJUSTED PCR CURE RATE** | | | | | AS+ MQ RESULT EFFICACY |
| 2003[120] Peru Iquitos | Marquiho W | 2000 | AS+MQ (Mepha) (AS: 4 mg/kg/d during 3 days and MQ single dose 15mg/kg) and MQ | N=61 5-50 | 100% |
| 2003[121] Ecuador Manabi, Pichincha. Esmeraldas, Guayas, Cahar & Los Rfos | Gomez L EA | | AS rectal suppository (Mepha) during 3 days – total dose of 30mg/kg + oral MQ (Mepha) 20 mg/kg on Dl | N=50 1-12 | D28: 96% and D60: 88% |
| | | | AS rectal suppository (Mepha) during 3 days – total dose of 30mg/kg + oral MQ 15-17mg/kg total dose on Dl and D3 | N=50 1-12 | D28: 94% and D 60: 80% |
| 2004[122] Bolivia Beni & Pando | Avila JC | 2001 | AS+MQ (Mepha) (AS: 4 mg/kg/d during 3 days and MQ 15mg/kg single dose) | N=70 5-60 | 100% |
| 2009[123] Peru | Gutman J | 2004-2005 | AS (Mepha)+MQ (Roche, Mepha & A:C: Pharma) (AS: 4 mg/kg/d during 3 days and MQ 15mg/kg on Dl and 10 mg/kg on D2) | N= 34 >18 -61 | 100% |
| 2011[124] Peru Iquitos | Macedo de Oliveira A | 2005-2006 | AS+MQ (A.C. Farma Laboratories) (AS: 4 mg/kg/d during 3 days and MQ 15mg/kg during 2 days), observed and not observed | N= 96 e 96 3-78 | 98,9% |
| 2010[125] Colombia Antioquia | Alvarez G | 2006-2007 | AS+MQ daily, for 3 days 12 and 15 mg/kg/d and AS+MQ+PQ (Manufacturer non speciried) | N=25 e 25 1-80 | 100% |
| 2012[62] Brazil Vale do Juruá Amazon region | Santelli A | 2006-2008 | ASMQ (Farmanguinhos) | N= 23.845 >6 months | >90% |

Source: Source: DND*i*, 2012. Report submitted for the inclusion of ASMQ FDC in the WHO List of Essential Medicines[v]

Conducting clinical trials for neglected diseases is an important way to support the adoption of a given technology in a specific setting. While the WHO malaria treatment recommendation suggests the use of an ACT, the combination of choice being selected according to the resistance profile of the drug combined with the artemisinin derivate, a clinical trial may provide more accurate information to help make this choice.

To illustrate: even though the AS+MQ association has been recommended as first-line therapy to treat uncomplicated P. falciparum malaria in Myanmar since 1996, the clinical trial conducted[54] between 2008 and 2009, which included five ACT schemes, confirmed that this association, and its fixed-dose combination was better than the other alternatives. Doctors Without Borders (MSF) participated in this trial[54], even though the organization did not use ASMQ FDC in their projects in a systematic way (A- DM-2; A-DM-1). In the MSF Treatment Guide, ASMQ is one of the recommended ACTs. N.B., the research team had difficulty finding this document [55].

Until 2012, AS+MQ was recommended for treating uncomplicated P. falciparum malaria in the national protocols of the following countries[v]:

a. Asia: Cambodia, Malaysia, Thailand and Myanmar as first-line therapy, and in Vietnam as a rescue treatment;

b. Latin America: Peru, Venezuela, Bolivia as a first-line treatment, in Brazil for the extra-Amazon region, and in Nicaragua as second line therapy.

The Cochrane Review on ACT[56] suggests that, depending on the grade of resistance to mefloquine, the AS+MQ association may be indicated for any setting in Asia, Latin America, and even Africa, for treatment of uncomplicated P. falciparum malaria.

Accordingly, two possible opportunities for the adoption of ASMQ FDC in additional settings were recently mentioned (A-IO- 4; A-IO-1):

a. The possibility of use in Africa for uncomplicated *P. falciparum* malaria, in light of WHO recommendations in 2010 (therapeutic protocol) and the results of the phase IV trial conducted by DND*i* in children in Tanzania, Burkina Faso and Kenya;

b. A potential indication for *Plasmodium vivax* malaria. [57]

Even though the registration and inclusion in national treatment protocols indicate their adoption on a national level, they were included in the "global adoption" section to demonstrate the global use of ASMQ FDC.

ASMQ FDC is registered in the following countries: Brazil (2008), India (2011), Myanmar (2012), Malaysia (2012), Vietnam (2013), Tanzania (2013), Niger (2014) and Burkina Faso (2014). The first drug registration received in Brazil was granted to Farmanguinhos by ANVISA. Certification was also granted to the Indian company Cipla, technology-recipient partner of Farmanguinhos.

A weakness mentioned by many interviewees (A-IO-3; B-IO-1; A-IO-2; B-DM-3; B-DM-1; B-IO-3; B-IO-2; B-DM-4) was Farmanguinhos' lack of experience in arranging for drug registration in other countries, and in handling exports. This reflects the limited commercial capacity of the public sector and a weakness of the pharmaceutical industry in Brazil. The quotes that follow show how the limited experience of Farmanguinhos as an international supplier impacted the partnership and the partners' expectations:

> *[...] the expectation that they [DNDi] had for this product at the time was the same they had with Sanofi, [...], because Sanofi has an international distribution network, its business is to sell drugs; Farmanguinhos' business is not selling drugs, its business is to distribute drugs within Brazil, within the Public Health System [...]" [B-IO-1]*

> *[...] in the case of artesunate mefloquine, as it was a laboratory with much less experience in this area, a laboratory intended to serve the Ministry of Health, to meet the needs of the Public Health System, the perspective on the global need of the product was cast aside [...] we did not do what we had to, so, when we ask, today, how many countries in Latin America is the product registered in?! How about Southeast Asia, how many countries have we registered the product in? [A-IO-2]*

Given the experience of the ASMQ technology-receiving partner in selling other products, such as ARV, in the international market, technology transfer contributed to expedite the adoption of the treatment by other countries, particularly in Asia.

In addition to this weakness presented by Farmanguinhos, the FACT Project did not originally include a comprehensive strategy for registration in different countries or partnerships that would support the use of the medication (A-DM-1, EU agreement analysis[II]).

This regulatory-related challenge for the global adoption of the treatment is not limited to Farmanguinhos, but falls on the project as a whole (A-IO-1). In addition, another challenge related to the adoption of the product relates to the organization of health services, including training of human resources, side-effect monitoring strategies and demand estimates (A-IO-1).

Another approach to facilitating international adoption is arranging for pre-qualification of the treatment by the World Health Organization (WHO-PQ). ASMQ was pre-qualified for the first time in 2012, and this was granted to the drug manufactured by Cipla, a company with broad experience in obtaining WHO-PQ. In 2015, Farmanguinhos also applied for WHO-PQ.

Having its product pre-qualified by WHO is a challenge and an important opportunity for Farmanguinhos. Farmanguinhos has learned a lot from this accreditation process (B-DM-3, B-IO-4, C-DM- 2). The factors listed for the long time this process has taken are characteristics typical of the public sector; which cannot be compared to the agility of the private sector (B-IO-2, B-IO-4,C-DM-2, B-IA-1). The novelty of this experience in Brazil was a challenge for the teams, but considered an opportunity for domestic manufacturing and global access to the medication that Brazil would export (B-IO-4, B-IA-1, B-IO-2, B-DM-3).

> *For the first time in Brazil there is a pre-qualification request. So far, no other public laboratory or the private sector have filed for pre-qualification by the World Health Organization. At the World Health Organization there are pre-qualified products from private labs in India, and perhaps South Africa, the Aspen laboratory, I think, but no Brazilian manufacturer, whether public or private, has filed for pre-qualification. It is the first time that we have an extremely complex process, as we must prepare four or five reports providing all the details. We even had external consultants to help out in this process. DNDi played a major role, not only the local office, but the person who came from Geneva a number of times, who was very experienced in dealing with this. It was a lesson we learned, and now we are capable of pre-qualifying other products in the future [...] It was an important learning process, this pre-qualification. [C-DM-2]*

In Latin America there are two important initiatives that characterize opportunities for the adoption of ASMQ FDC. The first is the Ravreda initiative, and the other is the PAHO Revolving Fund.

As mentioned elsewhere, Ravreda is a network organized jointly in 2001 by PAHO to study antimalarial drug resistance in the Amazon region, so that changes in protocols could be made in accordance with the new WHO recommendations. Many interviewees mentioned that one of the weaknesses of the ASMQ partnership was not having an early interaction with the different players and initiatives in the region that could have further contributed to the adoption of the product (A-IO-2; A-IO-4; A-DM-2; A-DM-1; B-DM-1; B-IO-3; B-IO-1; F-IA-3). For some, this contact should have been made by Farmanguinhos. However, although Farmanguinhos had never been assigned the role of coordinator, it is possible that the definition of such roles was not clear among partners from the outset.

The development of ASMQ FDC had no impact on the dynamics of Ravreda. Meetings were held, but there was no direct involvement of the Network in the product development process (D-IA-2). Some even believe that Farmanguinhos and Ravreda did not have an ongoing dialogue (A-DM-1).

The second initiative on a regional level relates to the PAHO Revolving Fund. Once some of the countries of the region had adopted the AS+MQ association as a first line of treatment, there was an opportunity for the FDC manufactured by Farmanguinhos (A-DM-1) to be procured through PAHO. Farmanguinhos, however, was not accredited by PAHO until 2013 since it needed to renew its Good Manufacturing Practices (GMP) accreditation by ANVISA; this was only granted in 2012, which made product availability in the region difficult (A- IO-2; A-IO-4; B-IO-3; B-IO-4). On one hand, different factors that made the adoption of ASMQ FDC difficult were identified (Farmanguinhos' export capability, drug registration in the countries), on the other hand, the product was released into a scenario where two FDC treatment alternatives already existed, AL and ASAQ, which meant competition, not only on price, but also as a therapeutic option to treat *P. falciparum* malaria.

## *NATIONAL ADOPTION – THE BRAZILIAN CASE*

Artemisinin derivatives (artemether, artesunate and dihydroartemisinin) were included in the national malaria treatment protocol in Brazil in 2001[58], when they were indicated as monotherapy or in association with other antimalarial agents for severe malaria in *P. falciparum* multidrug-resistant areas.

In 2006, the Ministry of Health published the document "Malaria Control Actions – a textbook for primary care health practitioners"[59], which, even though it did not replace the 2001 national protocol, already incorporated, among its recommendations, the use of therapeutic schemes with the *ACT* artemether + lumefantrine FDC (brand name Coartem®) for *P. falciparum* malaria, together with primaquine for mixed malaria (*P. vivax* and *P. falciparum*) cases; and for pregnant women in the 2nd and 3rd trimesters of pregnancy with *P. falciparum* malaria.

As discussed by Osorio-de-Castro *el al.*[60], booklets for health practitioners about the adoption of *ACT* artemether + lumefantrine FDC were made for distribution in the field[VI].

In 2010, the national protocol for the treatment of malaria was updated[61], and it included ASMQ FDC together with primaquine as the other first line option for the treatment of *P. falciparum* malaria, in addition to artemether + lumefantrine and primaquine.

In the National List of Essential Medications, artesunate and mefloquine were included in the editions published between 2002 and 2009 (the 3rd to 6th editions)[62-65]: artesunate 50 mg tablets and mefloquine 250 mg tablets. ASMQ FDC was included in 2010, in the 7th edition[66] and AL FDC in the

9th edition, in 2014[67]. The 7th edition of the National List of Essential Medications (RENAME) mentioned the recent manufacture of ASMQ FDC by Farmanguinhos and reported the evidence that this presentation is associated with fewer side-effects than mefloquine monotherapy.

Therefore, while AL was included in the National Malaria Control Program of Brazil (PNCM) in 2006 and in RENAME only in 2014, ASMQ was included in both in the same year - 2010. The difference between products listed in RENAME and those adopted by the PNCM reflects inconsistencies in the Ministry of Health guidelines.

Another important initiative that supported the adoption of this treatment in Brazil was an intervention study (phase IV) conducted in the state of Acre to assess ASMQ FDC effectiveness. The investigators of this study included representatives of PNCM, DND*i*, Farmanguinhos, PAHO, universities, and the Health Department of the State of Acre[38].

This was an interrupted time series study conducted from July 2004 to December 2008; the intervention with ASMQ was from July 2006 to December 2008, in three cities of the State of Acre. In the study, 23,845 patients received ASMQ FDC. The results indicated a decrease in incidence of *P. falciparum* malaria cases for all age groups (table 8), and no reports of serious adverse events.

**Chart 8. Incidence rates of Plasmodium falciparum (per 10,000 inhabitants) stratified by age (Vale do Juruá)**

| Year (population at risk) | <1 year | 1 to 6 years | 7 to 13 years | ≥14 years |
|---|---|---|---|---|
| **2004 (96496)** | 5.58 | 56.43 | 55.56 | 60.22 |
| **2005 (106882)** | 22.64 | 148.58 | 161.81 | 164.33 |
| **2006 (109827)** | 67.95 | 298.59 | 327.63 | 307.84 |
| **2007 (112755)** | 22.88 | 68.15 | 79.64 | 71.44 |
| **2008 (103799)** | 13.38 | 38.58 | 38.01 | 33.61 |

Source: Santelli *et al*., 2012.

A number of interviewees mentioned that the Acre study reflected the positive implementation of the partnership for the development of ASMQ FDC (F-IA-1; F-IA2; F-IA-3; F-DM-2; B-IO-1; A-IO-2; D-IA-2). The study, with the intervention beginning in 2006, also reflects the efforts for nationwide adoption of the treatment at the same time as the application for certification from ANVISA (granted in 2008). ASMQ FDC was included in the national therapeutic protocol in 2010 as result of these initiatives.

In addition, the Acre study contributed to demonstrating the effectiveness of ASMQ FDC, the enhancement of patient compliance and a decrease in the incidence of malaria; it also prompted Acre to make changes to the organization of its health services (F-IA-2; F-IA-1).

> *At that time, the study elicited information for us, so that we could discuss control tools for all malaria-control actions, not only for the treatment, but for all actions that were considered as priority, and would have to be set in motion [...] I think one of the advantages was to have many brains and many tools available; more importantly, we showed the practitioners that these tools would significantly improve the malaria control actions, and they embraced them. [...] We have used all possible instruments in this study, and to date we still use falciparum case control spreadsheets [...], patient follow-up, [...] The ASMQ project left a legacy for Acre, no question about that: the organization, the control, the commitment, the understanding, the technical-scientific experience [...] that is what's valuable, for us. [...] We improved our operational services a lot, the services that we provide to the population. [F-IA-2]*

Since at least 2010[68], the PNCM has had a Technical Advisory Committee to provide guidance regarding malaria control. In 2012, it became known as the Ministry of Health National Malaria Control Program Technical Advisory Committee (CTA- PNCM/MS)[69] with the mission of providing advice "in all technical and scientific aspects related to epidemiological surveillance, health management and care of malaria patients" (1st article). The Technical Committee included malaria experts from different institutions in Brazil.

In 2012, the Technical Committee recommended that ASMQ FDC be replaced by artemether + lumefantrine as the first therapeutic option for the Acre region[VII]; ASMQ FDC was the indicated therapy for the extra-Amazon region (F-IA-1; F-IA-2, F-IA3, A-OI2).

Almost all (99.5%) malaria cases in Brazil are in the Amazon region (which includes the states of Acre, Amapá, Amazonas, Maranhão, Mato Grosso, Pará, Rondônia, Roraima and Tocantins)[70]. Therefore, in practice, this means that ASMQ FDC is no longer the first treatment option.

Many interviewees (B-DM-3; B-IO-3; A-IO-2; A-DM-1; B-IO- 1; F-IA-3; F-IA-1; F-IA-2) stated that the Technical Committee's rationale was based on evidence of resistance to mefloquine.

Some have also suggested that the choice of using the other *ACT* might have been influenced by the cost, even though, according to others, the price difference between the two combinations is not significant (A-DM-1; B-IO-3). In the face-to-face workshop, the price-difference justification was strongly opposed by the participants.

The purchasing price of AL FDC paid by the Ministry of Health decreased during the period under investigation (2006-2014), particularly after the involvement of PAHO as an intermediary, even with the procurement of smaller quantities (table 2). The ASMQ manufactured by Farmanguinhos had an increase in price in 2011, followed by a drop if adjusted by the Extended National Consumer Price Index - IPCA (table 3). And yet, comparing the cost for an adult treatment with the medication manufactured by Farmanguinhos, in 2014 R$ 3.54 is lower than the price paid to CIPLA for AL FDC the last time it was bought, in 2010 (R$ 4.01), taking inflation into account (IPCA index-adjusted prices).

**Table 2. Total number of blister packs, cost per treatment, and total procurement cost and supplier of artemether + lumefantrine by the Minister of Health. Brazil, 2006-2014**

| ARTEMETER +LUMEFANTRINE (BLISTER) | 2006 NOVARTIS | | | 2007 NOVARTIS | | |
|---|---|---|---|---|---|---|
| | Total blisters | Price per treatment (R$) | Total cost (R$) | Total blisters | Price per treatment (R$) | Total cost (R$) |
| 20MG+120MG W/06 | 14,880 | 2.03 | 30,272.32 | 10,080 | 1.57 | 15,840.96 |
| 20MG+120MG W/12 | 14,880 | 3.74 | 55,597.88 | 14,400 | 3.14 | 45,259.91 |
| 20MG+120MG W/18 | 124,320 | 7.09 | 880,896.22 | 132,240 | 6.15 | 813,923.76 |
| 20MG+120MG W/24 | 115200 | 7.19 | 828,677.68 | 121200 | 6.29 | 761,875.03 |
| TOTAL | 269,280 | — | 1,795,444.10 | 277,920 | — | 1,636,899.66 |

| ARTEMETER +LUMEFANTRINE (BLISTER) | 2010 CIPLA | | | 2012 PAHO | | |
|---|---|---|---|---|---|---|
| | Total blisters | Price per treatment (R$) | Total cost (R$) | Total blisters | Price per treatment (R$) | Total cost (R$) |
| 20MG+120MG W/06 | 12,300 | 1.48 | 18,148.61 | 25,200 | 1.00 | 25,255.10 |
| 20MG+120MG W/12 | 20,160 | 2.35 | 47,319.57 | 32,400 | 1.52 | 49,252.08 |
| 20MG+120MG W/18 | 109,860 | 3.87 | 424,674.40 | 144,810 | 2.87 | 415,342.19 |
| 20MG+120MG W/24 | 89640 | 4.01 | 359,588.12 | 112650 | 2.97 | 334,626.17 |
| TOTAL | 231,960 | — | 849,730.71 | 315,060 | — | 824,475.54 |

Source: calculated from data provided by the Ministry of Health.

**Table 3. Total number of blister packs, cost per treatment, and total procurement cost and supplier of artesunate + mefloquine by the Ministry of Health. Brazil, 2009-2014**

| ARTESUNATO +MEFLOQUINA (blister) | 2009 FIOCRUZ | | | 2010 FIOCRUZ | | |
|---|---|---|---|---|---|---|
| | Total blisters | Price per treatment (R$) | Total cost (R$) | Total blisters | Price per treatment (R$) | Total cost (R$) |
| 100+220MG C/03 | 31,590 | 0.79 | 25,046.21 | 4,830 | 0.75 | 3,615.78 |
| 100+220MG C/06 | 126,420 | 0.79 | 100,232.37 | 34,800 | 0.75 | 26,051.61 |
| 25+55MG C/03 | 18,000 | 0.20 | 3,526.06 | 30,000 | 0.18 | 5,548.83 |
| 25+55MG C/06 | 36,000 | 0.20 | 7,052.12 | 72,000 | 0.18 | 13,317.19 |
| Total | 212,010 | — | 135,856.76 | 141,630 | — | 48,533.42 |

Source: calculated from IPCA-adjusted data provided by the Ministry of Health

| 2008 NOVARTIS | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 18,720 | 1.36 | 25,458.82 |
| 34,560 | 2.72 | 94,002.28 |
| 159,450 | 5.15 | 820,398.16 |
| 124890 | 5.44 | 679,394.97 |
| 337,620 | — | 1,619,254.22 |

| 2009 CIPLA | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 12,000 | 1.26 | 15,093.60 |
| 18,000 | 2.49 | 44,733.01 |
| 87,990 | 4.35 | 382,420.54 |
| 69990 | 4.54 | 317,620.23 |
| 187,980 | — | 759,867.38 |

| 2013 PAHO | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 16,140 | 1.09 | 17,629.74 |
| 20,340 | 1.67 | 34,042.44 |
| 103,920 | 2.83 | 293,709.79 |
| 83460 | 2.90 | 242,390.03 |
| 223,860 | — | 587,772.00 |

| 2014 PAHO | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 30 | 1.03 | 30.80 |
| 30 | 1.57 | 47.19 |
| 120 | 2.64 | 316.36 |
| 90 | 2.73 | 245.64 |
| 270 | — | 639.99 |

| 2011 FIOCRUZ | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 5,030 | 2.11 | 10,607.06 |
| 31,590 | 4.22 | 133,231.40 |
| 23,020 | 0.52 | 11,993.82 |
| 23,370 | 1.04 | 24,352.33 |
| 83,010 | — | 180,184.61 |

| 2012 FIOCRUZ | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 20,560 | 1.99 | 40,963.80 |
| 36,180 | 3.98 | 144,170.24 |
| 20,230 | 0.49 | 9,958.59 |
| 19,720 | 0.98 | 19,415.08 |
| 96,690 | — | 214,507.71 |

| 2014 FIOCRUZ | | |
|---|---|---|
| Total blisters | Price per treatment (R$) | Total cost (R$) |
| 1,000 | 1.77 | 1,767.90 |
| 1,500 | 3.54 | 5,303.70 |
| 1,000 | 0.44 | 435.00 |
| 1,000 | 0.87 | 873.60 |
| 4,500 | — | 8,380.20 |

There are different perceptions of the Technical Committee recommendation of AL FDC over ASMQ FDC. Even though recommendations are not mandatory decisions, typically the PNCM accepts all Committee recommendations; therefore, the Committee has a guiding role in the incorporation of technology. The Technical Committees were reformulated in 2011, and the National Committee for Health Technology Incorporation – CONITEC also took charge of decision-making. This is understandable, since the Ministry of Health has a seat in CONITEC (SVS). The act that created CONITEC, in January 2012[69], included seats for Conas, Conasems, PAHO, the Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Evandro Chagas Institute, Oswaldo Cruz Foundation, National Council of Indian Women, National Confederation of Workers in Agriculture, and the Brazilian Society of Tropical Medicine.

It is understandable and commendable that PNCM is autonomous in decision-making. Poor transparency is a problem in this decision-making process, evidence-review reports or records of meetings in which this issue was discussed, if they ever existed, were not easily accessible.

Another factor for consideration is that *ACT* replacement was a top-down decision made by the Ministry of Health to be complied with by the states, without them being heard, which resulted in dramatic changes in the practices of health services (F-IA-2).

Furthermore, the dialogue between the ASMQ development project partners (DND*i*/ Farmanguinhos) and the different players involved in the fight against malaria was not sufficient throughout the course of the project (F-IA-1; F-IA-3; B-IO-3; A-IO-2; A-DM-1; A-DM-2).

For instance, it was realized that the discussions with PNCM were delayed, starting well after the beginning of the FACT project. Even though there was this dialogue during the study in the state of, there was no conversation with the Malaria Technical Advisory Committee (F-IA-1; F-IA-3), which had the role of advising the program on technology incorporation.

In the specific case of the Technical Committee recommendation to replace the *ACT* used in the Amazon region in 2012, DND*i* wasn't even aware of the existence of such a Committee (A-DM-1). When this became known, DND*i* worked hard, based on scientific studies[71,72], to deconstruct the arguments that justified the drug replacement. For instance, DND*i* organized a meeting during the international congress on malaria[VIII], in September 2012, in Rio de Janeiro, with representatives of Farmanguinhos and the Technical Advisory Committee, to challenge the mefloquine-resistance argument (A-DM-1; B-IO-2).

A possible consequence of *ACT* replacement in the Amazon region was that the Ministry of Health did not order ASMQ FDC from Farmanguinhos in 2013 and only ordered a trivial amount in 2014 (1,000 treatments for each age-group) (B-DM-3; B-IO-2) (table 3), which compromised product manufacturing and delivery schedules.

Study investigations indicated some opportunities for reconsidering the use of ASMQ FDC[73] - a possible indication for *P. vivax* malaria cases (A-DM-1; B-IO-3; B-IO-1; F-IA-1), the possibility of reviewing the malaria therapeutic protocol in Brazil (F-IA-1), and even the possibility of considering ASMQ as a backup for cases resistant to the first option *ACT* (artemether + lumefantrine) (F-DM-2).

It was mentioned in the workshop that one reason for supporting the use of ASMQ FDC was that it favored treatment compliance, since ASMQ FDC requires fewer daily doses than AL FDC.

## Interviewees' perceptions of the success of the ASMQ development project

The question about how the success of the ASMQ project was perceived prompted a number of readings and thoughts that reflect the results presented in the previous sections. In short, the responses pointed out that the project was successful in terms of its development up to registration, but unsuccessful because the treatment was not broadly used by the people who needed it.

Among the factors determining the success of the project, there is a clear acknowledgement by both DND*i* and Farmanguinhos, that there was an improvement in capacity and an increase in knowledge about the different treatment development stages and manufacture (A-DM-1; A-IO-2; A-IO-3; A-IO-4; C-DM-2; C-DM-1; B-DM-3; B-IO-1; B-IO-3; B-IO-4). Perceived gains from the phase IV clinical trial conducted in the state of Acre between 2006 and 2008 also included a change in the organization of health services that contributed to the management of malaria in that region (F-IA-2).

Furthermore, for Fiocruz representatives, the partnership was the beginning of a new technological development model (the PDP model) (B-IO-1), which was a great promise (C-DM-1).

The development and launch of ASMQ FDC illustrates that Farmanguinhos fulfilled its mission of manufacturing a treatment that targeted public health (B-DM-2). The project was also seen as a milestone for Farmanguinhos (B-IO-3) in terms of incorporating different procedures for the operation of the organization, a rise in its status, and for receiving awards and international certificates (B-DM-3; B-IO-4).

Despite the perception of success due to improvements during the process and achieving registration of the product, it was also acknowledged that development took much longer than expected (A-IO-2; A-IO-3; B-DM-4; B-IO-1; B-IO-2; B-IA-1; F-DM-2).

Bottlenecks included difficulties in meeting deadlines and slow processes in Farmanguinhos, as well as varying prioritization of the project depending on the whim of different executive boards. These bottlenecks caused frustration, excessive demands of one partner on the other, and were felt to be very demanding on DND*i* (A-DM1; A-DM-2; B-IA-1). Experiences from the ASMQ project also led DND*i* to reflect on the criteria for selecting partners in the future, and the need to include technical and political factors (A- DM-1; A-IO-2).

To illustrate the delay mentioned by the interviewees, the first agreement made by the partnership was with the European Commission, and estimated a development period of three years up to registration, from 2002 to 2004. It was renewed for two more years (until 2006), but the certificate was only granted by ANVISA in 2008. In contrast, the other combination developed by the FACT consortium – ASAQ – was released in 2007.

Another problem cited by DND*i* (A-DM-1; A-IO-4) is the

potential difficulty of finding a partner that fulfils all the conditions for the development of a partnership, since the other partner may not learn how to move forward independently and autonomously.

On the other hand, it was also mentioned that there was not a well-defined regulatory framework in Brazil for the development of the treatment, and that many changes had to be made along the way. Despite the different context-related factors that might have hampered the development process, Fiocruz was blamed for almost all the problems faced, and it did not defend itself properly (B-IO-1).

In terms of timely availability of the product, the development of the treatment in Farmanguinhos was essential for the technology transfer to Cipla, which was able to have the treatment pre-qualified by WHO in 2012 and to make it available (i.e. registered) in many countries (A-IO-1; B-IA-1).

Thanks to the partnership, Farmanguinhos was able to file for pre-qualification of the treatment by WHO. This was the first product from a public laboratory in Latin America to receive such qualification, and was a tremendous learning experience despite the challenges faced during the process (A-DM-1; B-DM-1; B-IO-2).

As previously mentioned, despite the efforts made to assure product availability from at least two manufacturers, there was also frustration about the product not being broadly adopted in Brazil and Latin America (A-IO-1; A-IO-2; B-IO-1; B-IO-2).

In terms of manufacturing planning at Farmanguinhos, frustration was reported about the product not being manufactured on a large scale for Brazil (B-DM-3), because of the lack of a manufacturing planning scheme to ensure timely availability of the product (B-IO-2). This situation is reflected in the difficulties experienced in identifying suppliers in Latin America able to provide ASMQ in a timely fashion (D-IA-1).

In terms of challenging the non-adoption of the treatment in Brazil, it was felt that there was not enough communication with the technology incorporation body of the Ministry of Health to ensure that the medication was broadly adopted in Brazil (F-IA-1). However, the mefloquine-resistance argument prevailed in the decision-making process (F-DM-2; F-IA-1).

Table 9 summarizes the perceptions about the success of the partnership, considering the DND*i* core mission and the access dimensions of the theoretical model adopted in the study.

**Chart 9. Summary of perceptions related to the success of the partnership**

| | |
|---|---|
| **ABOUT DNDI'S MISSION** | |
| CAPACITY BUILDING | Yes. There was organizational and individual learning. |
| DELIVERY | Partially (yes, from the development up to registration, existence of two suppliers; no, in regards to broad use) |
| ADVOCACY | Yes (output of technical information and knowledge; possibility of treatment manufacture according to a new framework model - PDP) |
| **DIMENSIONS OF ACCESS** | |
| ARCHITECTURE | Little success, as the partners assigned different priority levels to the project, which caused tension |
| AVAILABILITY-OUTPUT | Partial success. There are two sources, however procuring API (mefloquine) is difficult and costly |
| AVAILABILITY-PLANNING | Little success. Difficult to know when countries will buy, and what quantity |
| AVAILABILITY- PROCUREMENT | No. Low availability in Farmanguinhos' target market |
| GLOBAL ADOPTION | Partial success. WHO pre-qualified and included as first line therapy in the protocols of eight countries, four of them in the Americas. |
| NATIONAL ADOPTION (BRAZIL) | Little success. Not broadly adopted by PNCM (only in the extra-Amazonian region; artemether-lumefantrine arrived first) |

## LESSONS LEARNED

### Architecture

- Awareness raising by different players triggered the mobilization of resources for neglected diseases, including by the European Commission, which started a specific project for fixed-dose combinations for the treatment of malaria. The initial agreement with the Commission specified access stages after the manufacture of the treatment (certification, pre-qualification, distribution channels, adoption in national and international markets). The innovative character of the project, which precedes the creation of DND*i*, should be noted**. It is important that the plan as a whole be considered, up until the adoption of the treatment by the users.** Even though the role of each partner was well established during project development, certain stages were missing, as well as alignment between them.

- At the time the decision was made to develop ASMQ, there were few research groups willing to work on the development of an **FDC for malaria.** This endeavour was part of a synergistic strategy to fight malaria in the settings where MSF operated, particularly in Africa. MSF's idea, along with the other partners was for the project was to have **"simple, affordable, easy to manage tools" for malaria.** Fiocruz was a founding partner of DND*i* (which would replace MSF as Project coordinator), and that favored its selection for the development of ASMQ.

- The project was clearly a priority for **DND*i* throughout its development, and the same general coordinator was kept for the whole period;** for **Farmanguinhos, the priority rating varied over time, most likely due to changes in the executive management**. In terms of coordination of the ASAMQ project, there was less HR turnover at **DND*i* than at Farmanguinhos, with the implied potential risk of losing project memory, orientation and political-institutional support**.

- **Despite the efforts of the coordination team, with periodic meetings and personal follow up, the roles and the goals of the project (development and certification of the product, distribution to the users) were not clear for some staff at both partner institutions**. Very clear agreement clauses were necessary from the beginning, encompassing all the project stages, particularly in long-term projects.

- **DND*i*, Fiocruz and MSF** shared a common goal of developing products for neglected diseases **with a number of specific characteristics** such as a convenient dosing schedule, final price de-linkage, and patent exemption**.** However, there were dissonant perspectives within **Fiocruz, and between Fiocruz and its partners MSF and DND*i***, specifically with regard to patents, which, initially, generated dissent about the approach to be taken to the project.

- The project makes evident the importance of Brazil as a relevant regional and global player**, the consolidation of DND*i* as an R&D organization for neglected diseases, and the importance of an international consortium for an innovative public-private partnership in the country. Most** interviewees were in favor of future partnerships.

- **There was a clear lack of consensus among the players involved about how to assess the project's success.** The treatment was developed up to the point of being registered, but it is frustrating to see that it is underused. Access strategies, and economic and epidemiologic studies were not properly thought out and articulated from the beginning of the project and throughout its development.

- The development of ASMQ and ASAQ FDCs was proposed as a response to an access problem, but this was not thought out in a comprehensive way, and was not adjusted to the epidemiologic changes that took place throughout the development process.

- Access strategies should be designed and reviewed throughout the life of the project, and adjusted according to the changes that take place.

- All partners agree with the idea that institutional and individual learnings about management, technical and policy issues is a major legacy of the project, and should be replicated in similar future initiatives.

### Availability

- The lack of a regulatory framework, the restructuring of ANVISA in the 2000s and a change in venue of the Farmanguinhos plant were challenges that lengthened the development of the treatment. Once developed, difficulties in renewing the GMP (Good Manufacturing Practices) certification made planning exports more challenging. These hurdles gave insights into the complex regulatory framework for the project and into some early commercial realities for this laboratory, which had to reorganize its facilities at the same time**.**

- **Challenges for the production process in terms of infrastructure, supply chain and labour outsourcing at Farmanguinhos were also mentioned, and should be analyzed when considering future projects**. Many of these challenges were identified during the process, but could not be overcome. There is a need for mechanisms that can be set in motion to implement solutions once problems have been identified.

- Because the primary focus of Farmanguinhos was to serve its own country, the institution had to learn how to deal with the international context (registration, exports, sales negotiation, country-dependent regulations, irregular, outbreak-dependent demand). **The competition between regional and international demand, and the needs of the Brazilian Public Health System (SUS) posed administrative, institutional and political challenges. Challenges like these may be overcome when a political decision about the role of a laboratory in a treatment-development process is made.**

- **One of the main challenges for the sustainability of production was the supply of the raw materials: the high cost of mefloquine and the variable price of artesunate at an international level; import difficulties and vulnerability as regards the international market. This should have been dealt with by identifying** more than one manufacturer and investigating the optimization of the mefloquine synthesis route; the early acknowledgement of pricing issues; and even the possibility of domestic manufacture of API, or synthesis at a global level, taking into account the existence of the plant (artemisinin) in Brazil.

- There is consensus that the sudden interruption of ASMQ orders by the Brazilian Ministry of Health posed production-planning challenges that seriously compromised product availability. It was concluded that the on-going communication with the political bodies in charge of treatment procurement throughout the development of the product was inadequate, particularly after the registration of the treatment, and posed a risk that manufacturing would be abandoned if national and international demands were not consolidated in the following years. A project to develop a new treatment requires ongoing communication with bodies responsible for the adoption of new technology.

- The fact that CIPLA supplied Farmanguinhos target-markets (Venezuela) when the latter could not do so, leads to a reflection about competition between public and private laboratories, with different interests, missions and administrative flexibilities. On the other hand, the existence of two manufacturers prevents treatment monopoly and ensures availability. **Therefore, it is important to know in advance the problems that may arise and define, through agreements, strategies to solve them.**

## Adoption

*GLOBAL*

- Despite institutional challenges in Farmanguinhos (labour instability due to outsourcing, slow procurement processes, lack of export experience), that delayed ASMQ development, these are not enough to account for its low rate of adoption**. This can be explained by external threats, the existence of alternative *ACT*-FDC therapies that are consolidated in the market and broadly used**, a decrease in the number of ***P. falciparum*** malaria cases, and increased resistance to artemisinin derivatives**.**

- Important initiatives within the framework of the partnership were implemented to ensure global adoption: **clinical trials, technology transfer to a partner in Asia, drug registration efforts, pre-qualification by WHO, and inclusion in the WHO List of Essential Medicines.** DND*i* also financed mock inspections at Farmanguinhos, to prepare the laboratory for the WHO pre-qualification process.

- **Thanks** to RAVREDA's initiatives, **the adoption of the AS+MQ combination into the treatment protocols of some countries of the** Latin America **region** (Peru, Bolivia, Colombia and Venezuela) is a key-opportunity to make the FDC formulation manufactured by Farmanguinhos available.

- The hurdle faced by Farmanguinhos for the pre-qualification of its product by the PAHO Revolving Fund (GMP approval by ANVISA) was overcome in 2013, and the product is certified for regional purchases**.**

- It is important to implement treatment resistance monitoring in the area, as well as monitoring strategies, to support the adoption of the treatment.

- Between 2002 and 2014, the period of the study, the national and international landscape for malaria changed in terms of epidemiology, international funding and global political action. This created at the same time both challenges and opportunities for the adoption of ASMQ FDC. The treatment is currently one of many *ACT* alternatives, and is indicated for uncomplicated *P. falciparum* malaria. Therefore, its adoption does not depend on the efforts of the FACT project partners alone. Other considerations and strategies of the governments of endemic countries and non-governmental organizations may lead to the adoption of other *ACT*s. This is a highly dynamic process. WHO recommends that *ACT* selection should be based on the resistance-profile of the drug associated with the artemisinin derivative.


*NATIONAL (BRAZIL)*

- Since 2006, the Ministry of Health has included *ACT* within its treatment options for malaria. **Many initiatives were implemented within the scope of the ASMQ-development partnership to make national adoption possible: obtaining certification from ANVISA and conducting a phase IV clinical trial in Brazil (the "Acre Study").** These initiatives probably supported the decision to include this treatment in the 2010 Brazilian protocol as a first-line treatment for *P. falciparum* malaria.

- Of note is the selection of the state of Acre for conducting the study. **The project had political support there, which made its implementation feasible by PNCM, DND*i*, Farmanguinhos and RAVREDA.** Political support is an important aspect for consideration when selecting phase IV study sites.

- **Despite adoption efforts, in 2012 the decision was made that another *ACT* would be used in the Amazon region, and ASMQ FDC was indicated for the extra-Amazonian region (1 to 2% of the cases).** This decision was based on mefloquine-resistance studies, but different interviewees questioned that justification. Furthermore, evidence-review documentation or discussions on which the decision was based were not available. One of the outcomes of this decision was that the Brazilian Ministry of Health suspended **ASMQ FDC orders from Farmanguinhos** for the past two years.

- There are alternatives paths for the project's sustainability. A recent study has shown a possible use of ASMQ for ***P. vivax*** cases, and upon restructuring of the treatment of malaria in Brazil (with less concern for mefloquine-resistance).

- Consideration should be given to significant changes in the epidemiological profile of *falciparum* malaria in Brazil and the world, with the drop in incidence. If it is not used as a first-line treatment, the demand for **ASMQ will be low, despite alternative paths for its sustainability.**

## FINAL CONSIDERATIONS

Despite the barriers faced, important advances were made during the ASMQ project. The product however, particularly the one manufactured by Farmanguinhos, is little used at present due to a number of factors. Internationally this is a treatment that competes with other *ACT*-FDC (ASAQ and A+L), and *P. Falciparum* malaria cases are markedly dropping in the world. On the domestic front, there were development problems that delayed drug certification, and Farmanguinhos faced difficulties in exporting to its target markets.

The delayed release of ASMQ FDC and the difficulties faced by Farmanguinhos during the product-development process are acknowledged in this study and serve as lessons for the future. However, these aspects alone do not justify the low demand for ASMQ FDC after its release in 2008. There were more comprehensive problems prior to 2008, which suggested that enhancement of access would be hampered, even if the treatment were released according to schedule.

Even though DND*i* continued to manage the project, its priority level at Farmanguinhos varied, probably due to changes in its executive board. In any case, there should have been better communication within the project as a whole, from the necessary development stages through to product availability to final users.

Neglected diseases affect needy populations, meaning that product procurement will be handled by governmental and non-governmental agencies, and big donors that have their own agendas and preferences in addition to other hurdles, such as difficult and bureaucratic import processes, and slow, complicated product certification.

The adoption of the product developed by Farmanguinhos for Latin America, its target market, has been hampered. In the case of Brazil, local problems excluded ASMQ as a therapeutic option. Since 2012, ASMQ is recommended for use in the extra-Amazonian region that has only 1 to 2% of cases. There is no question about the autonomy of the Brazilian Program regarding its decision-making mandate, but the lack of transparency of the process may be questioned, since no report with the evidence on which the decision was based was found. It is therefore not known what other factors could have improved this situation, beyond the proven effectiveness of the product ascertained in the clinical trial conducted in Acre and elsewhere, and the communication between DND*i* and Farmanguinhos with the National Malaria Control Program since the beginning of the project.

It should be noted that this was DND*i*'s first experience, and a new experience for Farmanguinhos, in an uncertain and changing scenario with changes in the drug registration process, the moving of the plant, and the previous release of other antimalarial treatments. Since 2001, WHO has recommended at least four *ACT*s, including AS+MQ. The fixed-dose combinations were encouraged equally to make compliance easier and lessen the risk of resistance. Thus, there has always been clear "competition" between the therapeutic alternatives (the four different *ACT*s), in terms of adoption to national protocols. Whenever a phase IV clinical trial (intervention study) is conducted, it helps select the best *ACT*. DND*i* did not find enough evidence to justify the selection of A+L over ASMQ in Brazil, including on price grounds. Different interviewees mentioned that this decision had more to do with relationships between stakeholders than with technical or economic reasons.

Much of the discussion and effort to combat neglected diseases is related to challenges in innovation, whether incremental or radical, to ensuring the supply of suitable products, and to product-related issues, such as patent ownership. Therefore, an important lesson learned in this study is that this is not sufficient in ensuring access. There is a complex chain of events and players that must be considered and included during the process, within an architecture that makes sure they are harmoniously integrated. Despite being successful in many of its stages, there was no connection between innovation and access in the FACT project.

Finally, the dimensions of DND*i*'s mission can be considered to have been fulfilled, as the number of players aware of the importance of R&D for treatments for neglected diseases expanded, in particular players involved in their implementation and adoption. All the partner institutions involved learned from the experience, and a number of people mentioned that they had also learned things as individuals, from foreign languages to technical, managerial and political issues, and how to behave in a multi-cultural environment.

## RECOMMENDATIONS

What follows was originated primarily from the participants of the workshop, with some additions made by the study team.

- To conduct market analysis and work on access-related issues, considering that the demand is insufficient, and *P. falciparum* malaria incidence is dropping;
- To participate in and influence the review of the PNCM Protocol, which is being updated;
- To reinforce the benefits of ASMQ with the Ministry of Health, emphasizing patient compliance to treatment, and deconstruct the mefloquine-resistance argument;
- To conduct trials, including on compliance to treatment, and to do a systematic review similar to NICE's, in order to generate and present scientific evidence.
- To have Farmanguinhos develop an internal mechanism for political communication with the Ministry of Health, and to address issues related to manufacturing, resistance and clinical trials;
- To jointly design a work-plan that includes Fiocruz/ Farmanguinhos and the Ministry of Health, with a task-force to work with ASMQ;
- To define Farmanguinhos' inventory volume, markets and export mechanisms, and to follow up on production, use and evolution of *P. falciparum* malaria cases in the target-markets and in the world;
- To ensure the support of international trade experts to advise on and conduct export processes;
- To generate and exchange information on purchases, sales and prescriptions;
- To discuss with MMV, PAHO and WHO the development of trials for the use of ASMQ in Brazil, and the need for clarity in international malaria guidelines on the indication of the different *ACT*s, depending on the different regions and their epidemiological history;
- To focus on *P. vivax*, in terms of conducting trials, compiling existing data and identifying opportunities to use the treatment for this therapeutic indication;
- To invest in process-improvement measures related to product development, such as, e.g. a dispersible pediatric formulation;
- To maintain pre-qualification efforts at WHO.

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## APPENDIX 1. THE "ASMQ PROJECT ASSESSMENT" INVESTIGATION SEMI-STRUCTURED INTERVIEW QUESTIONS

### *GOAL OF THE INVESTIGATION*

The goal of this investigation is to analyze the ASMQ development process according to the access to medication dimensions as proposed by Frost & Reich (2008).

1. Name:

2. Jobs held from 2002 to 2014, and corresponding organizations.

3. Undergraduate degree and highest graduate degree.

4. What role did you play in the ASMQ development project, and when was that?

5. What was the communication process like within your organization around the development of the project?

6. Was it a priority in your organization?
   a. If so, how would you describe the priority given?

7. What were the difficulties in implementing the project?
   a. Were the difficulties related to lack of financial resources, human resources, or infrastructure?
   b. Were the difficulties related to the partners involved? If so, what were they?

8. What were the positive aspects of the implementation of the project?
   a. In relation to the lack of financial resources, human resources or infrastructure?
   b. How did the partners involved contribute to the positive aspects?

9. Regarding the partners directly involved in the ASMQ Project implementation:
   a. Were the roles of each one clearly defined in the course of the process?
   b. Did the communication about the project progression flow among the members in a satisfactory way?
   c. Were there moments of tension? Could you describe them?

10. Once ASMQ was released, what were the main project sustainability challenges for your organization?
    a. In your assessment, was this partnership successful?
    b. What were the benefits perceived for your organization (explore individual and organizational learning aspects, and advocacy)?

11. Were there aspects that overwhelmed your organization? Which were they?
    a. If a new partnership for the development of a treatment were to be established, what would be the main lessons learned from the "ASMQ Project"?
    b. What initiatives should be repeated?

12. What initiatives should be avoided?

13. Do you believe your organization would be willing to engage in a similar project in the future?

14. What aspects of the project contributed to overcoming the challenges of products effectively reaching the final user, and being used properly? What could be improved?

15. Would you like to add anything?
    a. Could you indicate documents that ought to be studied?
    b. In your opinion, who should be interviewed in this investigation?

## APPENDIX 2 - INFORMED CONSENT FORM (ICF)

Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz
Escola Nacional de Saúde Pública Sergio Arouca

### Ethics in Research Committee, Sergio Arouca National School of Public Health

### Pharmaceutical Care Core Center

Departamento de Política de Medicamentos e Assistência Farmacêutica (NAF)
Centro Colaborador da OPAS-OMS em Políticas Farmacêuticas

ESCOLA NACIONAL DE SAÚDE PÚBLICA
SERGIO AROUCA
ENSP

*INFORMED CONSENT FORM*

Dear Participant,

You are invited to participate in the study "Partnership for the development of antimalarial combination therapy in Brazil: lessons for innovation in neglected diseases", under the coordination of Dr. Vera Lucia Luiza, investigator of the Pharmaceutical Care Core Center, Sergio Arouca National School of Public Health, Oswaldo Cruz Foundation (NAF/ ENSP/ Fiocruz) in collaboration with the Drugs for Neglected Diseases *initiative*, Latin America (DND*i* LA).

The goal of this investigation is to analyze the ASMQ development process according to the access-to-medication dimensions.

You were selected because you played a relevant role in the ASMQ project. Your participation is voluntary, not mandatory. You can decide whether or not to participate, and you can stop participating at any time. There is no penalty whatsoever if you decide not to participate or stop participating, and your refusal will not affect your relationship with the investigators. However, your participation is very important for the investigation. You will be asked some questions by a project investigator from an interview script. The interview will be recorded only if authorized by the interviewee, in which case it will be transcribed for analysis. The interview should take approximately 30 minutes.

The preference for this investigation is that the interviewee's responses are expressed during the study, in order to ensure greater accuracy and depth to the efforts to map the different visions and thoughts concerning the implementation of the project under study. The risk for the interviewee is his/ her potential exposure from the information provided at the interview.

If the interviewee does not feel comfortable with the exposure, he/she can ask for anonymity. However, depending on the information provided, there is a risk that the interviewee be identified, even while preserving anonymity, due to the job he/ she held.

The benefits of granting this interview are recording the experience of developing a treatment in Brazil, and indicating potential pitfalls that must be overcome in future treatment-development experiences in the country.

You will receive a copy of this form, with the phone number and address of the main investigator, and you will be able to ask about the project and your participation now or at any time. You and I (investigator in charge) will put our initials on the first page and sign the second.

At any time, during the investigation or afterwards, you can ask the investigator for information about your participation and/or the investigation; this can be done using the contact information indicated on this form.

The results of the investigation will be disclosed in a workshop and with the publication of an article in an international journal.

I STATE THAT I HAVE UNDERSTOOD THE GOALS, RISKS AND BENEFITS OF MY PARTICIPATION IN THE INVESTIGATION.

| | | |
|---|---|---|
| I AGREE TO PARTICIPATE IN THE INVESTIGATION | ( )YES | ( )NO |
| I AUTHORIZE THE RECORDING OF THE INTERVIEW. | ( )YES | ( )NO |
| I AUTHORIZE THAT MY QUOTES BE IDENTIFIED IN THE INVESTIGATION ANALYSIS. | ( )YES | ( )NO |
| I AUTHORIZE THE DISCLOSURE OF MY NAME IN THIS ACADEMIC STUDY. | ( )YES | ( )NO |

Vera Lucia Luiza
General Coordinator of the Investigation
Rua Leopoldo Bulhões 1480/632, Manguinhos
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Fax: (21) 2209-3076

Ethics Committee/ENSP
Rua Leopoldo Bulhões, 1480, Térreo, Manguinhos -
Rio de Janeiro - RJ / CEP. 21041-210 -
Telefax - (21) 2598-2863
e-mail:CEP@ensp.fiocruz.br
Site: http://www.ensp.fiocruz.br/etica

RIO DE JANEIRO, _____ 2014

I STATE THAT I HAVE UNDERSTOOD THE GOALS, RISKS AND BENEFITS OF MY PARTICIPATION IN THE INVESTIGATION AND I CONFIRM THE INFORMATION ABOVE.

_____
Investigation volunteer

_____
Field investigator

## APPENDIX 3. WORKSHOP AGENDA: PARTNERSHIP FOR THE DEVELOPMENT OF ANTIMALARIAL COMBINATION THERAPY IN BRAZIL: LESSONS FOR INNOVATION IN NEGLECTED DISEASES

### Presentation

Malaria is endemic in 106 countries. It is considered a neglected disease since it affects primarily low-income populations, and large pharmaceutical companies have therefore little interest in it. A partnership with public the laboratory Farmanguinhos/ Fiocruz was established to develop a fixed-dose combination of Artemisinin+Mefloquine (ASMQ).

In order to assess ASMQ development according to the access-to-medication dimensions proposed by Frost & Reich (2008) (architecture, availability, affordability and adoption), NAF/ ENSP/ Fiocruz in partnership with DND*i* conducted a case study to better understand the factors involved in partnering with a public laboratory in Brazil. The product development efforts resulted in the entry of the treatment into the market. However, there is only access when a treatment reaches the users and has a therapeutic effect. Thus, the release of the treatment into the market, in itself, does not solve the access challenge. There are important lessons to be shared in order to make future initiatives more effective, since there still are millions of needy people waiting for such innovations.

Twenty-five interviews were conducted with relevant players in the process between January and April 2015; their remarks were reviewed and evaluated in order to give an overview of the problems that will now be considered in more detail.

### Goal

To develop the outcomes of the investigation, considering in more depth, through the exchange of ideas, the achievements and challenges of the ASMQ development experience.

### Expected outcomes

- Identification of the main bottlenecks, and lessons learned in the development of ASMQ that may be replicated in future experiences;
- To complement the data collected with input from the most relevant elements;
- To use the core elements for the development of a user-centered access-to-medication agenda;
- The writing of a final report, including project details and discussion, for eventual publication.

Departamento de Política de Medicamentos e Assistência Farmacêutica (NAF)
Centro Colaborador da OPAS-OMS em Políticas Farmacêuticas

DNDi
Drugs for Neglected Diseases *initiative*
*Iniciativa* Medicamentos para Enfermedades Olvidadas
*Iniciativa* Medicamentos para Doenças Negligenciadas

ESCOLA NACIONAL DE SAÚDE PÚBLICA
SERGIO AROUCA
ENSP

Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz
Escola Nacional de Saúde Pública Sergio Arouca

### Agenda – Wednesday, June 10, 2015

Venue: FIOCRUZ/ Sala de Reuniões do Castelo (117)
Avenida Brasil, 4365, Manguinhos, Rio de Janeiro

| | |
|---|---|
| 9:00 – 9:30 | Opening remarks |
| 9:00 – 9:10 | Eric Stobbaerts - DNDi |
| 9:10 – 9:20 | Carlos Morel - Fiocruz |
| 9:20 – 9:30 | Vera Lucia Luiza – ENSP/ Projeto ASMQ |
| 09:30 – 09:45 PRESENTATION OF THE PARTICIPANTS | |
| 09:45 – 10:45 | Panel: Partnerships for the development of antimalarial drugs. Moderator: Maria Auxiliadora Oliveira |
| 09:45 – 10:00 | Setting: neglected diseases and treatment challenges -Eric Stobbaerts |
| 10:00 – 10:15 | Malaria and the FACT project –Jean-René Kiechel |
| 10:15 – 10:30 | Lifecycle of Innovations – Lia Hasenclever |
| 10:30 – 10:50 | Questions/ Discussion |
| 10:50 - 11:05 BREAK | |
| 11:05 – 12:45 | Panel: From development to access - ASMQ Project. Moderator: Carolina Batista |
| 11:05 – 11:15 | Theoretical Background – Gabriela Costa Chaves |
| 11:15 – 11:55 | Methods and Outcomes – Vera Lucia Luiza |
| 11:55 – 12:30<br>12:30 – 12:45 | Questions/ discussions.<br>Comments by – Paulo Gadelha |
| 12:45 – 14:15 LUNCH – FIOCRUZ (5' WALK) | |
| 14:15 – 15:45 | Work groups Research analysis review |
| 15:45 – 16:45 | Moderator: Lia Hasenclever: Discussion about the workgroup recommendations for the user-focused sustainable development of medication for neglected diseases |
| 16:45 – 17:00 | Close |

## APPENDIX 4.
## WORKSHOP PARTICIPANTS

| PARTICIPANT | INSITUTION | CONTRIBUTION FOR THE PROJECT/ DISCUSSION |
|---|---|---|
| Adriana Mendoza | Fiocruz | Vice President, Fiocruz |
| Alessandra Viçosa | Farmanguinhos | Worked in the ASMQ Project (quality), was mentioned by many interviewees |
| André Daher | Farmanguinhos | Interviewee |
| Ângela Esher | ENSP | Expert in access-related issues; staff member, Pharmaceutical Care Core Center; data analysis support |
| Betina Moura | DNDi | DNDi |
| Carlos Morel | Fiocruz | Interviewee |
| Cláudia Osório de Castro | ENSP | Malaria project coordinator; staff member, Pharmaceutical Care Core Center |
| Eloan Pinheiro | Farmanguinhos | Interviewee |
| Eric Stobbaerts | DNDi | Interviewee |
| Gabriela Chaves | ENSP | Project Participant |
| Hayne Felipe | Farmanguinhos | Interviewee |
| Jean-René Kiechel | DNDi | Interviewee |
| Jorge Mendonça | Farmanguinhos | Interviewee |
| José Ladislau | Ministry of Health | Interviewee |
| José Mendes Ribeiro | ENSP | Professor, National School of Public Health |
| Leonardo Mattos | ENSP | Rapporteur |
| Lia Hasenclever | UFRJ | Economist, investigator on innovation for the pharmaceutical industry |
| Luciana Gonçalves | Farmanguinhos/ DNDi | Interviewee |
| Maria Auxiliadora Oliveira | ENSP | Expert in access-related issues; staff member, Pharmaceutical Care Core Center; data analysis support |
| Maria Carolina dos Santos | DNDi | Project Participant |
| Maria Cristina Milen da Silveira Santos | Farmanguinhos | Potentially important for ASMQ sustainability |
| Maria Lucia de Brito Morley | Farmanguinhos | Potentially important for ASMQ sustainability |
| Marília Guttier | ENSP | Rapporteur |
| Martha Soares-Murtis | Fiocruz | Malaria expert investigator; collaborator, Pharmaceutical Care Core Center |
| Michel Lotrowska | DNDi | Interviewee |
| Michelle Childs | | Independent consultant |
| Nicola Palla | UFRJ | Student, working on ASMQ |
| Paola Marchesini | Ministry of Health | Involved with the ASMQ project (adoption); was mentioned by many interviewees |
| Robson William de Melo Matos | DAF - MS | Representative, Ministry of Health |
| Rondineli Mendes da Silva | ENSP | Expert in access-related issues (particularly logistics); staff member, Pharmaceutical Care Core Center; data analysis support |
| Shirley Trajano | Farmanguinhos | Interviewee |
| Tallane Teque de Oliveira Santana | Farmanguinhos | Potentially important for ASMQ sustainability |
| Tayná Marques | ENSP | Project Participant |
| Vera Luiza | ENSP | Project Participant |

## APPENDIX 5. REPORT OF THE WORKSHOP "PARTNERSHIP FOR THE DEVELOPMENT OF ANTIMALARIAL COMBINATION THERAPY IN BRAZIL: LESSONS FOR INNOVATION IN NEGLECTED DISEASES"

Leonardo Vidal Mattos and Marilia Guttier

### PANEL 1 – Partnership for the Development of Antimalarial Drugs

#### *ERIC STOBBAERTS*

There are flaws in a market that unbalances the development and manufacturing of medication, leading to major shortfalls in drugs, treatments and formulations for neglected diseases that are affordable and ensure proper, effective treatment. From 1975 to 1999, only 1.1% of the treatments developed targeted neglected diseases. Challenges for the development of treatments for this group of diseases include lack of funding, and lack of coordination and finances to drive innovation according to needs, not to the market. In terms of innovation, the world is expecting economic growth over the next few years, particularly in developing countries; this may favor cooperation and greater commitment of these countries to the development of treatments for neglected diseases.

In addition to manufacturing, innovation, and technological development related challenges, there are also major access related hurdles, not only with regard to treatments, but to health care as a whole. In terms of treatments, often these do not reach the people who need them or where they will actually be used.

During the ASMQ project development partnership, a number of goals were reached. Among the issues to be considered regarding the future of ASMQ is how to ensure that the treatment is not abandoned by governmental malaria control programs.

#### *JEAN-RENÉ KIECHEL*

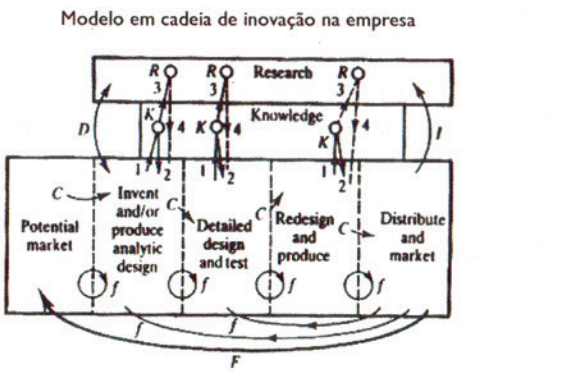
In the 1980s, resistance to chloroquine, the main malaria-management drug was observed. In 2001, WHO recommended the use of combination therapies with more than one active principle. In 2002, a consortium was formed for the development and manufacture of fixed-dose antimalarial combinations. In 2007, ASAQ was registered; in 2008, ASMQ was registered, and in 2009 the treatments were implemented in the countries.

Combination treatments were developed because they were considered to be easy to use for patients, with good aspect and affordable. The process involved communication between different partners, both public and private, during the development and manufacture of the treatment, during the conduct of clinical trials, and when gathering the necessary expertise to complete the process. ASAQ was pre-qualified by WHO in 2008. The cost per patient is less than 1 USD for adults, and less than 0.50 USD for children; it is easy to use and not patented. The multinational pharmaceutical company Sanofi registered this ACT in 30 African countries, India, Colombia and Ecuador. Sanofi was a development partner, and technology was transferred to the Tanzanian company Zenufa. More than 400 Million treatments have been distributed. ASMQ was registered in Brazil in 2008. This treatment was also registered in India, Malaysia, Myanmar, Vietnam, Thailand and Cambodia. Development and manufacturing were achieved in partnership with Farmanguinhos. More than 800,000 treatments have been distributed.

The project allowed the development of new concepts, and important innovations, and the results achieved so far are promising.

#### *LIA HASENCLEVER - THE LIFECYCLE OF INNOVATIONS*

Lia Hasenclever presented a new perspective on the process of innovation, pointing out the contributions, challenges and lessons learned from the partnership under discussion. The innovation process model includes economic and sociological issues, as different agencies and bodies participate. The project used a linear model, which should be changed in favour of a "chain-linked model", better suited to the innovation process. The logic sequence of the model was explained; learning and evolution occur from the feedback from each of the chain-progression stages.




Symbols on arrows: $C$ = central-chain-of-innovation; $f$ = feedback loops; $F$ = particularly important feedback. $K$–$R$: Links through knowledge to research and return paths. If problem solved at node $K$, link 3 to $R$ not activated. Return from research (link 4) is problematic – therefore dashed line. $D$: direct link to and from research from problems in invention and design. $I$: support of scientific research by instruments, machines, tools and procedures of technology

According to this model, public domain knowledge and research develops throughout the process, and leads to new knowledge and research questions, as opposed to the linear model, in which knowledge is centered on basic research. In the model that was presented, there is no deterministic hierarchical chain; there is no differentiation between the production and dissemination of the innovative product, as they occur at the same time. The transfer of technology that takes place during the process of innovation should be used not only as a solution, but also to generate new technologies and incremental innovations, leading to the acquisition of knowledge that will allow progress to be made. The transfer of technology must not be received passively, or we will remain a developing country that depends on the technology of other countries.

In this study from 1974, the separation between the adoption and dissemination of an innovative product was already under criticism. According to the chain model, the process may generate "S Curves" between the first chain and the feedback received.
"S Curve"

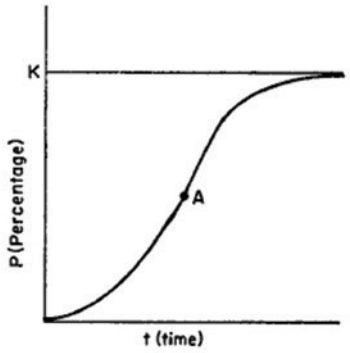


Fig. 1. The logistic.

*DISCUSSION*

Morel: Each private manufacturer, particularly the major ones, is highly capable of applying pressure and distributing its products. Independent evaluators of malaria treatments are necessary to reduce such bias.
Eloan: The government and its agencies are essential players in the coordination of the activities and stages of development and innovation, and they have the strategic vision to face particular problems. The government plays a pivotal role of making the connections between the stages. Brazil must face manufacturing-related problems, not only regarding treatments, but particularly regarding raw materials.
Hayne: Industrial policy is different from innovation policy; one should not criticize the timing, given the historical problems of the country.
Michelle: Some important questions include what the target population is and how to reduce the price.
Vera: Lia, how much of this scenario was foreseeable? How could interventions have changed the course? Despite the development of ASMQ, the competition still has the larger share of the market. Eric, I noticed how hard it is to estimate demand and adjust production accordingly. In the case of malaria, up to what point can one estimate demand? How can you measure that?
Claudia: It is essential to look also at services, not only manufacturing.
Lia: Pharmacists and doctors are resistant to accepting combined treatments; products made from an association of drugs are just not accepted. This is a sociological problem that must be faced.
Jean: At that time, we didn't know about the resistance. We should choose the best option and progress as fast as possible.
Panel 2 came next, with the presentation of the project and its findings.
There was an overall discussion in the afternoon; some of the issues addressed are highlighted in Table 10.

**Chart 10. Discussion of the ASMQ development study**

| |
|---|
| Mefloquine resistance was not tested in the combined treatment. The Ministry of Health based its decision not to use the ASMQ combination on mefloquine only resistance trials. |
| Mefloquine-resistance trials using the combined treatment should be conducted |
| On one hand, there is the resistance issue; on the other, the malaria landscape has changed, and the Brazilian and global agenda for the eradication of malaria changed |
| Manufacturing-focused actions |
| Streamlining the manufacturing process |
| Lack of endemic characteristics throughout the product development period |
| The decision made by the Ministry regarding ASMQ adoption is a problem. Difficulties in arguing in favor of the use of the combined medication, given the mefloquine-only resistance mindset. |

## Discussions about the Lessons Learned

Next, the Lesson-Learned text written by the project team, and the responses given to this question by the interviewees, were distributed.

*MICHEL LOTROWSKA*

About item 7 on architecture, there was no agreement about patents within Fiocruz, and between Fiocruz and MSF. Fiocruz did not have a clear stand, there was no consensus. Concerning the Global Adoption point number 1, the mock inspections of the plants, aimed at supporting Farmanguinhos' efforts in seeking pre-qualification by WHO, should be added. Two mock inspections, funded by DNDi, were conducted. One of the reports went missing during changes in the executive management. It should also be taken into account that UNITAID, for instance, works with adoption and has an entire department for creating demand, which is another way of "marketing the product".

### *ANDRÉ DAHER*

In terms of architecture, the agreement with the European Union does not include the access stage; this should be included in the next project. In addition, we should ask what actually characterizes the success of this project? We know it lacked economic studies. In terms of global adoption, its adoption in Latin America is important, with a need for resistance trials in Latin America. There are not enough patients for efficiency studies and so resistance needs to be monitored in other ways (this aspect was reinforced by Paola). For the future, there are opportunities with *vivax*. It is important to prove to the PNCM the advantages of ASMQ, developing trials, doing a systematic review, similar to NICE's.

### *CLAUDIA DE CASTRO*

Success is the accumulation of different activities. This is technology, as it relates to partnerships. The mechanics of co-operation is a soft technology. Who is the client for antimalarial treatments in Brazil? The Ministry of Health. Otherwise, the right to healthcare is not fulfilled. There was a lack of communication with the client for this treatment. There should be only one policy, Fiocruz should act in line with the Ministry of Health. For the future, we need more information on Brazil, about sales, procurement, prescription, observational data. It is progressively more difficult to conduct clinical trials. If the PNCM wants to eradicate malaria, it should consider compliance, needs-based demand. Given the Ministry of Health's goal of eradicating malaria, if there are two products with similar effectiveness, we should support ASMQ by focusing on compliance.

### *ISABELA RIBEIRO*

In terms of architecture, access and success are essential. This project started before DND*i* was created, and therefore these issues were not addressed from the beginning. Concerning point 12 of architecture, in terms of HR turnover, we should think about labour contracts, particularly for long-term projects. Regarding global adoption point 4, communication was not continuous, but it was started early in the process, it was not delayed. The national situation changed, the global malaria landscape changed, DND*i* changed, and, in this context, the dialogue, that started early on, got lost in the critical, post-registration phase. For the future, Farmanguinhos should have an internal mechanism to ensure the continuation of the project, both in terms of political communication with the Ministry of Health, and technically, with the conduct of clinical trials and resistance studies. How to dialogue with MMV? How to make the transition? What points should be investigated concerning the use of ASMQ in Brazil?

### *VERA LÚCIA LUIZA*

It is important to have all access stages in the architecture. The different stages of the contract can be developed by the same player, but the connection between them must be there.

### *JOSÉ LADISLAU*

The idea that the project was somewhat handcrafted, if you will, should be reviewed. The competences of each player were well established. The project was personalized, but the idea that people rather than institutions developed it is common in public health. At the time, the incidence of *P. falciparum* malaria was dropping. Therefore, only considering the domestic market was a big mistake; the international market should also have been considered. A striking feature of the project was that the Ministry of Health learned how to work with research and academia. In terms of marketing, a study of the market was missing. In addition, a study on epidemiological trends was also missing. It is important to know the epidemiological background in order to move forward with a treatment development process. The importance of selecting the state of Acre, in addition to the state of Pará, where even smuggling of the treatment occurred, should also be reinforced. In Acre, the project had political support. Phase IV studies should not be conducted in a single site.

### *JEAN-RENÉ KIECHEL*

We are at a critical moment for the project: a new architecture, a new plan, a new champion, new studies. Work should be done on access in order to achieve success, we should ask about today and tomorrow. This is real. There is not enough demand. The treatment is good, and tastes good. We should follow the clinical trials very closely.

### *ELOAN PINHEIRO*

Any demand regarding neglected diseases must be met by Farmanguinhos, since it is a Ministry of Health laboratory. Farmanguinhos has the mandate to ensure access to products for neglected diseases. This project cannot go under, because the Ministry of Health will review its program and acknowledge the importance of the project. For the future, Fiocruz/ Farmanguinhos together with the Ministry of Health should develop a work-plan about what needs to be done.

### *ERIC STOBBAERTS*

The importance of having a champion to carry this on, a task-force for ASMQ jointly with PNCM.

### *MARIA CAROLINA DOS SANTOS*

It is important to distinguish the malaria landscape at the beginning of the project from what it is today. To have a champion means to have a workgroup formed by many organizations that can connect all the dots, working jointly and considering our region and Africa. Now is a critical time, and we should take advantage of this to increase access.

*SHRILEY TRAJANO*

There were difficulties, but we have learned and are still learning from this project now, as it is being pre-qualified at WHO, and previously, with ANVISA. I am saddened by the statements. This project is technically excellent for Farmanguinhos. WHO will conduct inspections, and we have presented them with a different set of documents from what we used to. Jean-René checks on this every week. We had no idea of the size this project would reach. We need more demand.

*MARTA SOARES-MURTIS*

The product-development platform: Brazil is asked to do the R&D for neglected diseases, not the countries of the North.

*LIA HASENCLEVER*

The selected excerpts should actually include the lessons learned. There are repeated things in different places. I do not understand why the lack of regulatory framework and the lack of good manufacturing practices are listed under the same topic. One lesson learned is the importance of communicating the process from one end to the other, from manufacturing to access, which did occur. The importance of architecture in the beginning of the project, should be highlighted. Investigations must be conducted. The adoption of treatments should be supported by clinical trials.

*PAOLA MARCHESINI*

Coartem® and ASMQ are equally effective. The advantage of ASMQ lies in compliance. The Ministry of Health must be convinced that ASMQ is better because of compliance. The problem is how to design a new protocol taking the lessons into account and moving forward? Compliance alone is not enough, one must also consider the effectiveness of mefloquine, and that is what hampered adoption. It is very important to communicate with PAHO as well as WHO. Joint purchases should be discussed, due to low demand.

*ALESSANDRA VIÇOSA*

For the future, process improvements should be planned regarding product development. Farmanguinhos is currently focusing efforts on pre-qualification by WHO. For instance, the development of a dispersible pediatric formulation could be considered.

*RONDINELI DA SILVA*

There are so many opportunities for discussion in Brazil that different strategies could be considered, taking into account that the malaria landscape 10 years ago is different to what it is now. This project had some successes, we learned a lot from it, it provided opportunities. Having a project office for project management and prospection could be considered for the sustainability of a project

*HAYNE FELIPE*

Appendix 3 presents some value judgements. We must revisit the idea of defending a project and its relevance. Market analysis is essential, considering the external influences throughout the process. The workforce should be formed so that a strategy is defined, starting now. Not that the project was “amateurish”, as you are never sure of the outcome when a project is started. However, when a development process is set out, you cannot foresee the risk of other innovations affect the project. This is an unpredictable risk. Farmanguinhos does have a “project office”, like the one mentioned by Rondineli. There are some questions to be clarified: Will it focus on Brazil? Will it focus on other countries? How to conduct exports? Its management will meet with DND*i* to assess and move forward with the political recommendations.

*GABRIELA CHAVES*

With this project we deconstructed certainties. There is frustration resulting from the obstacles we faced, but there is a broader picture, and different perspectives. There is the possibility of exporting, in addition to supplying the Brazilian Public Health System – SUS, which is, at the same time, a lesson and an opportunity. ASMQ was developed in a context of several therapeutic alternatives for a single disease, which presents a challenge for its adoption in Brazil and the world. However, there are countries that adopt this association. Is it therefore possible for Farmanguinhos to have stock for export?

This session must be now closed because many participants have flights to catch. The files of the texts distributed will be sent out, so that participants can send their responses by e-mail in the next 15 days.

## EVALUATION OF THE WORKSHOP

In the opinion of many participants, this workshop was extremely important for allowing an in-depth assessment of the experiences accumulated during the ASMQ development process. The participants could share their different views and expand their understanding of the process as a whole, with its strengths and bottlenecks.
This study facilitated the clarification of some points and enriched the findings.

## APPENDIX 6. INTERVIEWEES

| NAME | JOB DURING THE PROJECT (2002-2014); CURRENT JOB |
|---|---|
| André Daher | Clinical trial coordinator 2003-2014/ DND*i* Consultant for Malaria 2009-2013; Clinical Trial Coordinator, Farmanguinhos. |
| Carlos Morel | Fiocruz Representative, DND*i* Board of Directors 2004-2014; Coordinator, Fiocruz Health Technology Development Center (CDTS) |
| CIPLA: Aparna Chaphalkar & Sweety Jimmy (written interview) | Group leaders (Business Development, Malaria): starting 2010 |
| Eduardo Costa | Farmanguinhos Director 2006-2009; Fundacentro President. |
| Eloan Pinheiro | Farmanguinhos Director 2002; DND*i* Consultant. |
| Eric Stobbaerts | DND*i* AL Director 2009-2014; DND*i* AL Director. |
| Érico Daemon | Project coordinator, Farmanguinhos 2009-2014; Project manager, International Cooperation Coordination. |
| Graciela Diap (Entrevista por escrito) | Medical Director CAME MSF 2002-2005/ Medical Coordinator for Malaria, DND*i* 2005- 2014; Medical Coordinator for Malaria, DND*i*. |
| Hayne Felipe | Farmanguinhos Director 2009-2014; Farmanguinhos Director. |
| Isabela Ribeiro | Consultant, WHO and Farmanguinhos 2002-2003/ Project Regional Coordinator 2005-2008; Head of Chagas Clinical Program, DND*i*. |
| Izanelda Magalhães | PNCM Collaborator, Agricultural Secretariat, state of Acre; Health Surveillance Director, state of Acre. |
| Jean-Herve Bradol | MSF Representative 2002-2014; MSF Representative. |
| Jean-René Kiechel | Head, Malaria project, DND*i* 2002-2015 |

| NAME | JOB DURING THE PROJECT (2002-2014); CURRENT JOB |
|---|---|
| Jorge Bermudez | DND*i* Working Group 1998-2002/ Vice President, Health Innovation and Production, Fiocruz 2011-2014; Vice President, Health Innovation and Production, Fiocruz. |
| Jorge Mendonça | Project coordination, Farmanguinhos 2003-2009; Deputy Director, Institutional Management, Farmanguinhos. |
| José Ladislau | Coordinator, PNCM 2002-2010; Public Health Manager, Norte Energia. |
| Laura Krech | Consultant, PQM and Farmanguinhos 2010-2014; Consultant, PQM. |
| Luciana Gonçalves | Analytical development coordinator, Farmanguinhos 2002-2007 and DND*i* Consultant/ DND*i* Consultant 2007-2011; Consultant, DND*i* and Farmanguinhos |
| Michel Lotrowska | CAME MSF Representative 2002-2008/ DND*i* Representative 2003-2014; DND*i* President |
| Nora Giron | Regional Coordinator, Strategic Funding, PAHO 2007-2014; Regional Coordinator, Strategic Funding, PAHO. |
| Núbia Boechat | Director, Farmanguinhos 2003-2005; Head, Synthesis department, Farmanguinhos. |
| Pedro Tauil | Member, Technical Advisory Committee on Malaria; Committee member and Collaborating Professor, University of Brasília. |
| Shirley Trajano | Quality Management Coordinator 2009-2014; Quality Management Coordinator. |

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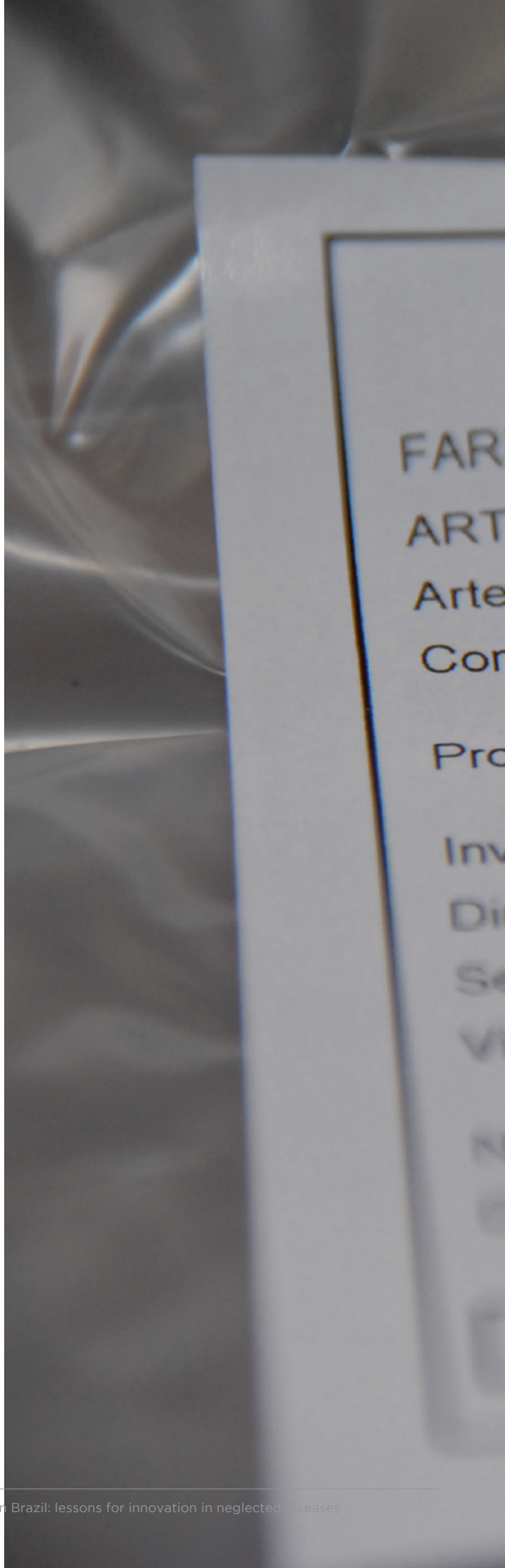

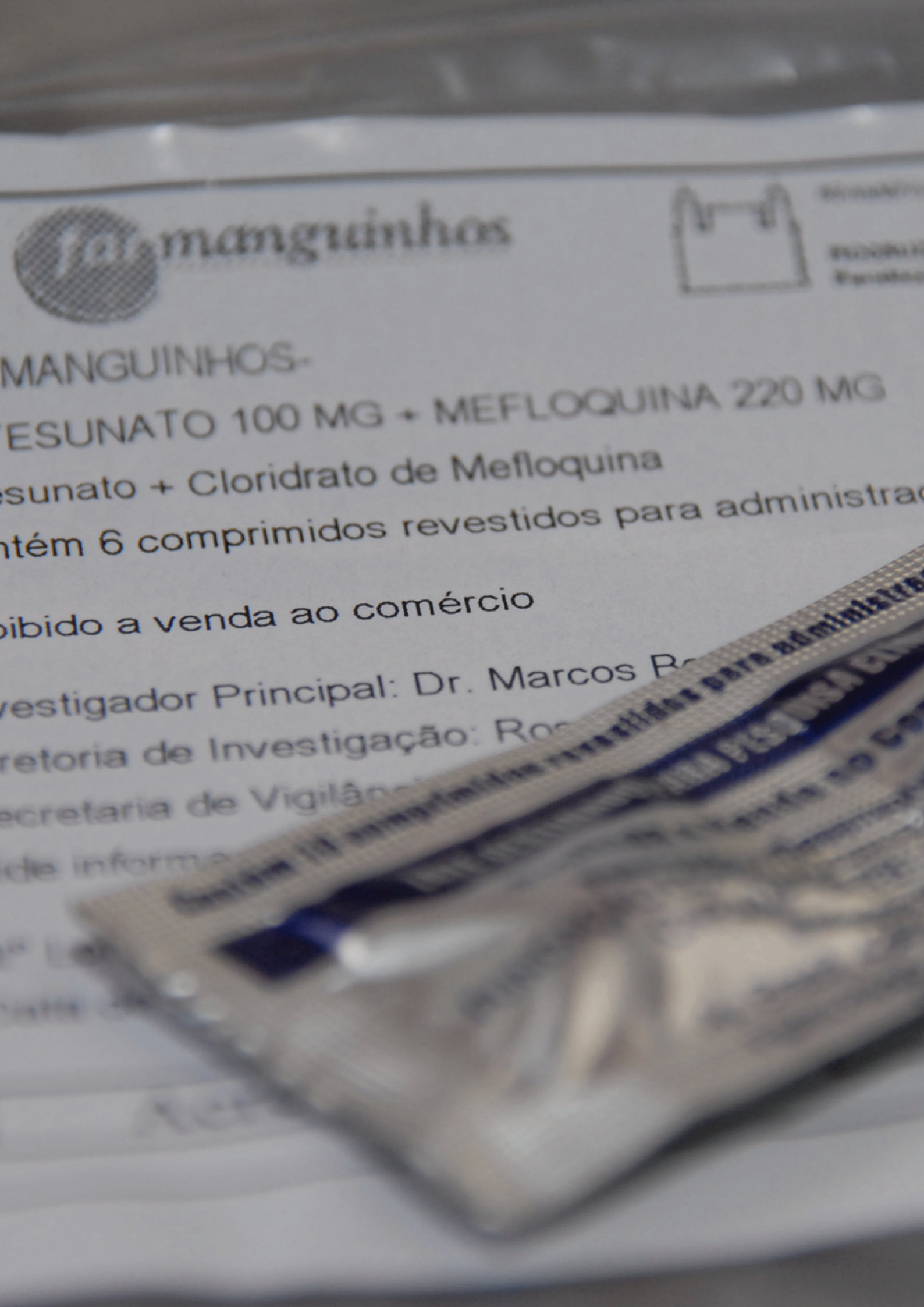
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DND*i* AMÉRICA LATINA

Drugs for Neglected Diseases *initiative*
*iniciativa* Medicamentos para Enfermedades Olvidadas
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