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Challenges in a product development partnership: a malaria treatment case study

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Abstract *This paper examines the development of a treatment – a fixed-dose combination of artesunate and mefloquine – in Brazil, from three points of view: in terms of access to medication; to record and report successes; and to look at the lessons learned. This product development took place in the ambit of a public-private partnership. Semi-structured interviews were held with key actors involved in the different phases of the development, and documents were analyzed. Two important points of reference orienting the design of the study and analysis were: a logical model for access to medication; and evaluation of programs. It is concluded that there were several successes over the course of the project, but insufficient attention was given in the project's architecture to planning of adoption of the product: irregularities in demand caused difficulties in planning and production, and adoption of the product was irregular in the Americas. It is concluded that the project can be considered to have been successful: the product was created, and the aims were met – strengthening of institutional and individual capacities and alliances, and advocacy. However, there were weaknesses in the process, which need to be mitigated in future projects of the same type.*
Key words *Non-profit drug production, Access to drugs, malaria, neglected diseases*

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Introduction

In 2001, the *Campaign for Access to Essential Medicines*, of *Médecins Sans Frontières* (MSF) and the Drugs for Neglected Diseases (DND) Working Group published a study with a mapping of the research and development efforts for the so-called neglected tropical diseases. The conclusion was clear: there was little or no R&D effort for these illnesses undertaken by the pharmaceutical companies[1]. It was evidenced that innovation in the pharmaceutical sector was oriented by market potential, leaving an important gap for the health needs of developing countries.

The lack of innovation for the neglected diseases was also recognized and prioritized by country-members of the World Health Organization (WHO). In 2003, a resolution was approved[2] in the World Health Assembly establishing a commission to seek balance between intellectual property rights, innovation and public health. The report of this Commission[3] also signaled that the intellectual property system established by the TRIPS accord of the World Trade Organization was not stimulating efforts for innovation in relation to the diseases that predominantly affected the developing countries (referred to as type III diseases).

In the last ten years one of the responses given to the R&D gaps for certain health needs of developing countries has been the establishment of Product Development Partnerships (PDPs)[4]. These PDPs mainly involved nonprofit institutions who manage a portfolio of projects in both the discovery and development phases for specific diseases. They bring together and coordinate efforts from different institutions, both public and private, for the implementation of these projects. The *Drugs for Neglected Diseases Initiative* (DNDi), created in 2003, is a PDP.

In relation to malaria, one of the neglected diseases[3], at the start of the 2000s there were several changes in the international context of the adoption of 'artemisinin-based combination therapy' (ACT) for its treatment[5,6]. Only the association of artemether+lumefantrine was available in the form of a fixed dose combination (FDC) (the brands Coartem® and Riamet® of Novartis Pharma AG)[6].

It is estimated that in 2000 there were 227 million cases of malaria in the world, with continuous transmission in 106 countries[7]. International and Brazilian efforts made efforts to reduce malaria incidence and mortality rates, with significant results, in which 64 countries came close to meeting the target (2000-2015) set in the Millennium Goals of reversing the incidence rate[8].

The change of orientation of malaria treatment for the ACTs was in the context of global recognition of the epidemic, and the establishment of major donors, who played an important part in the amplification of access to the treatment (the *Roll Back Malaria Partnership*[9], the *Global Fund to Combat HIV/Aids, Tuberculosis and Malaria*[10], and *Unitaid*[11]).

In 2002, MSF established the FACT (*Fixed-Dose Artesunate Combination Therapy*) consortium for development of combined therapies (FDC) for the treatment of malaria. In the 2001 WHO strategy[5] for retarding development of resistance to anti-malarial drugs, the fixed-dose combination of Artesunate (AS) + Mefloquine (MQ) was assessed as being the most appropriate for Latin America and Asia.

In Brazil, the partnership with the public pharmaceutical laboratory *Farmanguinhos*, of the Oswaldo Cruz Foundation (Fiocruz) was established under the aegis of the FACT project, the objective of which was the development of the ASMQ FDC[12].

Few studies were found in the literature that sought to go into any depth of detail on the case of the development of ASMQ-FDC[13,14]. This article aims to analyze the development process of the fixed dose combination of artesunate and mefloquine in Brazil in light of the dimensions of access to medicines, in order to register the successes and lessons learned.

Method

This is a case study of the development of ASMQ-FDC. The approach chosen aims for understanding of the phenomena involved[15], with a priority for explanation, rather than quantification[16].

The logical model of access to drugs proposed by Frost and Reich[17] and the evaluation of health programs[18] were central references in designing the study and the analysis.

Semi-structured interviews were held with key actors involved in the various phases of the development of ASMQ-FDC. Complementarily, documents provided by the interviewees were analyzed.

After the initial indication of interviewees by DNDi, the initial sample was expanded using the 'snowball' principle[19].

They are identified according to their institutional link (A = DNDi; B = Farmanguinhos;

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C = Fiocruz (other than Farmanguinhos); D = Internacional agencies (PAHO; OMS; Unitaid); E = Cipla; F = Brazilian Health Ministry/ Brazilian government; G = MSF) and their role in the ASMQ-FDC development project: 'Decision-maker' (DM): important in the decision on the agenda, but little control over decisions on the alternatives and the final result; 'Implementor – Operational' (IO): role in the implementation of the development process (up to the registry with health authorities); 'Implementor – Adoption' (IA): role in the implementation of the process of development (after registration with the health authorities), especially in subjects outside the DNDi-Farmanguinhos partnership). Although the absolute majority of the interviewees allowed their names to be cited, we opted to present the opinions according to these categories, since we believe that their role in the process is more important than their individual identification.

25 interviews were held over the period January-April 2015, conducted individually by three of the authors: most were in person; six were via Skype; and two of the reports were, at the interviewee's request, sent in writing.

The interviews were transcribed and submitted to subject content analysis. The analysis categories were the *dimensions* of the logical model of access to medication adopted (Chart 1) – in an effort to identify elements related to the obstacles

Chart 1. Dimensions and activities of access to drugs according to the logical model proposed by Frost and Reich.

Access activities	Description
Architecture: organizational structures and relationships established with the objective of coordination and management of the activities of availability, accessibility and adoption	
Availability: involves the logistics of production, purchase, transport, warehousing, distribution and delivery of a new health technology to ensure that it reaches the hands (or the mouth) of the final user.	
Production	Transformation of raw materials into finished products for use or sale.
Planning	Estimation of quantitative product to be acquired or used, and at what price.
Procurement	Process of obtaining of health technologies by private or public suppliers: includes all the decisions related to the specific quantities, the prices paid, and the quality of the health technologies received.
Distribution	Technology transfer process through public or private channels or a public-private mix.
Provision	Point on the supply chain in which the technology is physically transferred for its allocation to the final user through private or public channels.
Affordability: implies guaranteeing that the health technologies and the related services are not too expensive for the people who need them.	
Affordability by governments and NGOs	Accessibility of the technology for acquisition by the purchasing units of the national governments in the developing countries and by NGOs.
affordability for the final user	Accessibility of the technology for acquisition by the final users.
Adoption: involves acceptance, thus creating a demand for new health technology from global organizations, government actors, suppliers and distributors, prescribers and individual patients.	
Global adoption	Acceptance of the technology by the international organizations such as WHO, UNICEF, UNAIDS, UNFPA, and by technical experts.
National adoption	Acceptance of the technology by policy makers in the ministries of developing countries, involving political commitment, regulatory approval and adoption of treatment protocols.
Adoption by providers and prescribers	Acceptance of the technology by the provider, and proper prescription by health professionals.
Adoption by final user, and appropriate use	Acceptance of the technology by the patient or consumer, which includes its proper use.

Source: Frost and Reich[17].

and scopes in each one of them. The *phases* were: definition of the logical model; familiarization with the field material; indexing of the findings; mapping; and interpretation.

Having in mind that this investigation focused principally on the point of view of the supplier (the supply side) and that acquisition capacity is an aspect that must necessarily take into account the consumer (on the demand side), the consumer dimension was not a central part of the approach.

The documents included are indicated with the following codes:

- DOC1: 1. Model Contract (Confidential): Cost reimbursement for research and technological development projects, 2003.
- DOC2: Confidential. Amendment to Model Contract: Cost reimbursement for research and technological development projects, 2003.
- DOC3: Pan-American Health Organization, Brazil Office. The PAHO office of the WHO in Brazil, a member of the Malaria Technical Advisory Group, 2012.
- DOC4: International Federation for Tropical Medicine (IFTM). 18th International Congress for Tropical Medicine and Malaria and 18th Congress of the Brazilian Society for Tropical Medicine, 2012.

After pre-analysis of the material, on June 10, 2015 a workshop was held at Fiocruz for the purpose of both reporting the findings to the interested parties, and their validation. As well as the interviewees, this workshop included specialists in analysis of public policies and health evaluation, and decision makers of Fiocruz and DNDi.

The project was submitted to the Research Ethics Committee of ENSP/Fiocruz, and approved in December 2014.

Results

Architecture

Architecture is here taken to mean everything from the agreements for establishment of the DNDi-Farmanguinhos partnership through to the conduct of the strategies for access in the post-registration period (2008-2014). The principal phases are summarized in Figure 1.

The approximation between MSF and Farmanguinhos took place because of the local public production of anti-retrovirus (ARV) drugs that were not patented (A-DM-1; A-DM-2; B-DM-2). The insertion of Farmanguinhos in the discussion on drugs for neglected illnesses intensified under the scope of the *DND Working Group* (B-DM-2).

Having decided the priority of FDC for malaria, a diagnosis was made that there were few research groups in existence willing to invest in this development (A-IO-1).

The WHO *Special Program for Research and Training in Tropical Diseases* (TDR) carried out the technical coordination in the initial phase of the FACT project with MSF. Begun in 2002, the project involved various international partners [Université Victor Segalen (Bordeaux II); Wellcome Trust – Mahidol; University of Oxford; University of Sciece, Malaysia; Mahidol University of Thailand; World Health Organization; and Centre National de Recherche et de Formation sur le Paludisme] (DOC1). As from January 2005, MSF passed the coordination of the project to the recently-created "Drugs for Neglected Diseases Initiative") (DOC2).

Farmanguinhos became involved in the project contributing, among other aspects, to the technical team for development of the pharmaceutical formulation (B-DM-1). The DNDi-Farmanguinhos partnership was promising due to the high compliance of the project with the ideology of the institutions and partners involved (A-DM-2; A-IO-1). This was by way of being a contestation of the system of monopolies and patents, which is recognized as providing insufficient incentives to ensure development of drugs for neglected diseases (A-DM-2).

Fiocruz subsequently became one of the founding partners of the DNDi in 2003, with a seat on its board (A-DM-1; A-DM-2; C-DM-1; C-DM-1; B-DM-2; B-IO-1).

The components specified in the agreement financed by the European Union (UE), which provided for three years' duration from its start in July 2002, covered a range of factors from the decision on the new formulation and scale-up of production, development of the data on safety, efficacy, bioavailability, carrying out of non-clinical and clinical studies, assessment of stability, to the obtaining of the health registry of the new formulations (DOC1). No plan was identified in the agreement on how the access to these drugs would be made feasible after obtaining of the registrations from health authorities.

The project was of maximum priority in the DNDi (A-DM-1; A-DM-2; A-IO-1; A-IO-2; A-IO-3), especially at its beginning (A-DM-1; A-IO-2; A-IO-3). It operated as a catalyst in the creation of the DNDi. Initially it received a lot of

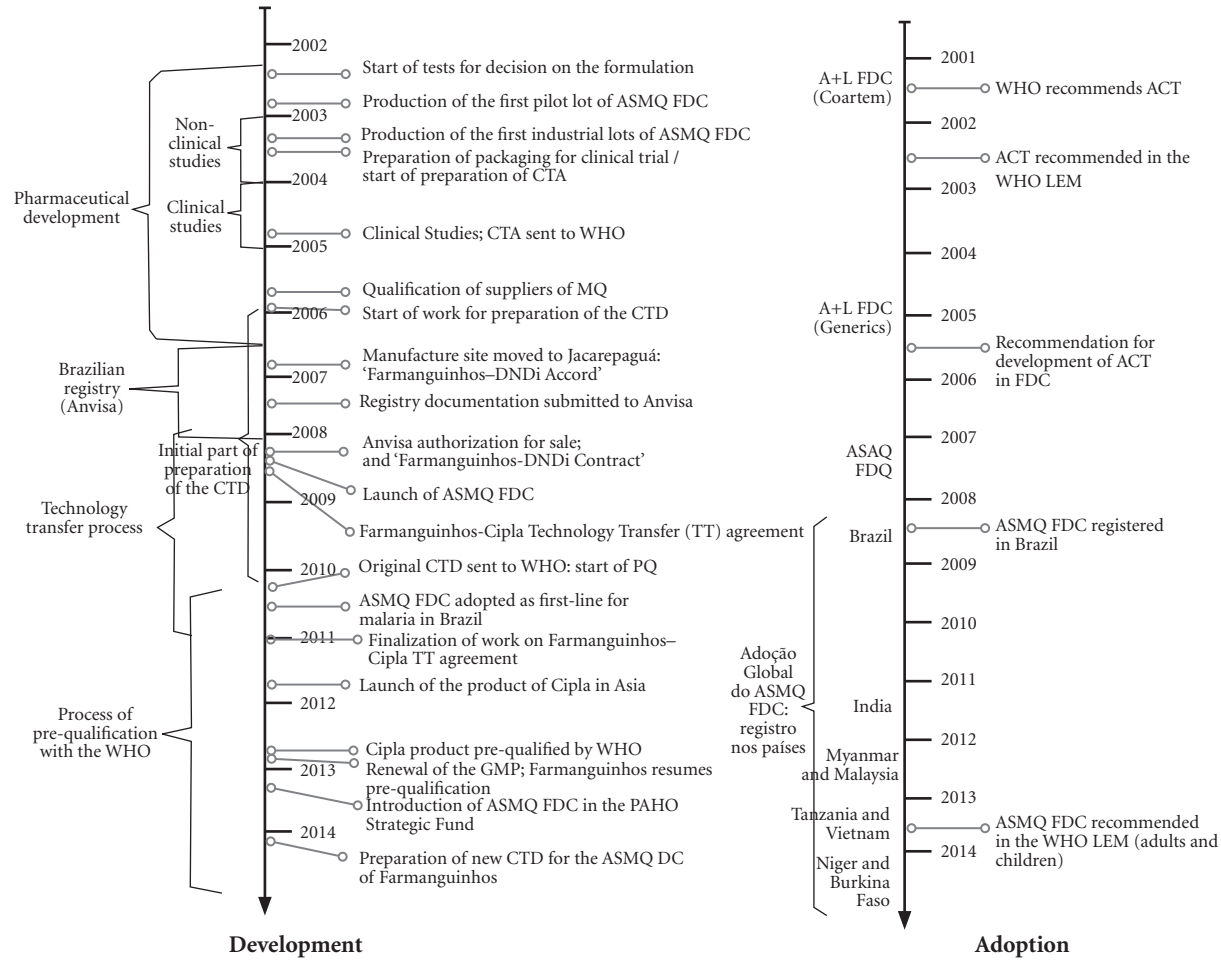

Figure 1. Stages of development – pre- and post- registration; and stages of adoption, of the Artesunate-Mefloquine fixed-dose combination (ASMQ-FDC), 2002–2014.

Key: BR= Brazil; ASMQ= Artesunate + mefloquine; FDC= Fixed Dose Combination; WHO = World Health Organization; GMP = Good Manufacturing Practices; PQ = Pre-qualification; CTD = Common Technical Dossier; PAHO = Pan-American Health Organization; Anvisa= Brazilian Health Supervision Authority.

attention, considerable funding and the cooperation of the directors of Farmanguinhos, which took every opportunity to facilitate the project happening (A-DM-1).

Variations in the project's degree of priority within Farmanguinhos were reported, over time, and with the different managements, often as a function of the other projects in progress (C-DM-1, B-DM-1, A-IO-1, B-DM-4; B-IO-1). One of the reasons for this was an organizational culture centered on meeting Brazilian needs (C-DM-1). There was no consensus about these variations, but there were perceptions that the project had been considered as high priority by a group of implementors over the whole of its duration (C-DM-2).

The majority of those interviewed recognized the efforts to promote clarity of objectives and roles within the project, but indicated problems. Among those mentioned included the interactions with the wide spectrum of international partners, involving different organizational cultures, internal changes in the team (especially in Farmanguinhos), incorporation of the new work

processes, and heterogeneity in understanding of the stages within the operational teams.

Events that were mentioned as moments of tension included: the way in which the patenting of the product would be treated, the excessive time between development and supply of the product (B-DM-2, B-IO-3, A-DM-2) and changes in the priority of the project inside Farmanguinhos.

The stages subsequent to obtaining of the health registration from Anvisa included: technology transfer (TT) to the Indian company Cipla (to supply the location area); incorporation of ASMQ FDC into the treatment protocol of the Brazilian Health Ministry in 2010; the start of the process of pre-qualification with the WHO; and inclusion of the product for purchase by the Strategic Fund of the PAHO (Figure 1).

In the Adoption phase, the following were mentioned as factors giving rise to tension: the limited experience of Farmanguinhos in aspects relating to exportation and international regulation; the renegotiation of the DNDi-Farmanguinhos relationship in 2009; the negotiation and implementation of the agreement for transfer of technology to Cipla (A-IO-2, A-IO-3, A-IO-4, B-DM-3, B-DM-4, B-IO-2,C-DM-1); and supply of Venezuela by Cipla in 2014 when this was originally to be a region to be supplied by Farmanguinhos.

The majority of the interviewees were in favor of the idea of a future partnership involving the same actors, provided care was taken in matters such as greater horizontalization of decisions, better prior negotiations, clearer agreements and better prospecting of the consumer market for the technology involved.

There was disagreement on what would constitute a mark of success for the project that evolved during its development – for example: achieving preparation of the production? adoption by the final user? exportation? good manufacturing practices? –When the project was agreed to have been completed, some fundamental actions for access by users were incomplete or had not even been provided for. (A-DM-1)

Availability

The questions that have implications for availability can be better understood in two distinct periods, the Pre- (launch of the innovation), and the Post- (factors determining the supply of the technology) – in relation to the moment of obtaining the health registration in Brazil.

The principal issue of the pre-registry period (2002–2008) was the delay in obtaining the registration itself.

The main factors reported in speech by the interviewees as explaining the delay in the registry were: the interruption in the supply of the active pharmaceutical ingredient (API) mefloquine; the long time taken for grant of the registration by Anvisa; the change in the manufacture location from Farmanguinhos; and logistical problems.

At the beginning of the project, it was decided that only one single supplier of mefloquine would be chosen, with an industrial production route that was very dependent on the characteristics of the API. At the time, simple production processes were sought that were susceptible to technology transfer to other developing countries (B-IO-2).

The supplier interrupted the production of mefloquine without any prior advice to Farmanguinhos or to the DNDi. This resulted in a need to re-execute many of the phases of the process of development with a new supplier of API, in an effort exercised in the technical, regulatory and logistical spheres (B-IO-1, B-IO-2, B-IO-3, A-IO-2, B-IO-4, A-IO-3, A-IO-4).

The period of submission of the registry at Anvisa coincided with internal restructurings and reorganization of staff (B-IO-2; B-IO-3). Thus, in spite of the attempts at constant contact with the regulatory body over the period of application for registration, new demands were made and the process took one year and 8 months, instead of the 3 to 6 months expected.

The manufacturing location of Farmanguinhos moved to a new plant. This called for adaptations for the manufacturing, and at least six additional months of work for the transfer and qualification of the facilities (A-IO-4). Challenges related to infrastructure, to the supply chain and to outsourcing of the work in Farmanguinhos were also referred to as bottlenecks in the production process (B-DM-3, B-IO-2, C-DM-2).

The period considered as post-registration, 2008-2014, was also subject to important challenges that involved efforts of confrontation.

The first of these refers to the availability and the price of mefloquine, and also the dependence on Brazilian domestic producers (B-IO-3, A-DM-2, B-IO-4, B-DM-3, B-DM-2). The supply of this API by Brazilian pharmaco-chemical companies was one of the options referred to in the interviews for sustainability of production.

A second point that was raised was that the cost of new treatment would be a barrier to ac-

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cess, but this hypothesis was contested during the workshop by representatives of the Brazilian Health Ministry.

The irregular demand for the drug was also highlighted as a factor that generated difficulties in programming of the production by Farmanguinhos. The lack of clarity of the Health Ministry on the demand and the pattern of occurrence of illnesses in surges were indicated as reasons for the difficulty of prior planning for the production. There were situations of immobilized inventory at Farmanguinhos, in the absence of demand by the Health Ministry. One of the exit routes was the donation to Venezuela in 2013.

The other challenge mentioned was the series of difficulties found in handling the process of exportation, since the principal activity of Farmanguinhos is to supply the Brazilian Single Health System (SUS). To this was added the fact that there is a wide diversity of mechanisms of importation, and absence of registration of the product with health authorities in some countries. The solutions sought included: the possibility of purchase by the Strategic Fund of the PAHO; and implementation of the process of pre-qualification of the product by the OMS. Some cases of donations were also seen as alternatives for meeting the purchase orders received, so as to meet the international demand appropriately.

In the period 2008-2015, a total of 1,373,671 treatments were supplied worldwide (Chart 2) by Farmanguinhos and Cipla, with Farmanguinhos being responsible for 72% of this total.

Another argument for the low availability of ASMQ-FDC refers to changes in the panorama of malaria in Brazil, and worldwide, for example as a result of the significant reduction of cases of malaria through *P. falciparum*. Another explanatory factor is the availability of other FDCs as alternatives for malaria therapy.

Chart 2. ASMQ-FDC treatments acquired (packets) by country and supplier, 2008-2015.

Country	Treatments acquired 2008-12	Treatments acquired 2013	Treatments acquired 2014	Treatments acquired 2015
Brazil	260,000 including clinical trials and donations (Farmanguinhos)			
	533,340 acquired by Brazilian Health Ministry* (Farmanguinhos)		4,500 acquired by Brazilian Health Ministry* (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 and Myanmar	169 patients in 2008-2009 for clinical trial (Farmanguinhos)			2,500 for clinical trials (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% of the quantities supplied by Farmanguinhos, 28% by Cipla)**			

* Data collected under Brazilian Freedom of Information Act.

Adoption

As from 2005, the WHO recommended the adoption and development of FDC for the treatment of uncomplicated malaria by *P. falciparum*[10].

The second edition of the Malaria Treatment Guidelines[20], published in 2010, maintained the recommendation for the use of ACT for treatment of uncomplicated falciparum malaria, orienting the use of one of the following options: artemether+lumefantrine (AL; Coartemâ), artesunate+amodiaquine, artesunate+mefloquine (ASMQ), artesunate+sulfadoxin pirimetamin and dihydroartemisinin+piperaquine. The last of these was incorporated in the edition referred to. The orientation was that the therapeutic option should consider the profile of resistance to mefloquine existing in and arising from the various contexts.

Another indicator of the worldwide adoption is the *WHO Model List of Essential Medicines* which we abbreviate here to *LEM*. ASMQ-FDC was included in the 18th edition of the LEM, as from 2013, resulting from a decision made by the DNDi in 2012[21]. AL-FDC was already part of previous LEMs.

A final direction of effort for global and Brazilian adoption of the drug refers to the various clinical studies carried out up to the present day. Between 1992 and 2011, 91 open and randomized clinical studies were carried out in 22 countries involving the association of AS+MQ, with administration of the drugs in isolation or in and FDC[21]. The FDC of ASMQ was present in studies carried out in Thailand, Myanmar and Brazil. In the region of Latin America, 10 studies were carried out in five countries (Peru, Bolivia, Ecuador, Colombia and Brazil).

Although the health authority registration, and inclusion of the Brazilian treatment protocols are indicators of adoption at the Brazilian level, a choice was made to consider them in terms of 'global adoption' to show the worldwide panorama of the use of ASMQ in FDC form. Until 2012, AS+MQ was recommended in Brazilian protocols for uncomplicated *P. falciparum* malaria in the following countries[21]: Cambodia, Malaysia, Thailand and Myanmar, as first-line treatment options; in Vietnam as a salvage protocol; in Peru, Venezuela, Bolivia as first-line treatment; in Brazil for the non-Amazon region, and in Nicaragua as a second-line option.

At the time of conclusion of the survey, ASMQ FDC was registered in the following countries: Brazil (2008), India (2011), Myanmar (2012), Malaysia (2012), Vietnam (2013), Tanzania (2013), Niger (2014) and Burkina Faso (2014).

As recorded above, several interviewees mentioned Farmanguinhos's lack of experience in organizing health registrations and in exportation as a weak factor, compromising global adoption. However, the transfer of technology to a partner with experience in exportation helped the product to be pre-qualified in the WHO in 2012, and registered in some countries of Asia and Africa.

In spite of this identified weakness of Farmanguinhos, it was also recognized that the FACT Project in its original conception did not provide for a wide-ranging strategy for registration in the various countries, nor partnerships that would contribute to its use (A-DM-1, DOC1).

As suggestions for the adoption of ASMQ-FDC, some interviewees indicated the possibility of recommendation in the African context for uncomplicated *P. falciparum* malaria, and the potential indication of malaria caused by *P. vivax*.

The first initiative for sustaining the adoption at the Brazilian level was an intervention study (Phase IV) in Acre for evaluation of the effectiveness of ASMQ FDC, which had the benefit of representatives of the Brazilian National Malaria Control Program (PNCM), DNDi, Farmanguinhos, PAHO, universities and the Health Department of the State of Acre. This study took place from July 2004 to December 2008, and the intervention involving the ASMQ-FDC covered the period from July 2006 to December 2008 in three municipalities of Acre. Approximately 24,000 patients received ASMQ FDC and the results indicated a reduction of the rate of incidence of cases of malaria from *P. falciparum* in all age groups, with no serious adverse event[22]. The study in Acre was indicated as a positive result of implementation of the partnership for development of ASMQ FDC (F-IA-1; F-IA2; F-IA-3; F-DM-2; B-IO-1; A-IO-2; D-IA-2).

In 2010, the Brazilian national treatment protocol for malaria was updated[23], incorporating also ASMQ-FDC, together with primaquine, as one more first-choice option for treatment of malaria from *P. falciparum*, along with artemether+lumefantrine and primaquine.

In the same year, ASMQ-FDC was incorporated in the 7th Edition[24], and AL-FDC in the 9th Edition, 2014[25], of the Brazilian List of Essential Medicines (*Relação Nacional de Medicamentos Essenciais*, or RENAME). Thus, while AL-FDC was included in the PNCM in 2006, and in the

RENAME only in 2014, ASMQ-FDC was included in both in the same year, 2010.

In 2012, the technical scientific advisory committee to the Brazilian National Malaria Control Program (PNCM) recommended the substitution of ASMQ-FDC by AL-FDC as first option in the region of Acre[26]. AL-FDC then became the first option for the Amazon region, which has 99.5% of the cases, while ASMQ-FDC was recommended for areas outside the Amazon region (F-IA-1; F-IA-2, F-IA3, A-OI2).

It was indicated that the justification for the recommendation by the Technical Committee was based on the evidences of resistance to mefloquine (B-DM-3; B-IO-3; A-IO-2; A-DM-1; B-IO-1; F-IA-3; F-IA-1; F-IA-2). Some also suggested that the option for the other ACT-FDC might have been influenced by the price (A-DM-1; B-IO-3), but during the in-person workshop this argument was contested, which can be verified in the Ministry of Health purchases (Tables 1 and 2).

The decision for substitution of the ACT option as first-line was considered to be of the 'top-down', type, coming from the Health Ministry to the states, without involving their participation in the discussion, and causing significant changes in the practices now implemented in the health services (F-IA-2).

One of the possible effects of the decision for substitution of ACT in the Amazon region was the absence of demand for ASMQ-FDC to Farmanguinhos in 2013 by the Health Ministry, an insignificant quantity having been requested in 2014 (1,000 treatments for each age group) (B-DM-3; B-IO-2) – this compromised strategies of programming for production and delivery of the product.

One of the possibilities mentioned for the problems of Brazilian adoption was that there was insufficient dialogue between the representatives of the ASMQ-FDC development project (DNDi/Farmanguinhos) and the various actors involved in confronting malaria, over the time of the project (F-IA-1; F-IA-3; B-IO-3; A-IO-2; A-DM-1; A-DM-2). There were some disagreements on this aspect, which was discussed in the workshop, since the study of Acre was the occasion of strong and important interaction between the actors. At the same time, the partners of the project would not have participated in processes in incorporation of technology in the Health Ministry. As part of the effort of approximation with the Technical Advisory Committee of the PNCM, DNDi organized a meeting during the International Congress for Tropical Medicine and Malaria, in September 2012, in Rio de Janeiro, with the intention of raising counter-argument to the justification of resistance to mefloquine (A-DM-1; B-IO-2).

Some opportunities for a potential reconsideration of the ASMQ-FDC that were indicated were: possible indication for cases of malaria caused by *P. vivax* (A-DM-1; B-IO-3; B-IO-1; F-IA-1); revision of the protocol of malaria therapy in the country (F-IA-1); possibility of ASMQ being a 'backup' for cases of resistance to the first option of ACT (AL-FDC) (F-DM-2); and advantages of adopting the treatment due to the low number of daily applications.

Discussion

The study analyzed a case that represented the first product arising from a partnership for development of products for neglected diseases. It is considered that the principal contribution of this analysis is in its seeking a perspective focused on the final user, also considering the other chains that intervene in relation to the viability of the product reaching these users.

As to the barriers confronted, important successes were mentioned in development of the product – which was completed, registered in Brazil and other countries, and internationally certified, with more than one producer. However, the product, especially the one manufactured by Farmanguinhos, is little used today. Various issues contributed to this. In the external context, one can mention the fact that it is a product whose indication competes with other ACT-FDCs (ASAQ and A+L) and there has been a pronounced fall in cases of *P. falciparum* in the world[8]. In the domestic Brazilian context, there have been challenges of development that resulted in delay in the registration, as well as the difficulties of Farmanguinhos in exportation to its target markets.

The architecture of the FACT Project was formed within a group of efforts that aimed for development and production of drugs for neglected diseases. There are important characteristics that form a market of high-prevalence diseases, but one which is predominant in poor populations, who have low purchasing power in terms of being able to interest the large innovator industries.

One of the targets of the FACT project was to achieve the development of products for ne-

Table 1. Total number of packets, price per treatment, total purchase value and supplier: Brazilian Health Ministry, Brazil, 2006-2014.

ARTEMETHER + LUMEFANTRINE (blister)	2006 NOVARTIS			2007 NOVARTIS		
	Total packets	Price per treatment (R$)	Total amount (R$)	Total packets	Price per treatment (R$)	Total amount (R$)
20MG+120MG W/06	14880	2.03	30272.32	10080	1.57	15840.96
20MG+120MG W/12	14880	3.74	55597.88	14400	3.14	45259.91
20MG+120MG W/18	124320	7.09	880896.22	132240	6.15	813923.76
20MG+120MG W/24	115200	7.19	828677.68	121200	6.29	761875.03
Total	**269280**	—	**1795444.10**	**277920**	—	**1636899.66**

ARTEMETHER + LUMEFANTRINE (blister)	2008 NOVARTIS			2009 CIPLA		
	Total packets	Price per treatment (R$)	Total amount (R$)	Total packets	Price per treatment (R$)	Total amount (R$)
20MG+120MG W/06	18720	1.36	25458.82	12000	1.26	15093.60
20MG+120MG W/12	34560	2.72	94002.28	18000	2.49	44733.01
20MG+120MG W/18	159450	5.15	820398.16	87990	4.35	382420.54
20MG+120MG W/24	124890	5.44	679394.97	69990	4.54	317620.23
Total	**337620**	—	**1619254.22**	**187980**	—	**759867.38**

ARTEMETHER + LUMEFANTRINE (blister)	2010 CIPLA			2012 OPAS		
	Total packets	Price per treatment (R$)	Total amount (R$)	Total packets	Price per treatmento (R$)	Total amount (R$)
20MG+120MG W/06	12300	1.48	18148.61	25200	1.00	25255.10
20MG+120MG W/12	20160	2.35	47319.57	32400	1.52	49252.08
20MG+120MG W/18	109860	3.87	424674.40	144810	2.87	415342.19
20MG+120MG W/24	89640	4.01	359588.12	112650	2.97	334626.17
Total	**231960**	—	**849730.71**	**315060**	—	**824475.54**

ARTEMETHER + LUMEFANTRINE (blister)	2013 OPAS			2014 OPAS		
	Total packets	Price per treatment (R$)	Total amount (R$)	Total packets	Price per treatment (R$)	Total amount (R$)
20MG+120MG W/06	16140	1.09	17629.74	30	1.03	30.80
20MG+120MG W/12	20340	1.67	34042.44	30	1.57	47.19
20MG+120MG W/18	103920	2.83	293709.79	120	2.64	316.36
20MG+120MG W/24	83460	2.90	242390.03	90	2.73	245.64
Total	**223860**	—	**587772.00**	**270**	—	**639.99**

Source: Calculated based on data supplied by Brazilian Health Ministry; prices updated by the IPCA inflation index of 2014.

glected diseases based on a different approach, ensuring important principles such as involvement of endemic countries in the development and sustainable financing of all the stages, and assured supply, at accessible prices[14,27]. Another central principle is the multiplicity of sources of production. These principles were important points of convergence with the partner Fiocruz, which was an active participant in various arenas in common with MSF in the arguments in favor

Table 2. Artesunate + mefloquine: Total number of packets, price per treatment, total purchase value and supplier: Brazilian Health Ministry, Brazil, 2009-2014.

ARTESUNATE + MEFLOQUINE (blister)	2009		
	FIOCRUZ		
	Total packets	Price per treatment (R$)	Total amount (R$)
100+220MG C/03	31,590	0.79	25,046,21
100+220MG C/06	126,420	0.79	100,232,37
25+55MG C/03	18,000	0.20	3,526,06
25+55MG C/06	36,000	0.20	7,052,12
Total	**212,010**	—	**135,856,76**
ARTESUNATE + MEFLOQUINE (blister)	**2010**		
	FIOCRUZ		
	Total packets	Price per treatment (R$)	Total amount (R$)
100+220MG C/03	4,830	0.75	3,615,78
100+220MG C/06	34,800	0.75	26,051,61
25+55MG C/03	30,000	0.18	5,548,83
25+55MG C/06	72,000	0.18	13,317,19
Total	**141,630**	—	**48,533,42**
ARTESUNATE + MEFLOQUINE (blister)	**2011**		
	FIOCRUZ		
	Total packets	Price per treatment (R$)	Total amount (R$)
100+220MG C/03	5,030	2.11	10,607,06
100+220MG C/06	31,590	4.22	133,231,40
25+55MG C/03	23,020	0.52	11,993,82
25+55MG C/06	23,370	1.04	24,352,33
Total	**83,010**	—	**180,184,61**
ARTESUNATE + MEFLOQUINE (blister)	**2012**		
	FIOCRUZ		
	Total packets	Price per treatment (R$)	Total amount (R$)
100+220MG C/03	20,560	1.99	40,963,80
100+220MG C/06	36,180	3.98	144,170,24
25+55MG C/03	20,230	0.49	9,958,59
25+55MG C/06	19,720	0.98	19,415,08
Total	**96,690**	—	**214,507,71**
ARTESUNATE + MEFLOQUINE (blister)	**2014**		
	FIOCRUZ		
	Total packets	Price per treatment (R$)	Total amount (R$)
100+220MG C/03	1,000	1.77	1,767,90
100+220MG C/06	1,500	3.54	5,303,70
25+55MG C/03	1,000	0.44	435,00
25+55MG C/06	1,000	0.87	873,60
Total	**4,500**	—	**8,380,20**

Source: Calculated based on data supplied by Brazilian Health Ministry; prices updated by the IPCA inflation index of 2014.

of access to medication[28]. This harmony of principles was also expressed in the fact of Fiocruz being a founder member of Drugs for Neglected Diseases Initiative (DNDi), an event which was in turn set off by the project for development of ASMQ-FDC within FACT.

FACT sought to foresee all these situations. Malaria is an illness with important epidemiology in Brazil, especially in the Amazon region. In 2002, at the time when the FACT was beginning, Brazil had 40% of the cases of malaria in the Americas[29]. Although there is evidence of prog-

ress in the reduction of cases and mortality, due to the implementation of the Plan for Intensification of Actions for Malaria Control (PIACM) in the Amazon Region in 2000, these numbers still fell short of the stipulated targets[30]. In the region of the Americas, *P. falciparum* was responsible for 25% of the cases[29].

The choice of Brazil for the partnership with MSF took place as a result of the convergence of principles between the actors and institutions involved, and due to the existence of an institution with some experience in development of products.

The project of ASMQ did not involve an application for patent protection. Although this aspect was agreed from the start of the project, there was mention of differing perspectives as to this over the course of the project. However, in relation to the importance of the innovative scope produced in the context of a PDP, it is not clear whether the product would obtain patent protection, due to its being an association of two existing compounds[31].

Additionally, the transfer from the public partner to the private partner, an entity in India, was arranged. This was an important aspect, the final purpose of which was to provide supply of the product in the event of problems with one of the producers, as well as potentially ensuring some price competition.

Overall, the interviewees agreed that the appropriate choice had been made – regarding the disease and the product , for a first research and development initiative on this model, which was thus referred to as 'low hanging fruit' because it involved a combination of existing drugs, which had already been applied in association for malaria, although in separate preparations. However, this was not enough to eliminate a group of problems and anxieties that were confronted over the length of the process – which was successful at the end.

Another challenge for the process was handling a multi-site project, with partners in five continents, which combine different organizational cultures, which was a recognized aspect of influence for the innovation – this was able to behave both as a barrier and as a strengh[32]. The capacity to handle the project in this environment was certainly one of the major learning processes for the institutions involved, with positive potential impact on subsequent projects, since this working model is increasingly a standard in the modern world. The DNDi model of innovation considers, among other aspects, the virtual aspect of development of product, which is cuts across all the initiatives taken by the organization[14].

There were two key moments in the approach to availability. In the pre-registry period, the delay in obtaining the registry was reported as arising from problems of various types: some inherent to the institution, and some with contracts for outsourced labor or the change in location of the production plant of Farmanguinhos. As to the external environment, examples of issues include the interruption of supply of mefloquine, and the changes in the procedures of Anvisa at the time of the application for registry. It can be said that both aspects are hard to alter in the short term, both because they are part of the international rules, and because they are inherent to the external environment, in which the actors of the project are difficult to govern.

The difficulties in dealing with the mechanisms of exportation can be attributed both to the limited experience of Farmanguinhos in dealing with the necessary procedures, and also to the legal structure to which it is subject as a Brazilian public institution. The experience of ASMQ can be seen as a factor to impel Farmanguinhos to deal with the existing distribution channels. The absence of health registry in other countries of the region of the Americas, the target market of Farmanguinhos, was overcome with the inclusion in the Strategic Fund of the PAHO and in the WHO pre-qualification process. The latter was at a very advanced stage at the moment of completion of this paper, with the chance of imminently becoming the first Latin American product to obtain this certification[33].

The adoption at global level the result of the discussion that preceded the decision on the development of the product which arose from its recognized importance in the approach to *falciparum* malaria. Adoption by countries – including its incorporation into treatment guidelines, into the lists of essential medicines, and the use recommendation type – was very variable, indicating the need to take this aspect into account in the architecture of future projects.

In Brazil, the difference between the products specified in the *Rename* and those adopted by the *PNCM* indicates an inconsistency of the orientations of the Health Ministry itself. The interpretation of this is that ASMQ-FDC has been incorporated in the Brazilian therapy guidelines in 2010 as a consequence of these initiatives (the study in Acre, and the obtaining of the registry). There are various perceptions relating to the recommendation of AL-FDC to the detriment of ASMQ-FDC

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made by the Brazilian Technical Committee. Although it has the character of a recommendation and not a decision, one of the views is that the PNCM adopted all the recommendations made by the Committee, but the Committee also had a role in the orientation of the incorporation of technologies. This argument is understandable, in that there was a representation of the Health Ministry itself inside the Committee[34].

The autonomy of decision of the PNCM is understandable and praiseworthy. The issue is the low transparency of this decision process, since the dossiers of review of evidence or the records of the meetings in which the subject was discussed, if they exist, were not easy to access.

The withdrawal of the ASMQ-FDC from the first-line recommendations for treatment of malaria by *P. falciparum* in the Amazon region, at a strategic moment of implementation of the access initiatives, reflects the importance of coordination of the various government entities involved in the process.

As for the evaluation model used, it is considered that the principles of participation were complied with. The demand for the study came from one of the partners, the DNDi. The project consisted of a collective construction, and one which sought a design that was appropriate to its objective. The data was shared in a workshop that was highly participative, which promoted interaction of relevant actors in the various dimensions of access to the drug in question. The interviewees had first-hand access to the report produced on the study, which summarizes the lessons learned in each dimension studied of the access to the drug and also lists recommendations formulated based on the workshop and by the study team.

As for the limitations indicated[35] for the chosen drug access model[17], the option was taken to adopt it because it had already been used, with a similar method and in an equivalent situation, in initiatives to promote access that involved factors ranging from P&D of specific technology to adoption by the users. Further, it was considered important to incorporate production as an activity of availability.

The case study involved a series of partners of various nationalities and contexts over the course of its process of development. Also, the interviewees had different degrees of prior interaction with the interviewers. Thus, there is the heterogeneous possibility that some actors felt more comfortable than others in indicating negative aspects or obstacles that were identified over the course of the process.

The evaluation involved actors who were both internal and external to the principal theme, with differing degrees of interaction with each other, and with various interviewees over the course of their professional histories, which could have influenced, in an unpredictable manner, the answers given at the moment of the interview.

Final considerations

The launch of ASMQ-FDC at a moment later than previously planned, and the difficulties experienced by Farmanguinhos in the process of development of the product, are aspects recognized in this study, and they carry lessons for the future. However, these aspects alone do not explain the low demand for the drug after its launch in 2008. The low demand for ASMQ-FDC is part of a wider context involving various aspects which are prior to 2008, which suggests that the challenges encountered for expansion of the access of this drug would perhaps have been present even if the product had been launched within the initially planned deadline.

The achievements of the project are undeniable: the product has been obtained, produced and established, and its pre-qualification by the WHO is at an advanced stage. Other important achievements are the organizational learning that it gave rise to, the strengthening of institutional alliances, and the incorporation of advocacy for the neglected diseases by the actors involved. However, aspects such as better preparation of the institutional environments, monitoring of the epidemiological indicators of the target diseases for better prospecting of demand, and monitoring of the external factors, so as to anticipate, as far as possible, potential adverse effects, should be considered in the architecture of future projects of this type. It is very clear that the whole progress of P&D, up to adoption by the final user, which is a fundamental factor for consummation of access, requires planning, monitoring and management that ensure the systematic development of the phases, and enable the challenges imposed by the external environment to be minimized.

Collaborations

VL Luiza, GC Chaves, E Stobbaerts, LPB Gonçalves and TMT Barboza contributed equally to the conception and analysis of data. TMT Barboza, GC Chaves and VL Luiza carried out the collection and systematization of data. All authors approved the final version of the text.

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