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Could Innovative Drugs be Developed and Distributed through a Commons Based Approach?

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Projet de Recherche EnCommuns

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*Could Innovative Drugs be Developed and
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Lessons from the Case Study of an FDC Antimalarial

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Could Innovative Drugs be Developed and Distributed through a Commons Based Approach?

Lessons from the Case Study of an FDC Antimalarial (Synriam™)

Introduction

The commons can be regarded as an institutional system where a resource is managed and shared by a group of individuals through effective governance arrangements. The approach relies on social organization consisting of formal and informal rules, agreements, appropriate property rights and management structures that do not rely on the standard price-driven market mechanism or hierarchical organization by the state. It provides a platform for communities to achieve their shared objective through self-governance and regulation over a good or system of resources while allowing its sustainable management. In fact, collective action for devising rules facilitating the provision, access, and maintenance of resources is an intrinsic characteristic of the commons (Ostrom, 2010, Coriat, 2015).

In essence, there is no limit on the type of resources which can be subjected to a commons-based approach. The resource can be natural or an artifact, tangible or intangible, geo-localized or global and exploited by small communities or large. The early scientific scholarship on commons grew out of research on natural resources such as forests, fisheries and irrigation systems (Ostrom, 1990). Evidently, these archetypal common-pool resources (CPR) are tangible and limited in availability nevertheless, renewable. They are characterized by high subtractability in use and high difficulty in excluding potential beneficiaries (Ostrom, 2010).

Social scientists have extended and applied the concept towards the understanding of “knowledge commons” that concerns information and knowledge and also the products created from their application (Coriat, 2015b; Hess & Ostrom, 2007). These resources are typically non-rivalrous and non-excludable. Interestingly, unlike natural-resource commons, knowledge or informational commons are not preexisting but rather the outcome of the conscious collective action. Even more so, they highlight social resistance against the “enclosure” through the commodification of what was previously “open” and “accessible” (Boyle, 2003). The most notable example being that of the “free/libre and open-source software (F/LOSS)”. The movement was born out of frustration of the programmer community due to the private appropriation of “source codes”, the building blocks for writing and modifying programs, through intellectual property rights (IPR) (Boyle, 2003; Coriat, 2012; Hippel & Krogh, 2003).

The commons discourse has thus enabled the society to employ alternative but efficient economic models to show their dissatisfaction with the pure market-based mechanisms. We ask if the commons-based economic models can work for the development of pharmaceutical products to ensure affordable access to the most fragile populations.

Historically, diseases that only affect people living in developing countries where social securities and insurance usually do not exist, and poverty prevents people from paying a high price for medicines have not been lucrative for the pharmaceutical industry (Yamey & Torreele, 2002). These diseases include the big three – HIV/AIDS¹, tuberculosis (TB), and malaria and various tropical diseases such as leishmaniasis, human African trypanosomiasis (sleeping sickness), filaria, Buruli ulcer, and trachoma among many others (Bhutta, Sommerfeld, Lassi, Salam, & Das, 2014; Harper, 2007; Hotez, Fenwick, Savioli, & Molyneux, 2009)². These infectious diseases have a disproportionately high burden in the South. WHO reports that together they cause 32% of the burden of ill health in Africa and severely impact health outcomes in every region of the world (WHO, 2016). Most of these diseases require new pharmaceutical technologies because either there is no existing product or improved products adapted to patients are needed (Hotez et al., 2016; Policy Cures Research, 2016). However, the insufficient commercial market has led to underinvestment of private R&D addressing these diseases.

To address this problem of market failure a new breed of private, not-for-profit organizations have emerged over the last two decades. These so-called Product Development Partnerships (PDPs) are alternative in the way how financing is secured, how R&D is organized, how results are shared, and how the final product is delivered (Muñoz, Visentin, Foray, & Gaulé, 2014). They have brought a new culture of collaborative R&D by bringing together various actors of the innovation system including funding partners, academia, public laboratories, contract research organizations, and pharmaceutical companies towards the common goal of developing medical technologies needed by patients in developing countries (Chataway, Brusoni, Cacciatori, Hanlin, & Orsenigo, 2007). Within a short span, these organizations have achieved significant success and have played an essential role in shaping the global public health agenda. In fact, PDPs were the primary sponsor of more than half of the 20 new medical products

¹ HIV is neither a tropical disease nor is neglected by pharmaceutical companies. However, it is often included among neglected tropical diseases because of its extremely high burden in the global South and lack of investment in research for developing formulations dedicated to children (Policy Cures Research, 2016).

² Together they are also called Neglected Tropical Diseases (NTDs)

targeting neglected diseases approved during 2009-2013 (Cohen, Sturgeon, & Cohen, 2014). As of 2015, there were more than 140 neglected disease drugs, diagnostics, and vaccine development projects in the combined PDP portfolio (Kiddle-Monroe, Greenberg, & Basey, 2016).

The novel approach exemplified by the PDP-model has drawn the interest of several researchers who have worked towards explaining the organization and functioning of PDPs and their role in transforming neglected diseases landscape (Branciard, 2012; Chataway et al., 2007; Chataway, Hanlin, Mugwagwa, & Muraguri, 2010; Grace, 2010; Moran, 2005; Munos, 2006; Muñoz et al., 2014). This study extends the literature by looking at PDPs through the lenses of the commons. More specifically, we intend to examine if PDP-model of drug development can be regarded as a commons-based approach by analyzing the features of the Medicines for Malaria Venture (MMV) – a PDP dedicated to developing antimalarial medicines – and the development of Synriam™ (Synriam).

Synriam is a new fixed-dose combination (FDC) antimalarial that combines two parasitocidal drugs with independent modes of action – faster-acting arterolane maleate (arterolane) and longer acting piperazine phosphate (piperazine). It offers a “three days-three tablets” treatment regimen where each tablet consists of 150 mg of arterolane and 750 mg of piperazine.

Synriam is unique in many respects. One of its components, arterolane, is the outcome of PDP-funded research by Medicines for Malaria Venture (MMV). For the further development of the molecule, MMV partnered with an Indian firm Ranbaxy³. However, unsatisfied with the early clinical trial outcomes of arterolane, MMV left the partnership, but it gave Ranbaxy an exclusive license over intellectual property rights (IPR) to continue product development. After the withdrawal of MMV from the project, Ranbaxy partnered with the Government of India to complete the clinical trials of the combination of arterolane and piperazine, trademarked under the brand name of Synriam. The drug was first approved by the Drug Controller General of India (DCGI) in 2011 for treating acute, uncomplicated *P. falciparum* malaria in patients from 12 to 65 years of age.

The data for the study was collected through five semi-structured interviews conducted between September 2016 and August 2017. Three participants were employees of the erstwhile

³ Ranbaxy was acquired by Sun Pharma in a landmark deal on 25th March 2015.

Ranbaxy and closely worked with the clinical development, regulatory approvals and marketing of Synriam. Another interview was carried out with a senior scientist from the Indian Council of Malaria Research (ICMR) which was the partner organization for conducting clinical trials for Synriam. The last participant was a senior manager at the MMV and involved with the arterolane project. The diversity of participants regarding knowledge and involvement with Synriam allowed capturing a detailed understanding of its development process. Additional information was gathered from a review of scientific literature, reports, websites, and news articles. Further, an expert panel on the development of pharmaceutical products through PDP-model was also attended to understand PDP organization and functioning.

The study is organized as follows: Section 1 presents the background conditions that necessitated the need for alternative R&D approaches. It also sheds light on the innovativeness of PDPs. Section 2 is dedicated to explaining the development of Synriam which started as an MMV-funded project. Section 3 critically analyzes the extent to which MMV's model can be considered as a commons-based approach. Section 4 offers a brief conclusion.

1. The need for alternative R&D?

In this section, we recall how the open science paradigm has been eroded, and present PDPs as innovative responses to this erosion and as alternative mechanisms to develop new drugs.

1.1. Changes in open science paradigm and disconnected research agenda

The discovery and development of medical technologies to meet healthcare needs of the society are ingrained in the relationship between academia, industry, and government. The justification of this relationship is rooted in the principles of open science where basic research is mainly done in universities or public research labs primarily on public funding through government grants. Results of these researches are made available through peer-reviewed scientific publications that assure the scientific quality of the work. Researchers also get recognition for their work in a race to be the “first to publish” on a scientific issue (Coriat, 2015a; Dasgupta & David, 1994). The system thus offers both the incentive to discover and controls the validity of its findings. It is also transparent and offers an equal playing field for other researchers who might be interested in further developing that idea. Further, firms in the field of applied sciences use this common pool of scientific knowledge to invent new products and processes, which advances the technology. They protect their inventions through patents – an exclusive but

temporary monopoly right given to the inventor to enjoy the proceeds of the invention including the right to exclude others (Orsi & Coriat, 2005). This arrangement ensures that the fruits of basic research will remain in public domain so that it can easily be accessed by future innovators (Nelson, 1959, 2004)

Such institutionalization of science was the result of a long history of “trials and errors” and “conflicts and compromises” between different actors involved in the production of knowledge (Coriat, 2015a). To better understand the rationale behind the systems of open science and patents one must refer to the two seminal papers by Nelson (1959) and Arrow (1962). Nelson argued in favor of the importance of basic and fundamental research for economic and social growth while Arrow described the problems faced in the creation of knowledge and its “non-market” based solutions. Pursuance of science produces knowledge. However, once scientific knowledge is converted into information it becomes “non-rival” in nature which means it can be reproduced infinitely without the loss of intrinsic qualities and can be jointly possessed and used by many individuals. This “indivisible” nature of knowledge leads to the “free rider” problem. In a market economy, each firm will wait for its competitor to invest in the production of knowledge first while itself being the free rider and benefiting from the competitor’s innovation without having invested for it. As the production of knowledge is a costly affair and the innovators run a risk of not being able to appropriate the fruits of their innovation fully, market mechanism has a tendency to discourage the socially optimal investment in knowledge production (Coriat, Orsi, & D’Almeida, 2006; Dasgupta & David, 1994; Orsi & Coriat, 2005). To overcome this “market failure” three non-market mechanisms or institutional arrangements have been proposed (Dasgupta & David, 1994).

- i. Government Expenditure: The government engages itself in the production of knowledge for the overall good of society and allows free use of it. Research conducted in universities and public laboratories come under this scheme. It is funded by general taxation, and it is the government who decides the total expenditure and the areas of knowledge production.
- ii. Patents: A patent is essentially a “contract” between the society and the innovators. The society grants the innovator an exclusive but temporary monopoly (including the right to exclude) in return for information disclosure. Thus, the patent system creates the market for knowledge production on the one hand and allows for its disclosure to the society on the other.

- iii. Public Subsidies: This scheme incentivizes private production for knowledge by offering public subsidies (e.g., tax rebate) to R&D activities. The result of such research has to be made publicly and freely available so that anyone can use it. The cost of such subsidies is bared by the taxpayers in return for “goods” and “information” that offer overall wellbeing of the society.

It is essential to understand that the outcome of these “non-market mechanisms” must be so that the net social value created by knowledge production is greater than the social cost paid by the society. Thus, an optimal patent system should not only create incentives for the private production of knowledge but also guarantee that patents do not become a tool for compromising social welfare.

In the system of patents, it is equally important to define the “patentable subject matter”, that is to say, draw the line which separates the kind of knowledge that can be patented from those that cannot be. The fruits of basic research should not be patented as its specific purpose is to provide a common knowledge base which serves as input to other research activities.

From the period after the World War II until the mid-1970s, the system of open science worked well towards creation and diffusion of knowledge. This period was the *golden age* of the pharmaceutical industry that resulted in many new treatments (Coriat, 2015a). However, from the 1980s onwards several policy changes in the US led to a new modified IPR regime that was contradictory to the idea of open science and had far-reaching significance. These changes were the consequence of both “new laws” and “court rulings” that not only changed the definition of patentable subject matter but also opened the field of patents to public sector players (Orsi, 2002; Sampat, 2006)

The principal legal change was the Bayh-Dole Act (or The Patent and Trademark Law Amendments Act) passed by the United States Congress in December 1980. This legislation has two main features. First, it allowed universities and other research organizations to patent the outcomes of their research even if it was publically funded. Second, these patents could be licensed out to private firms (Orsi, 2002; Orsi & Coriat, 2006). It was supported by the argument that it would facilitate private firms to make “practical use” of research outcomes if they intend to do so under a protective license (Nelson, 2004). As a consequence, universities could now pursue the ownership of their invention which would have been in the public domain otherwise. A second major piece of legislation was the Stevenson-Wydler Technology Innovation Act (Public Law 96-480), as amended by the Federal Technology Transfer Act of

1986 (Public Law 99-502) which allowed federal laboratories to patent and commercialize the outcome of public-funded research (Eisenberg, 1996; Stevens et al., 2011).

At the same time when the implications of Bayh-Dole Act were still manifesting, several court rulings brought previously not patentable things under the scope of patentability. The most noteworthy of these was *Diamond v. Chakrabarty* case of 1980 (famously known as Chakrabarty Ruling) where the United States Supreme Court decided in favor of General Electric to have a patent for a genetically engineered bacteria that was capable of breaking down crude oil (Gallini, 2002; Orsi, 2002; Scharper & Cunningham, 2006). In 1981, another Supreme Court decision in *Diamond v. Diehr* permitted the patentability of software, and in 1998 a Federal Circuit Court approved the patentability of business methods in *State Street Bank and Trust v. Signature Financial Group* (Gallini, 2002; Sampat, 2006)

Further, in 1995, a Federal Circuit Appeal Court loosened the “practical utility” criteria for patents, and the USPTO responded by modifying the patentability criteria for genes (Orsi & Coriat, 2005). These rulings set the way for the patentability of genetically modified organisms, genes, and partial genetic sequences. The famous example is “OncoMouse” or Harvard Mouse which was genetically modified to be susceptible to carcinogens (Scharper & Cunningham, 2006).

These institutional changes in the patent regime led to the erosion of the distinction between production of basic knowledge by public organizations and its commercial utilization by the private sector. Universities became the owner of the research outputs funded by public money and got the freedom for its commercial exploitation. This is evident from the increase in the number of US universities involved in patenting and licensing activities post-Bayh-Dole Act. In fact, the number of universities with technology licensing and transfer offices increased from 25 in 1980 to 200 in 1990 (Mowery, Nelson, Sampat, & Ziedonis, 2001; Sampat, 2006; Shane, 2004). The licensing revenue of universities increased from about \$160 million in 1991 to nearly \$2 billion in 2013 (Huggett, 2014; Siegel, Veugelers, & Wright, 2007).

Researchers have argued that Bayh-Dole act may have created incentives for researchers to concentrate on topics that are more likely to be commercialized (Henderson, Jaffe, & Trajtenberg, 1998; Mowery et al., 2001). This means that researchers have more interest to focus on those diseases that have a potential to be taken by pharmaceutical companies for further development and these linkages can also influence the direction of public funding (Lanjouw & Cockburn, 2001).

This is particularly true for diseases that primarily affect Southern countries. In fact, a report by the Global Forum for Health Research (2000) pointed out that less than 10% of global R&D investment was directed towards health conditions primarily affecting 90% of the global population. These findings were substantiated by two landmark studies providing evidence that the outcome of global pharmaceutical R&D is skewed towards the diseases that are prevalent in developed countries. In their analysis of 1393 new chemical entities (NCEs) marketed between 1975 and 1999, Trouiller et al.(2002) found that only 16 were for tropical diseases and TB (Trouiller et al., 2002). They also noted that the chance of a drug to be brought to market for cancer or central-nervous-system disorders is thirteen times higher compared to a neglected disease. Extending the findings of Trouiller et al. (2002), Pedrique and colleagues (2013) reported that of the 850 new products registered in the period 2000-2011, only 37 were indicated for neglected diseases comprising 25 products with a new indication or formulation and eight vaccines or biological products. During the same period, 336 NCEs were approved of which only 4 targeted neglected diseases: three for malaria, one for diarrheal disease. Thus, during the 37 years (1975-2011) only 1.1% of all approved NCEs were targeted to treat tropical diseases which represent 11% of the global disease burden⁴.

In 2015, the research-based pharmaceutical industry had invested an expected \$149.8 billion in pharmaceutical R&D (Evaluate Pharma, 2016). In the same year, the global contribution to neglected tropical diseases (NTDs) R&D was about \$3 billion. Pharmaceutical industry contributed 15% (\$471 million) of this amount, and the rest was mainly funded by governments from developed countries and philanthropic organizations (Policy Cures Research, 2016). This means that only 0.3% of the total R&D investment by the pharmaceutical industry was targeted to NTDs.

1.2. PDPs as alternative approaches to catalyze NTD research

Discussion in the previous section highlights the failure of the market in steering pharmaceutical R&D to provide the unmet health needs of the South. It was in this institutional lacuna that several independent, disease-focused organizations were envisioned as alternative solutions to accelerate the development of new medical technologies for tropical diseases (Muñoz et al., 2014; Olliaro, Kuesel, & Reeder, 2015). PDPs are self-governing, private, not-

⁴ <https://www.dndi.org/diseases-projects/#ftn1>

for-profit organizations which are driven by public health need rather than commercial returns (Grace, 2010; Muñoz et al., 2014). They are social experiments and organizational innovations that aim to deliver medical technologies like drugs, vaccines, and diagnostics to address the unmet health needs of the poor (Chataway et al., 2007, 2010). In a short span of fewer than two decades, PDPs have managed to bring several medical technologies to market that includes new chemical entities, new indications, and formulation of existing drugs, vaccines and diagnostics (Cohen et al., 2014).

PDPs can be broadly grouped by their target disease profile and the type of technology they intend to develop (Grace, 2010; Muñoz et al., 2014). Most PDPs focus on a single disease and a single product type. For example, MMV focuses on developing new drugs for malaria while the efforts of the International AIDS Vaccine Initiative (IVAI) is directed towards developing vaccines for HIV/AIDS. However, few organizations like Drugs for Neglected Diseases Initiative (DNDi) and Foundation for Innovative New Diagnostics (FIND) target six diseases or more.

Nevertheless, PDPs share many similar features. First, PDPs are mainly financed through grants from governments and philanthropic organizations which allows them to adopt a not-for-profit business model. They are not guided by the return on investment into R&D but rather the need of patients in developing countries for safe and effective medical technologies which are adequately available and acceptable to end-users. Further, they are working not only to bring products to market but also to guarantee affordability. Their non-profit investment into R&D creates space to de-link R&D costs from product pricing. These alternative initiatives actively negotiate the process management of intellectual property with academic and institutional partners often with flexibilities that allow for easier technology transfer and licensing agreements to developing country manufacturers.

Second, they allow for the adoption of innovative approaches to R&D by emulating the collaborative features of the open innovation concept. Most PDPs do not have in-house R&D capabilities, but instead, they work in conjunction with external partners which include academia, public research laboratories, contract research organizations and pharmaceutical firms. PDPs slice and dice the development project into small packets and outsource it to partners throughout the value-chain. This allows them to engage and leverage diverse resources and capabilities of partners that do not reside within the PDP itself. In this respect, PDPs mimic a virtual pharmaceutical company (Hughes & Wareham, 2010). They use private sector

management practices to drive product development. Each PDP manages a portfolio of projects which allows them to pursue multiple avenues of innovation while diversifying risk and increasing the chance of success (Grace, 2010; Muñoz et al., 2014). Their main managerial task is the selection of projects and partners, management of R&D portfolio and coordination of information throughout the R&D chain. PDPs have independent scientific-advisory boards which are tasked with the selection of projects and partners based on the scientific merit, technical feasibility and ability to meet the priority health needs of developing countries.

Another common aspect of PDPs originates from their collaborative action with a diverse set of partners which requires integrating the various parts of the innovation process (Chataway et al., 2007). Academia and other public health institutions do not have all the necessary capabilities needed for bringing a pharmaceutical product to market even if there is a will to do so. Research organizations are involved primarily in making early phase discovery and optimization of medicines which are limited to laboratory scale. However, successful product development involves further steps that include passing through clinical trials, regulatory approvals, and scale-up from laboratory to industrial manufacturing, sales, and distribution. These capabilities lie with the pharmaceutical firms who do not see diseases specific to developing countries as profitable business avenues. PDPs act as hubs and integrators by bringing these disparate actors together to work towards a common goal. They also undertake brokering activities which mainly involves global advocacy to spread information and awareness regarding their target neglected diseases (Chataway et al., 2007).

2. The Synriam story

The Synriam story is intrinsically linked to the one of the MMV. So, we begin by presenting the conditions that led to the birth of the MMV initiative

2.1. MMV: a PDP dedicated to developing antimalarial drugs

By the late 1990s, antimalarial resistance had already emerged against most of the classic drugs like quinine, chloroquine, proguanil, and mefloquine and malaria was killing over a million people mainly concentrated in sub-Saharan Africa (Lin, Juliano, & Wongsrichanalai, 2010; Murray et al., 2012; Wongsrichanalai, 2002). Despite breakthroughs in medical sciences investment into R&D for new antimalarial drugs by the US government had significantly reduced post-Vietnam conflict and private sector had no interest in developing medicines for

which return on investment was low (Arrow, Panosian, & Gelband, 2004, p. 305). It was in this context that several public and private stakeholders joined hands to create Medicines for Malaria Venture (MMV). MMV was among the first public-private partnership to address the lack of pharmaceutical R&D for a dominant global disease. Among the partners in the initial discussion were the WHO Special Programme for Research and Training in Tropical Diseases (TDR), the Rockefeller Foundation, the Wellcome Trust, the Global Forum for Health Research, the World Bank, the Swiss Agency for Development and Cooperation, the Association of the British Pharmaceutical Industry, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Glaxo Wellcome and Hoffmann-La Roche (Roche) (MMV, 2000). It was conceptualized with the idea to bring the relative strengths of pharmaceutical industry in drug discovery and development and public sector in basic biology, clinical medicine, chemistry, and field experience to create a dynamic partnership to handle malaria drug discovery *for public health as a global public good* (Arrow et al., 2004, p. 305; MMV, 2000). MMV underwent an incubation period (1998-1999) at the WHO/TDR until it was officially launched as an independent Swiss foundation in November 1999 with the initial seed finance of \$4 million from the Government of Switzerland, UK Department for International Development, the Government of the Netherlands, The World Bank and Rockefeller Foundation.

MMV pursues a not-for-profit business model and is governed by an independent board of directors chosen explicitly for their scientific expertise in malaria and related fields and business management experience. Each year it launches a call for research proposals which are reviewed by an Expert Scientific Advisory Committee (ESAC) consisting of members from both industry and academia covering a full range of expertise needed to assess the complex drug development process. Selected projects are included in MMV's portfolio, and R&D is outsourced to a consortium of partners. Each project is handled by a specific project manager who is responsible for its monitoring and coordinating with partners. Further, all projects undergo an annual review process by the ESAC which decides their continuation or termination. MMV collaborates with an industrial partner with good manufacturing and distribution capabilities, ideally before phase III clinical trials, for clinical development and bringing the final product to market. The contractual agreement is negotiated to ensure that medicines will be adequately available and affordable in endemic malaria countries (MMV, 2016).

The business operation of MMV is funded through donations from governments and philanthropic organizations, the most notable being the Bill and Melinda Gates Foundation. Since its establishment, MMV has spent \$778 million to create a dynamic portfolio of 47 projects including six already in the market (MMV, 2017).

2.2. Origins of Synriam

Origin of Synriam lies in the research project that investigated the potential to synthesize and develop synthetic peroxides as potential antimalarial candidates. The project was started by Roche in the early 1990s. Roche collaborated with a group of chemists under Prof. Jonathan Vennerstrom at the University of Nebraska. However, it stopped all antimalarial development in the mid-1990s (1996/97) but not before transferring some of its equipment and even technicians to the Swiss Tropical and Public Health Institute (Swiss TPH).

In 2000, when MMV became truly operational, the synthetic peroxide research was one of the first projects that it started to support and manage. A consortium was formed between three academic partners under the guidance and funding from the MMV: University of Nebraska Medical Center under Prof. Vennerstrom's group to do the chemistry, Swiss TPH (Prof. Reto Brun) to do parasitology work, and the team of Prof. William Charman at Monash University to conduct pharmacokinetic and metabolism studies. The project also received pro bono support from Roche during the project.⁵ The combined expertise of these research groups led to the discovery of arterolane, and the patent was filed in 2002⁶ (also known as OZ277 or RBx-11160). The molecule exhibited structural simplicity, economic feasibility and scalable synthesis, superior antimalarial activity and enhanced biopharmaceutical profile (Vennerstrom et al., 2004). Arterolane was then selected as the optimal candidate to go into Good Laboratories Practices (GLP) compliant pre-clinical testing and human trials.

An industrial partner was needed to take the molecule through the clinical development and manufacturing. Roche had already indicated that it was not interested to re-enter the malaria

⁵ Heinrich Urwyler who used to work on anti-infectives in Roche as pre-clinical toxicology expert moved to Basilea Pharmaceutica Ltd. (A spin-off from Roche). He had a greenlight from the Baselia management that he could spend a certain amount of his time supporting the MMV collaboration. There was also a parasitologist scientist from Roche who spent 10-15% of his time on this project.

⁶ <https://www.google.com/patents/US6906205>

space even though the molecule resulted from its initial work. The intention of MMV was to engage with a company from a malaria-endemic country. MMV went directly to India, and that's when Ranbaxy was selected as a partner, and a formal contract was signed in 2003. In line with its mission, MMV did not expect any return on investment, and the objective was to make the drug affordably available in malaria-endemic countries. The contract separated public and premium markets. The primary focus was the public market to which Ranbaxy agreed to supply the final product in adequate quantities at cost plus a very small mark up. A premium market such as the US could be subjected to a different pricing arrangement and from that MMV expected a milestone royalty payment. The agreement also stated that if one partner withdraws from the project, then that partner will grant a license to the other partner so that it can move the project forward.

By 2005, the program had moved from pre-clinical to clinical studies. The results of the phase II trials of artemolane monotherapy were disappointing for MMV as the effect of artemolane was aberrant, and efficacy was low. First, artemolane showed decreased exposure, i.e., low plasma concentration in malaria patients compared to healthy volunteers (Saha et al., 2014; Valecha et al., 2010). This is to say that malaria parasite had direct contact with the drug for a shorter time as the drug was quickly eliminated from the body. What it means that the effect did not last long and patients had to take more drugs than what was originally expected. Second, even at the high concentration (once daily dose of 200 mg for 7 days), the recrudescence was between 28% and 37% (Valecha et al., 2010). This was much higher compared to artesunate monotherapy which has a cure rate of over 90% for a six-day treatment. This did not fit MMV's target product profile. Based on these results, MMV expert committee recommended not to invest in this molecule and in 2006, MMV decided to pull out of the project. By the time MMV left, it had already invested nearly \$28.8 million of which \$7 million was dedicated to on discovery activities, and rest was directed to pre-clinical toxicology, phase I and phase II trials and manufacturing. MMV received financial support to fund the project from public and philanthropic organizations. In the beginning, funding mainly came from the Swiss Department for Foreign Aid, UK DFID, Wellcome Trust and Rockefeller Foundation. By 2004, Gates Foundation also started supporting the project.

2.3. Ranbaxy gets the IPR, Indian government steps in

By the time MMV parted ways, phase II clinical trial of the single agent (arterolane) and phase I of the combination consisting of arterolane and piperazine (Synriam)⁷ has been done. Ranbaxy found that combination product had no such issues that were observed in arterolane monotherapy and management decided to take the project further. This was a new chemical entity (NCE) in the mid-stage of development, and there was a confidence that this could become a product. Thus, the principal tasks that were left included multiple dose trial for phase I, phase II and phase III of the combination drug. All the pre-clinical part was already done by the time MMV left. As a part of the break-up, Ranbaxy also got the right to exploit the patent on arterolane without any conditions as stated in the initial contract. However, Ranbaxy had internal financial targets and was in no position to divert to the project and the Ranbaxy management considered that the return on investment on antimalarial drugs was not going to be much.

The initial idea was to develop a full range of products (pills, intravenous, rectal suppository) but the withdrawal of finances required Ranbaxy to rethink the strategy. It was decided that it might be possible to develop the basic product which would not require a lot of resources. Help came from the Department of Science and Technology, Government of India. It signed a public-private partnership with Ranbaxy under Drugs & Pharmaceutical Research Program and provided financial support through a loan of \$1 million in 2007.⁸ Phase II trials were finished in 2008. In the same year, a Japanese firm, Daiichi Sankyo acquired Ranbaxy. It was evident that they overtook it for its generic business. The Japanese focused on the generic development with the argument that it is where that the strength of the company lies. In the reorganization, drug discovery division of Ranbaxy became the part of Daiichi Sankyo's portfolio, and Ranbaxy was limited to generic business only. Nevertheless, Synriam project remained with Ranbaxy. Indian government once again extended a grant-in-aid⁹ of \$2 million towards phase III trials and the development of a pediatric formulation with Ranbaxy's commitment to supply the final product to the public sector at a preferential price. Part one of the phase III trials were done in India as the government wanted most of the money to be spent in the country. Nevertheless, heat waves and the resulting drought caused a reduction in the cases of malaria.

⁷ This combination product would be later branded and marketed as Synriam by Ranbaxy.

⁸ <http://dst.gov.in/sites/default/files/drugs%26pharma06-07.pdf>

⁹ <http://dst.gov.in/sites/default/files/drugs-08-09.pdf>

So, new collaborations were searched, and Ranbaxy identified several sites in Africa and Asia (Democratic Republic of Congo, Malawi, Mali, Ivory Coast, Senegal, Mozambique, Bangladesh, and Thailand) (Toure et al., 2016).

2.4. Launching the product in India

Arterolane component of Synriam was a new chemical entity, and Ranbaxy was the first company to bring the product to market requiring Ranbaxy to generate its own safety and efficacy data. Going to stringent regulatory authorities such as EMA or USFDA was difficult and expensive, and Ranbaxy was already facing budget constraints post MMV exit from the project. So, the company decided to register the product first in India where regulatory requirements are not as stringent as those of the USFDA or the EMA. This was regarded as the shortest path to bring the product to market. The strategy was to introduce the drug in the Indian market and take the Indian stakeholders into confidence. In 2011, Synriam was granted a market authorization for treatment against *falciparum* malaria in adults by the Drug Controller General of India based on an interim analysis of Phase III data.

There was a question of trust among stakeholders as to why MMV had left. So, Ranbaxy created a *Universal Product Team* and engaged in active campaigning to create awareness regarding the product through meetings, conferences, and workshops, especially among the key decisions makers such as doctors and researchers. Earlier, Ranbaxy had also brought scientists leading the malaria research in India on board to conduct phase II and phase III clinical trials so that they have the first-hand experience regarding the efficacy of the drug. The idea was to create a noise vis-à-vis the product before its launch. The unique selling point was the low pill burden of Synriam. It was one tablet a day, three days regimen – an advantage over existing ACTs. The company also sponsored articles in newspapers to create awareness about malaria among the general population. It was officially brought to the Indian market in April 2012 to become the first NCE to be launched by an Indian company. Synriam was launched with a big fanfare by then the health minister of India and received widespread media attention.

2.5. Launch in Africa

Since the beginning of product development, the target was the international market. Ranbaxy was well aware that the market was competitive and all existing ACTs were already listed on the WHO treatment guidelines for malaria and many firms already had a prequalification. Based on its approval in India, Ranbaxy intended to introduce Synriam in sub-Saharan Africa. Target countries were selected on the basis of high malaria burden (incidence) and ease of registration. It meant selecting countries which did not require being on the national list of essential medicines or a prequalification by the WHO as criteria for registration. Further, it was also ensured that Ranbaxy already had business operations in target countries. Thus, countries were chosen as such that they have large malaria market and entry is not restricted by the absence of a WHO prequalification. Most countries where the product was launched needed only a *certificate of pharmaceutical product (COPP)* from the government of India. Moreover, certain countries have a very good image of Indian companies, for example, in Kenya. While there are others that are not so open to Indian companies.

Further, Ranbaxy planned to introduce it in as many countries as possible. First, because even if Ranbaxy could not trap all the market, but it could make its presence felt. Then there was the motivation of data generation regarding the effectiveness of the medicine. Multiple Phase II and one phase III trial data are not sufficient in themselves. Moreover, if a country like Kenya approves the medicine, then there are certain countries which will follow suit. In fact, countries like Kenya, Uganda, and Tanzania have a better regulatory system. So, if awareness is created in these countries and product is approved then it will create a noise in the region, and subsequent registration in the neighboring countries would be easy. Marketing team got in contact with malaria experts in the region; lots of workshops were organized to create awareness. Buzz was created in every country Synriam got approval, or registration was filed.

By 2015, the product had received marketing approval in 12 sub-Saharan countries and was launched in 9 (Table 1). Furthermore, Synriam also received DCGI approval for the treatment of adult patients against *vivax* malaria in 2013. Also, permission was granted to start phase III clinical trials in pediatric patients for both *falciparum* and *vivax* malaria.

Table 1: History of development, testing and regulatory approval of Synriam

Year	Achievement(s)
2002	Patent for Spiro and dispiro 1,2,4-trioxolane antimalarials filed with the USPTO (US6906205 B2)
2003	The agreement was signed between MMV and Ranbaxy for the development of a new antimalarial drug (then code-named OZ 277 and later arterolane). Pre-clinical and pharmaceutical development of arterolane was initiated
2004	First-in-human study with arterolane completed in the UK
2005	Proof of concept trial completed in Thailand; piperaquine identified as partner drug
2006	Phase II trial with arterolane conducted in Thailand, Tanzania and India and Phase I study of combination drug initiated
2007	MMV left the project; Collaboration between Ranbaxy and Department of Science and Technology, Government of India. Phase II trial of the combination initiated in India and Thailand
2008	Completed Phase II trial and received approval for Phase III trial
2009	Phase III trials in <i>Plasmodium falciparum</i> malaria initiated in India, Democratic Republic of Congo (DRC), Malawi, Mali, Ivory Coast, Senegal, Mozambique, Bangladesh, and Thailand
2011	Drug Controller General of India (DCGI) granted approval to India's first new drug, Synriam for the treatment of acute uncomplicated <i>P. falciparum</i> malaria
2012	Synriam, India's first new drug, an anti-malarial product was launched successfully.
2013	Synriam got DCGI approval for the treatment of adult patients with <i>P. vivax</i> malaria. DCGI approval was received for conducting phase III study in pediatric patients with <i>P. falciparum</i> malaria
2015	DCGI approval was received for the conduct of Phase III study in pediatric patients with uncomplicated <i>P. vivax</i> malaria
2013-2015	Synriam has received marketing approval in 12 African countries (Senegal, Guinea, Kenya, Nigeria, Uganda, Cameroon, Mali, Ivory Coast, Malawi, Gabon, DRC, Mauritania) and launched in 9 countries (Senegal, Guinea, Kenya, Nigeria, Uganda, Cameroon, Mali, Gabon, DRC).
2017	Phase III study in pediatric patients with <i>P. falciparum</i> malaria completed

Source: MMV, interviews, and literature

3. Learnings from the development of Synriam

The previous two sections have focused on highlighting the need for alternative pharmaceutical R&D, primarily for neglected diseases prevalent in developing countries, and describing the development of Synriam. In the current section, we critically appraise the PDP-model of MMV,

which was crucial for the development of Synriam, to see if can be regarded as belonging to a commons-based approach.

The analysis of commons is challenged by the fact that there are significant variations across the commons in terms of resources, communities, rules, scope and functioning among others to be captured in an all-encompassing and fixed set of principles (Bollier, 2007; Ostrom, 2010). Nevertheless, there are also certain recurring features which can facilitate their analysis. Based on the works of Elinor Ostrom, researchers (Coriat, 2011; Coriat, 2015) have suggested examining three attributes of a commons-based system. The first concerns with the nature of the CPR and its physical characteristics like subtractability and excludability in use. However, the existence and the nature of a resource are only a necessary but not a sufficient condition for the emergence of the commons. Indeed, a CPR such as a fishery, forest or groundwater reserve can be privately owned and managed, and the owners may not grant rights to access or use to third parties (Coriat, 2011, Ostrom 2010). So, these resources which could have been managed as the commons, would never achieve that status.

Second, a commons is characterized by original and specific property regimen associated with the resource. Unlike mainstream conceptualization of “exclusive” private property rights, a commons is based on a “bundle of rights” which are independent of each other, and a participant can simultaneously enjoy one or more rights (Coriat, 2011; Orsi, 2013; Schlager & Ostrom, 1992). However, there is not a fixed format of what constitutes the “bundle”, and it can vary from one commons to another. For example, in a typical case of natural-resource commons, the bundle of rights consists of five rights: access, withdrawal, management, exclusion and alienation (Schlager & Ostrom, 1992). However, in the case of digital commons, Ostrom & Hess (2007) add two additional rights of participation and extraction.

Lastly, a commons involves a plurality of participants working towards a shared goal, but it does not necessarily mean that all participating actors have similar identities and interests. As such, a governance structure defining the do’s and don’ts of participants is integral to the commons. It lays down the rules for day-to-day decision making and serves to maintain cooperation among a diverse group of participants with conflicting interests. The stability and long-term survival of a commons depend upon the effectiveness of the rules in place and the degree of adhesion to these rules by the participants (Coriat, 2011). We shall discuss these three points in relation to the MMV’s model of operation and the development of Synriam.

3.1. Creation of a “scientific CPR” of antimalarial medicines and the innovation ecosystem of MMV

Medicines definitely fall within the domain of knowledge commons but the one which is highly technical. So, we start by examining the “scientific CPR” formed by the collective action of MMV and its partners by drawing analogies with natural CPR resources (Hess, 1995; Hess & Ostrom, 2001). Here we look at the boundary conditions of the CPR, the process of its formation and physical attributes such as the degree of subtractability and excludability in use. This is crucial because the first and the essential step in creating a commons of medicines is to bring it into existence. Unlike natural commons physical technologies such pharmaceutical products do not exist in nature. They must be generated through active R&D which is an expensive and complex process that can take years, involves multiple steps and is highly uncertain (Lipsky & Sharp, 2001; Scherer, 2010). The process also requires inputs from a broad spectrum of research areas which includes but is not limited to chemistry, biology, genetics, parasitology, toxicology, clinical trials, and regulatory affairs.

The very first step in the creation of a scientific CPR of potential pharmaceutical products is defining its boundary conditions. In the case of PDPs, the boundary is defined by its mission and mandate. Each PDP has its target disease and product type which sets the framework for their operation. In the case of MMV, the target disease is malaria, and target products are drugs and not vaccines or diagnostics. MMV also sets the profile of products it intends to develop which involves making choices like treatment vs. prevention, single dose vs. multiple doses, or tablet vs. injection, pediatric vs. adults and so on. Thus, the boundary conditions set the domain of the resulting CPR.

Next, PDPs like MMV do not have their own research laboratories or manufacturing plants (Chataway et al., 2007; Munos, 2006; Muñoz et al., 2014). The uniqueness of MMV lies in its ability to overcome this challenge by employing “open innovation” approach. According to Chesbrough (2003), open innovation allows a firm to look for new sources of innovation beyond its own boundaries. Thus, the boundary of the firm becomes permeable, and knowledge can flow both ways. Nevertheless, the PDP model differs from the existing conceptualizations of ecosystem centered around firms (Adner, 2006; Adner & Kapoor, 2010; Li & Garnsey, 2014). The emergence of the innovation ecosystem in this alternative approach to drug development is not brought about by firms or governments. Instead, it is the product of the voluntary and deliberate action of the PDPs motivated by social goals.

Each year MMV announces the call for proposals and entries are evaluated by its “Expert Scientific Advisory Committee”. Selected projects are distributed by MMV to ideal partners who specialize in a particular domain of drug development. This process of project selection results in the creation of the “scientific CPR” or the product portfolio where each project represents a potential resource unit at a different stage of development. They only become ready for harvesting after getting the safety and efficacy approval by the appropriate regulatory agency. When a pharmaceutical firm gets access to such a resource unit, it does not get a physical product in a real sense. Instead, it gets the right to use the know-how to produce the product. The know-how itself is intangible and non-rival in nature. It is also non-excludable in the pure sense because if it was not for the IPR, which is an artificial creation, it could be used simultaneously by multiple firms to generate the same product. As we shall see later, this is where MMV uses an innovative approach to create a bundle of rights linked to the resource units, in this case, potential antimalarial medicines. Also, the annual addition of new projects and evaluation of ongoing projects maintains the health of the CPR and prevents its degradation.

We must also emphasize the importance of collective action. The operational model of MMV leads to the formation of an innovation ecosystem consisting of a variety of actors involved in knowledge generation. The ecosystem functions towards the specific goal of discovering, developing and delivering a selected pharmaceutical product at affordable prices to patients in the global South. All actors in such an ecosystem have different organizational identities, and each actor adds some unique resource or capability to the system (Brinkerhoff & Brinkerhoff, 2004; Li & Garnsey, 2014; Moran, 2005). The MMV assumes the central role of integration and coordination as it did in the case of initial development of Synriam.

The arterolane component of Synriam originated from the scientific CPR of MMV highlighting the organizational capability of MMV to form an innovation ecosystem which is fundamental for the transformation of knowledge into a tangible pharmaceutical product. Arterolane was the outcome of a diverse set of actors like pharmaceutical companies, public and private philanthropic donors, universities, research labs and contract organizations working in collaboration (Figure 1). Working as an ecosystem allows the participating agents to create values and attain goals that none of them could have achieved alone (Adner, 2006; Li & Garnsey, 2014). Further, as in the case of arterolane, the ecosystem created by MMV is not a geographically localized cluster but rather a global network of partners. This allows trapping the knowledge infrastructure which surpasses national boundaries.

Moreover, each ecosystem is a unique and sophisticated unit dedicated to a single product with specific partners. Since the organization of research, development, and delivery is oriented around a target product, the same PDP can have numerous sets of ecosystem depending upon the richness of its scientific CPR or product portfolio. MMV has over 47 products in its portfolio which are at different stages of development. This shows a complex and intricate network of relationships between partners some of which can be working on multiple projects. The complexity of such relationship is even further increased if we take into account that few pharmaceutical companies, donors, research labs and contract research organizations work across PDPs. Thus, we find that MMV uses the collaborative attributes of open innovation to create a scientific CPR of antimalarial medicines with a fixed set of boundaries. However, the existence of a CPR alone is not enough to characterize a commons, and so we must look at the associated bundle of rights and the governance structure.

3.2. Distribution of intellectual property as the “bundle of rights”

The PDP backed innovation system for drug development functions within the framework of existing institutions of safety and efficacy rules, medical ethics, and IPR regime. Yet, the arrival of the PDP-model has opened the way for new constitutive and regulatory rules as to how pharmaceutical R&D should be conducted and how its fruits should be distributed.

In the case of medicines, legal protection can be granted for compounds, processes, and products. As such, a single pharmaceutical product can be protected by multiple patents which allow patent holders to prevent others from undertaking any commercial activity in relation to the product. Pharmaceutical firms prefer exclusive property rights and aggressively defend their position through litigations (Correa, 2004). They put more emphasis on market valuation and capital accumulation over public interest (D’Mello, 2002). Exclusive rights over intellectual property pertaining to pharmaceutical research not only deters further innovation by blocking valuable inputs but it also creates barriers to access to treatment (Orsi & Coriat, 2005; Orsi, Hasenclever, Fialho, Tigre, & Coriat, 2003; Sampat, 2009).

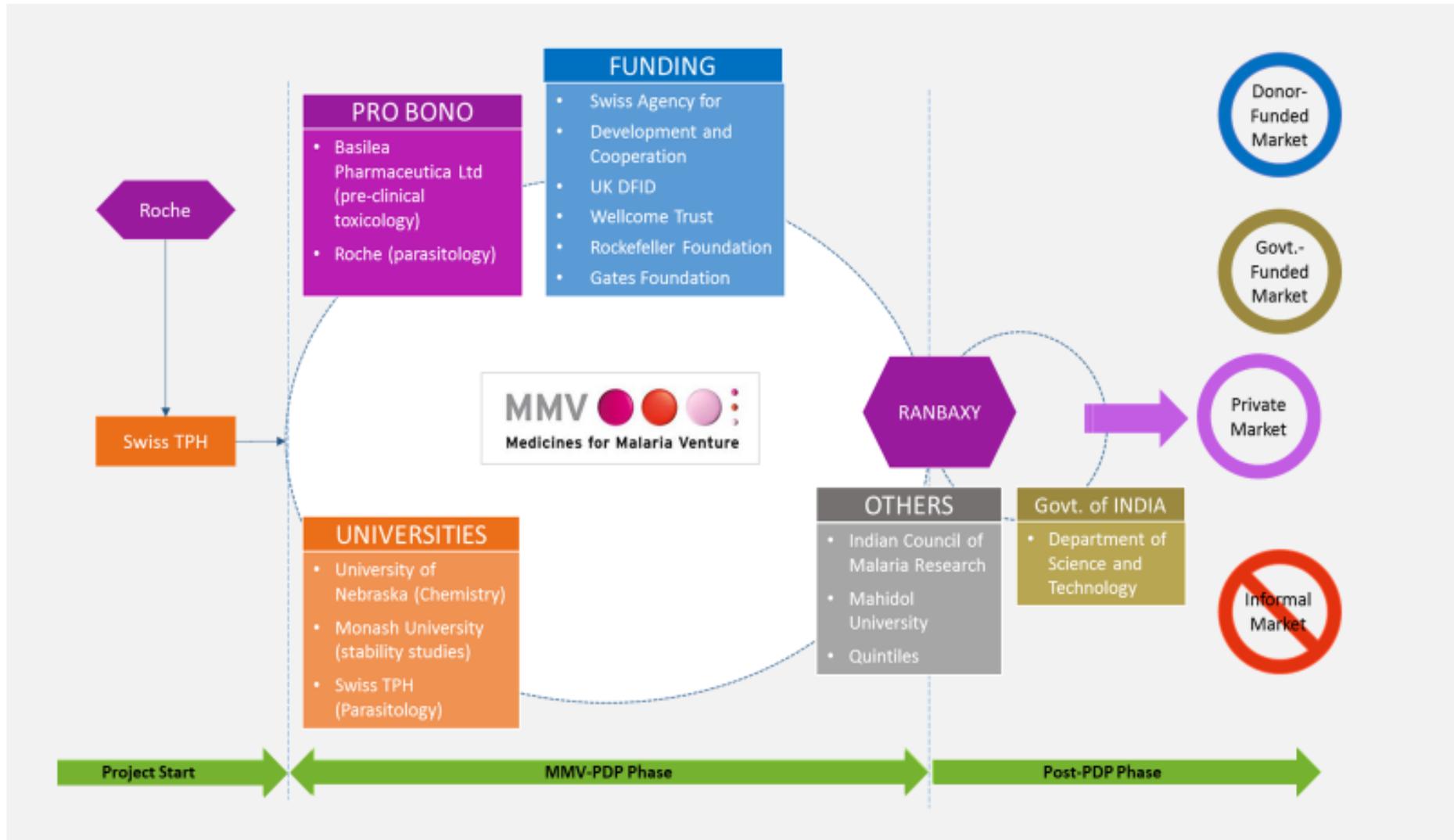


Figure 1: Innovation Ecosystem in the development of Synriam

A salient feature of MMV is its active involvement in the management of IPRs with academic and industrial partners and breaking the norm of exclusive property rights.¹⁰ MMV's management of IPR is unique because it is not rooted in the absence of rights. Instead, it is more subtle and related to how the patent is intended to be used, i.e., how these rights can be used to ensure equitable access. It involves deciding how the rights over the knowledge and products created during the research are shared, whether the product can be commercialized and if so by whom and under what conditions.

In the case of Synriam, the partnership between MMV and Ranbaxy was broken after early clinical phases due to different visions regarding what should be the ideal product profile. The separation granted Ranbaxy exclusive rights to exploit the IPR and carry on further product development. However, the initial contract clearly specified that if the product was brought to market by the joint-partnership, then the market will be differentiated between public and premium. Ranbaxy would charge only cost plus a little markup for public sector while it could charge a premium price in developed country markets such as the US and Europe. In fact, MMV has continued this approach with other products it brought to market. For example, it developed a child-friendly dispersible fixed-dose combination (FDC) of “artemether-lumefantrine” in partnership with Novartis and the latter agreed to supply it at cost for public-sector purchases in endemic countries (Fonteilles-Drabek, Banerji, & Reddy, 2016).

The IPR policy of MMV explicitly states that it is not essential that it will take an ownership position in the IPRs resulting from the program. However, MMV will ensure that it has “exclusive, worldwide, royalty-free, sub-licensable” license to guarantee that potential antimalarials are brought to market while ensuring safety and affordability¹¹ (Fonteilles-Drabek et al., 2016).

¹⁰ Interestingly, the management of IPR is not associated only with the MMV but has emerged as a distinct and recurring feature of other PDPs as well. For example, “artesunate-amodiaquine” FDC was developed by DNDi-Sanofi partnership as a “non-exclusive, not-patented, not-for-profit public good” (Pécoul, Sevesik, Amuasi, Diap, & Kiechel, 2008). Similarly, “artesunate-mefloquine” FDC was developed by DNDi and Farmanguinhos/Fiocruz. Later, DNDi assisted an agreement between Farmanguinhos/Fiocruz and Cipla which agreed to supply the medicine at pre-agreed affordable prices (Wells, Diap, & Kiechel, 2013). However, we must also take into account that different PDPs have different subjective conceptualization of the “right way” to manage the distribution of IPR.

¹¹MMV IPR policy can be accessed at: <https://www.mmv.org/partnering/socially-responsible-agreements>

Each medicine emerging from the scientific CPR of MMV is special in terms of product characteristics (like dosage form and route of administration), collaborators (academic and industrial), and development process (new chemical entity or new formulation of existing molecules). As such, the scope of distribution of rights may vary from one product to another. Nevertheless, on a broader scale, it is always oriented towards the goal of making safe and effective antimalarial medicines available in sufficient quantities at affordable prices for patients in developing countries. It is important to understand that analogous to natural-resource commons, the “authorized users” of the CPR are pharmaceutical firms, but the final beneficiaries are “the patients”. A single firm may have user rights over one or more projects in the MMV portfolio. However, within the domain of the natural resources like a fishery, fishers can sell their authorized resource units following market mechanism. That is, there is no inbuilt control over prices or territories of operation. On the contrary, the commons in the case of medicines cannot exist without guaranteeing the access to patients, who are the final beneficiaries. In this direction, MMV actively negotiates with its commercial partners to supply to public sector buyers in disease-endemic developing countries on a “no profit, no loss” basis. Further, to ensure that the pricing conditions are met, MMV reserves the right to verify the cost structure with third-party audits (Fonteilles-Drabek, Banerji, & Reddy, 2016).

Such management of IP reminds of the *copyleft* and *F/LOSS* movements in the sense that it does not go beyond the existing legal IPR regime, but the rights are so processed that guarantees access (Coriat, 2015a). It has been argued that in the broad spectrum between “exclusive private goods” and “pure public goods” there exist numerous possibilities of organizing property rights (Coriat, 2011). In this light, MMV seems to have achieved a governance structure for the management and use of IPR of pharmaceutical technologies by creating a *bundle of rights*. This allows attaining the balance between genuine return on investment and equitable and affordable access to any products that come out alternative pharmaceutical R&D.

Pharmaceutical products are at the same time “Knowledge” and “tangible” goods and as such there is an inherent cost of their production and distribution. Any pharmaceutical partner will need to recover these costs and capture some additional revenue. MMV draws well-defined boundaries within which the possibility of making such revenues by an industrial partner, if any, remains marginal. But outside these boundaries, partner firms have the possibility of making profits in the classical way. Thus, it offers a unique approach to respond to the policy debate over pharmaceutical IPR which stops at the dichotomous choice between the existence of patents or complete their complete abolition. MMV’s PDP-model demonstrates that IPRs

can be used as an instrument to achieve the goal of equitable access to safe and effective medicines. They show that, to some extent, it is possible to get over the dilemma that arises when IPRs conflict with human welfare rights (Reisel & Sama, 2003). Here, we are not passing from an exclusive to inclusive right as such. However, by including the terms of use of IPR in contractual agreements with partners, it highlights the possibility of achieving a delicate balance between creating incentives for innovation and socially desirable outcomes by mitigating the negative externalities associated with the IPR tradition.

However, certain aspects of MMV's IPR policy remain ambiguous and there it perhaps escapes the domain of the commons. While it specifies that patent protection on products coming out of its research will not extend to malaria-endemic countries, it explicitly excludes India, China, and Brazil – three large economies accounting for almost 40% of the global population. The main rationale behind this approach is to have a legal mechanism for extracting additional (and perhaps higher) profits from the molecule if it is found to be effective against diseases other than malaria but provides no information regarding the potential pricing structure (Fonteilles-Drabek, Banerji, & Reddy, 2016). This raises concerns about affordable and equitable access to patients in both developing and developed countries. The fear in such circumstances is that a medicine developed and distributed through a commons-based arrangement for malaria would start behaving as exclusive property in case of other diseases and thus jeopardize the status of the commons.

3.3. Structure of governance

A knowledge commons emerges when a group of individuals takes conscious collective action to create and manage a system of resources with a view to achieving a shared objective. The plurality of actors who often have different skills, assets, and interests requires a governance structure consisting of the common's internal protocols and procedures to which the participants agree to submit and in which no asymmetry in power is installed. It outlines the rules for decision making, and mechanisms for monitoring and enforcing adherence to those rules as well as problem-solving devices to resolve tensions and conflicts. Researchers (Coriat, 2015b; Ostrom, 1990, 2009, 2010; Ostrom & Gardner, 1993) have noted that the structure of governance is not only crucial for defining and characterizing a commons but is also vital for its efficient functioning and durability.

MMV brings together funding agencies, academia, research labs, contract research and clinical trial organizations, and pharmaceutical firms on the same platform. However, even if the partners join hands to meet a predefined goal, they possess different skills and capabilities, and their interests are not necessarily compatible.

Financial partners such as philanthropic organizations and government agencies are motivated by social welfare goals. Academic institutions may be drawn to new sources of funding, interest in the research domain and reputational advantage emanating from scientific publications. Multinational companies may not primarily be motivated by commercial returns, but they may join such alternative partnerships for improving their public image, towards corporate social responsibility, or for strategic considerations like positioning themselves in the developing country markets (Moran, 2005). On the other hand, small firms have not only commercial interests but also the incentive to build capabilities, gain reputation and legitimacy (Li & Garnsey, 2014; Moran, 2005) as was in the case of Ranbaxy's partnership with MMV.

This multitude of actors and their interests has required MMV to design rules to align incentives across partners while assuring that those incentives do not interfere with the goal of delivering affordable medicines. It has clearly defined policies regarding fundraising, intellectual property, conflict of interest, and product quality among others.¹² A transparent set of design principles sends advance signals to willing partners regarding what to expect on critical issues like sharing of IPR and pricing conditions. It also safeguards MMV's operational independence as the rules are not set by the state or influenced by profit-driven market mechanisms even though MMV frequently works in liaison with government agencies and market actors.

The disagreement between Ranbaxy and MMV over the continuation of arterolane development shows that the creation of knowledge and innovation is a social process which includes cooperation, contradictions, and conflicts. The role of the governance structure is to provide a framework for maintaining cooperation and problem-solving devices to resolve any conflicts so that all partners can share the same vision of the problem and seek a mutually agreed solution. When arterolane did not satisfy the product profile as envisioned by MMV, it decided to withdraw its support following the recommendations of its expert committee while allowing Ranbaxy to continue. As a consequence, even though Synriam emerged from a commons-based mechanism, it came under the exclusive control of Ranbaxy. Nevertheless, it

¹² These policies can be accessed at MMV website: <https://www.mmv.org>

shows the resilience of the MMV's governance structure to withstand adverse episodes. Post-arterolane, it diverted its resources to support other potential drugs and has successfully supported the delivery of six new quality-assured antimalarial formulations for adults and children and maintains a healthy pipeline of new chemical entities in advanced phases of development¹³.

However, in direct contrast to commons, final beneficiaries, i.e., patients do not seem to have a direct representation within the MMV's "Board of Directors" which is the highest decision-making body. For a commons-based pharmaceutical system, it is crucial for patients to be represented on the board or at least be able to defend their rights. Additionally, we did not find relevant information to ascertain the distribution of power between actors within the MMV board. For a commons, it is equally essential to have a fair distribution of power within the governing body so that the decision making is not influenced by the interest of particular groups, for example, donors or the Big Pharma.

4. Conclusion

Our analysis of MMV and Synriam confirms that the PDP-model of drug development is congruent with the key characteristics of a commons-based approach. In the essence of the theory of the commons, PDP like MMV uses collaborations with diverse actors in the pharmaceutical innovation system to create and maintain a scientific CPR of drug candidates in various phases of development. This is further complemented by conditional processing of IPRs by defining the terms of uses and pricing conditions, all guided by a well-defined governance structure¹⁴.

The study also points out that pharmaceutical R&D is a social process where conflicts and contradictions as evident from the different perspectives of MMV and Ranbaxy over the ideal product profile. Yet, the success of a commons does not depend on the outcome of single resource unit but rather on the performance of the entire CPR. The ability of MMV to recover

¹³ MMV portfolio can be accessed at: <https://www.mmv.org/research-development/mmv-supported-projects>

¹⁴ Even if, not in all PDP's, patients are represented in the governing structure. For Ostrom it is one of the 11 basic "design principles" that "appropriators" (i.e. : beneficiaries of the resource should be represented in the governing structure)

from the shock and deliver several new antimalarials all the while maintaining a robust pipeline provides credence that its operational design principles are sound and resilient.

Nevertheless, the study also raises certain questions. First, PDPs operate on a not-for-profit business model which allows for delinking R&D expenditure from final product pricing. However, a report by Policy Cures Research (2016) found that nearly half of all PDPs received more than half of their funding from the Gates Foundation. So, there is a growing need for diversification of funding sources to avoid the risk to be captured by the agenda of the donors, if the latter is in position, through the funds distributed, to influence the policy of the PDP. The not-for-profit business model is only sustainable if PDPs receive sufficient funding for their R&D projects and operations from diversified donors and if they can freely operate with the multiple partners engaged in their different projects.

Second, the Indian government's stance to support Ranbaxy post-MMV withdrawal from the project was conditional on the supply of final product at preferential prices to the public sector. This offers an insight into the role that governments can play to regulate how the fruits of publicly-funded research should be distributed to society. Governments of developed economies especially the US¹⁵ and European countries fund pharmaceutical research through grants, tax cuts, and subsidies. Active and appropriate negotiation with the private sector putting affordability conditions for commercializing public funded research can further strengthen the equitable access to medicines.

Third, MMV is one of many PDPs working towards bringing new medical technologies for diseases prevalent in developing countries. Each PDP has its own organizational features and policies, as such, they are not perfectly comparable. While we note that several elements of MMV's design principles resemble a commons-based approach, we do not know to what extent the same holds true for other PDPs. We need more studies comparing the design principles of multiple PDPs to better understand what a commons-based system of medicines would look like.

Lastly, while the MMV's PDP-model shows that it is possible to conduct pharmaceutical R&D following a commons-based approach, their influence is limited to disease primarily prevalent in the South. Given that medicines are becoming increasingly unaffordable and unsustainable

¹⁵ The most recent example is that of the National Institute of Health's (NIH) proposed license to Gilead for CD-30 CAR T technology. <https://www.keionline.org/book/government-funded-inventions/gilead-cd-30-car-t/>

for the healthcare system in developed economies as well, it could be valuable to analyze the applicability of the commons design principles into the R&D of diseases that affect developed and developing countries alike.

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