Open source pharma and its developmental potential

OSP e seu potencial de desenvolvimento

Valeria Arza [*]

Sol Sebastian [**]

RESUMO

A Open Source Pharma (OSP) é uma forma inovadora de realinhar a pesquisa farmacêutica com as demandas em saúde, em particular na busca de soluções para doenças infecciosas relacionadas à pobreza. A OSP significa a colaboração aberta, o acesso aberto a dados e outros resultados, e as licenças abertas para compartilhamento e distribuição de resultados de pesquisa. O artigo apresenta uma análise exploratória das práticas atuais e dos modelos de negócios adotados pela OSP a partir da revisão da literatura e de uma entrevista aprofundada com Matthew Todd, líder do projeto Open Source Malaria. Concluímos que a OSP pode se tornar uma alternativa de trabalho mais promissora do que a indústria farmacêutica tradicional, quando recebem apoio de políticas públicas, de modo que os seus benefícios possam se tornar plenamente visíveis.

Palavras-chave: Open Source Pharma; Doenças Infecciosas Relacionadas à Pobreza; Ciência Aberta; Saúde Pública; Descoberta de Drogas.

ABSTRACT

Open Source Pharma (OSP) stands out as an innovative way to re-align pharmaceutical research with health needs, in particular to find solutions to poverty-related infectious diseases. OSP means open collaboration, to open access to data and other results, and open licenses for sharing and distribution of research outcomes. This paper provides an exploratory analysis of OSP current practices and business models, based on literature review and one in-depth interview with Matthew Todd, leader of the Open Source Malaria project. We claim that OSP may become a working and more promising alternative to traditional pharma as long as it is supported by public policy so as to fully emerge and visibilise its benefits.

Keywords: Open Source Pharma; Poverty-related infectious diseases; open science; public health; drug discovery.

[*] Valeria Arza has a degree in Economics (Buenos Aires University) a Master in Development (London School of Economics) and a PhD in Studies of Science and Technology Policy (SPRU, Sussex University), is an independent researcher of National Research Council for Scientific and Technical Research (CONICET) and Research Center for the Transformation (CENIT), Economic and Business School (EEYN), San Martin University (UNSAM). E-mail: varza@fund-cenit.org.ar.

[**] Sol Sebastian has a degree in Sociology (Buenos Aires University) and is a doctoral fellow for the National Research Council for Scientific and Technical Research (CONICET) and Research Center for the Transformation (CENIT), Economic and Business School (EEYN), San Martin University (UNSAM). E-mail address: sol.sebastian@fund-cenit.org.ar.

INTRODUCTION

The pharmaceutical industry has become less efficient: the success rate of research and development (R&D) is shrinking, the therapeutic value of new drugs is marginal and as a result the productivity of medical R&D investment has decreased (Scannell, Blanckley, Boldon, & Warrington, 2012). In turn, a global problem persists: diseases affecting a big share of global population, such as malaria and tuberculosis, still cannot find suitable drugs. In fact, despite major advances in science and technology, mortality from diseases affecting poor countries have not declined (Kyle & McGahan, 2012).

The adoption of ever-stronger intellectual property (IP) regulation worldwide has not led to an increase in the discovery of new chemical entities (Dosi and Stiglitz 2014). Quite the opposite, as pharmaceutical industry motivations and business models are largely based on IP, drug development has become more and more inefficient and further separated from health needs. The patent system motivates secrecy to get the prize of exclusive rights; but pooling existing knowledge is at the core of scientific progress, which is cumulative by nature. Secrecy, then, means wasting resources. Scientists step over the same stone again and again. This necessarily duplicates efforts. Exclusive rights also waste opportunities; instead of using existing knowledge, research processes often need to circumvent what is known already to avoid litigation. In summary, by means of wasting resources and opportunities secrecy and exclusive rights raise discovery costs (Balasegaram et al., 2017a).

In addition, it is not just a question of costs, but also a question of target. The prize of getting exclusivity may create incentives to develop certain types of drugs for which profitable markets exist. However, profits due to exclusivity do not work as an incentive to invest in research for drugs to be used primarily in poor countries.[1] This IP system impoverishes pharmaceutical production: while 75% of new drugs that reach the market present no added therapeutic value (Prescrire International, 2015), necessary drugs, especially those related to poverty, which affect greatest portion of worldwide population, never get there.

The disappointing outcomes of the pharmaceutical industry have pushed for the emergence of several alternative models that attempt to overcome one of its rotten elements: the lack of incentives to collaborate (see examples in Balasegaram et al. (2017b). Most of them do not solve the root problem, since IP continues to be at the core of their business model.

In this context, there is a need of a truly innovative way to provide useful solutions to health problems, especially in the context of development (Maurer, Rai, & Sali, 2004; Munos, 2010). We bring the attention here to open source pharma (OSP) (Balasegaram et al., 2017a), which is based on three dimensions of openness (Masum & Harris, 2011):

> open collaboration: a diversity of contributors could participate on the project regardless of organizational and geographical borders (Årdal & Røttingen, 2012)
> open access: all type of data and outputs from the project must be accessible to everyone without barriers (Årdal & Røttingen, 2012);

[1] For example, using counterfactual analysis Chaudhuri, Goldberg, and Jia (2006) showed that profits achieved by multinational companies exploiting exclusive rights in antibiotics in India, were very tiny, and definitely not enough to engage in R&D for discovering new drugs.

> open licenses: project solutions should be shared with Creative Commons (CC) Licenses, which allows third parties to copy and distribute them, so that results diffuse widely and affordably.

These three pillars jointly attack the root problem, since they imply no secrecy and no exclusivity.

This paper provides an exploratory analysis of OSP current practices and business models. We reflect on how this model could contribute with solutions to health needs, especially those for poverty-related infectious diseases, and how it could be further expanded. To that end we gather sparse evidence in the academic literature, grey literature and one in-depth interview with Matthew Todd,[2] the Open Source Malaria project leader.

Section I presents the context of analysis describing main practices in pharmaceutical production. Section II discusses how open source production could be transformative and introduce OSP. Section III presents OSP potential benefits. Section IV describes specific OSP projects and their outcomes. Section V aims at characterizing OSP business models. Section VI concludes and reflects on OSP potential.

THE CONTEXT: PHARMACEUTICAL PRODUCTION

The pharmaceutical industry business model is based on "chevron" diagram of drug discovery and development. This implies that all key phases from drug conception to distribution in the market, which comprises discovery, development, clinical trials, production and distribution of medicines, are managed by a single actor, who assumes the risks and appropriates rewards (Balasegaram et al., 2017b).

Knowledge complexity has pushed the industry to outsource part of the key activities requiring specialized knowledge or managerial capabilities in contract research organizations (CRO), which are increasingly responsible of several phases in clinical trials. The industry has also increasingly relied on expertise and infrastructure of public research organisations for discovery phases and on public hospitals infrastructure for later development phases. The scope of participating actors in drug discovery and development has widened. In fact, some authors claim that the industry is moving towards an 'open innovation' model, where internal efforts are very much oriented towards connecting with the right actors (Dosi & Stiglitz, 2014). Essential scientific inputs are developed outside the firms, which are then internalized at some point throughout the R&D process. Thus, the overall productivity in the sector is enhanced by the quality of firms' linkages with third parties (Bountra, Lee Hwa, & Lezaun, 2017).

However, IP continues to be a strategic asset in open innovation. Its business model is very much around alternative strategies to benefit from IP rights held by firms and their external partners, and, in fact, there is a positive association between cumulative patents and open innovation strategies (Zobel, 2016).

Thus, while open innovation seeks to increase collaboration, it does not question secrecy, quite the opposite; its very strategy is about how to use IP rights more productively. Yet, the fact that drug discovery and development is being increasingly

[2] The interview was carried out in May 2017. Unless otherwise stated, direct and indirect quotes mentioning his name come from this interview.

organized on an innovation platform where several actors participate, could contribute towards building support for OSP. Many actors are already used to widen collaboration and some are familiar with task partition and distribution. But they need to experience the virtuosity of sharing everything and avoiding monopolies.

THE TRANSFORMATIVE GOALS OF OPEN SOURCE PRODUCTION

The term *open source* originates from computer software where developers make the source code of their programs publicly viewable and commendable. This source code is shared allowing other developers to use it and change it. Modularisation of knowledge and tasks is at the core of open source software development, and the existence of a wide community of actors spread around the world willing to test and to make incremental contributions, its main competitive advantage. To keep IP rights out of the way, open source software relies on copyright law, elements of which are included in CC licenses. Currently, open source software competes successfully with proprietary software in the market and its often superior performance has pushed information and communication technologies (ICT) firms to use open source software and sometimes even to adopt its business model.

Although there are important technical, market and regulatory differences between producing software and producing drugs, the prospect to modularize activities -so to promote wider collaboration- and the principle that 'sharing sums up' remains. For the former, there are structural differences in the possibility for creating 'building blocks' with intangible and tangible technologies (Bonvoisin, Mies, Boujut, & Stark, 2017). Moreover, some have claimed that this is particularly cumbersome in science-based context, such as biotechnology research, where knowledge is not yet matured and it is difficult to break up the problem into subcomponents (Pisano, 2010). However, there are some precedents of dividing tasks and adopting open innovation business models in the industry (Bountra et al., 2017; Dosi & Stiglitz, 2014).

For the latter, although there is evidence that drugs developed patent-free, like penicillin, have great social impact, there are not yet examples in the industry on how more productive (in terms of cost efficiency, product quality and health impact) drug development could be had the whole R&D process been shared in the open (Todd, 2017).

The goal of OSP is both, to make the industry more productive and to better align drug development with health needs. The paper focuses mostly on the analysis of the first stage of discovering new medicines. This is to analyse specific diseases' causes by breaking down disease component to find abnormal events that could be treated with chemical or biological compounds. It also involves the identification and screening of compounds, the analysis of their main characteristics, and synthesizing and testing of analogues. Most OSP initiatives are within this stage.[3]

POTENTIAL BENEFITS OF OSP

The literature has pointed out to several potential benefits associated to the three dimensions of OSP: open access, open collaboration and open licences.

[3] Drug development, the consecutive phase, is when candidate drugs are tested in pre-clinical and clinical trials to prove that they are effective and safe.

Open access aims to reduce resource waste since results are openly accessible for everyone and many different actors could get involved to use them for different purposes. The publication of positive as well negative data leads to the elimination of duplicative work which results into better allocation of resources (Osterath, 2013). Moreover, other researchers from public and private organisations get access to data and this could be useful to solve different problems to the one originally addressed.

Open collaboration expands resources for research, as many different actors contribute to projects. This allows to solve problems more efficiently (Nielsen, 2012), increases transparency and reliability of knowledge (Franzoni & Sauermann, 2014), and expands the range of scientific issues that can be addressed at reasonable cost.

In addition, while traditional pharma projects employ highly qualified specialists, OSP promotes diversity of research resources, bringing together individuals from different geographical regions and educational backgrounds. Diversity may drive up performance because product targets would be validated among a wide community of students, researchers and practitioners (DiStefano & Maznevski, 2000).

Open sources processes could be particularly appealing for drugs repurposing, which is to analyse whether drugs that have already passed clinical trials could work for treating different diseases (Balasegaram et al., 2017b).

Thus, open access and open collaboration generate efficient gains in drug discovery or repurposing. Efficiency gains in turn may reduce the price of drugs.

Open licenses further~~s~~ enhance price reductions. Drugs developed in patent free roads show lower prices in the market, making medicines accessible for more people (Marden, 2010). This contributes to social relevance of OSP and could motivate more people to participate.

Perhaps one of the most important benefits is the potential of OSP models for targeting drugs that are very much needed, especially in poor countries, and this is also associated to open licenses. Project outputs do not compete against private companies, which are then less reluctant to litigate and in some cases they may be even inclined to provide material, inputs and insights. OSP projects do not seek profitability, which then better aligns research motivations towards the common good. This, in turn, facilitates donations and fund raising by charity organisations, and it could also imply better commitment to the project by private actors, since the project products are not regarded as competing products, Todd argued that:

> "My university is ok with the open source conditions of the project. The inputs from the private sector are interesting: I think that the clarity around the way the project works means that industry can contribute quite easily, because they aren't concerned that what we do will lead to a direct competitor gaining an advantage or making more money".

With OSP the expectation of IP rights vanishes and ~~so~~ target products are more likely to be better aligned to priority needs rather than to profitable drugs. Researches would choose those targets because there is a better prospective for technical success in less studied drugs and because success in this case also means making something meaningful for the society.

CHARACTERIZING AND ILLUSTRATING OPEN SOURCE DRUG DISCOVERY

We now turn to data collected for seven initiatives of OSP. We analyse them in terms of "open access", "open collaboration" and "open licenses" and we also describe their main outcomes. The initiatives are the following (see more details in boxes in the Annex):

a) *The Synaptic Leap's Schistosomiasis Project (TSLS)* started in 2006 and its main goal was to create an off-patent schistosomiasis drug, praziquantel, as a single enantiomer. The project reached this goal in 2011. (Box 1)

b) *The Open Source Malaria* Project (OSM) aims at finding a cure for malaria using open source methods. It began by developing a compound that could become a preclinical candidate drug to be further developed in Phase I trials and beyond. (Box 2)

c) *The Open Access Malaria Box* was a project initiated by the Medicines for Malaria Venture (MMV)[4] in 2012 to catalyse malaria drug discovery and research. It consisted of a box composed of 400 promising antimalarial compounds that were sent out to research groups, with the condition that they were to place their results in the public domain. (Box 3)

d) *The Pathogen Box* is an initiative from MMV to help catalysing poverty-related infectious diseases drug discovery and follows up the model of the Malaria Box. (Box 4)

e) *Project Marilyn* is a scientific initiative to bring to clinical trial a potential cancer fighting drug called 9-deoxysibiromycin (9DS). This drug is patent free and this project relied in crowdfunding campaigns to finance the future trials and development. (Box 5)

f) *Open Insulin* aims at developing an open source protocol to produce insulin that would then enable generics manufacturers to fabricate insulin cheaper, increasing accessibility. (Box 6)

g) *The CSIR Team India Consortium's Open Source Drug Discovery Project (CSIR-OSDD)* is an initiative that aims at providing affordable healthcare and at discovering therapies for poverty-related infectious diseases. Currently, their focus lies on Tuberculosis. (Box 7)

Open access

Projects like Malaria Box (Box 3) or The Pathogen Box (Box 4) ask researchers to commit to placing the data -meaning both, final and raw data- in the public domain to help continue the virtuous cycle of research.

Similarly, TSLS Project (Box 1) places all its data publicly-available, and access does not require registration. Google searches for related TSLS content redirects to all

[4] The MMV is a leading product development partnership specialised in drug R&D for neglected tropical diseases and especially Malaria launched in November 1999. Initial funding came from the Government of Switzerland, the UK Department for International Development, the Government of the Netherlands, the World Bank and Rockefeller Foundation. MMV funds R&D projects of new and innovative antimalarial medicines (MMV, 2013).

TSLS websites (TSLS Website; TSLS Drupal; TSLS GitHub; etc.) making it easier for potential contributors to find the project. TSLS websites allow open collaboration. Raw data is placed online and peer review is done virtually. Additional peer review may be obtained through publications in scientific journals (Årdal & Røttingen, 2012).

Yet, some projects restrict the access to certain areas. For example, the Malaria Box (Box 3) and the Pathogen Box (Box 4) request users of their compounds to publish open access, but there is no condition imposed for opening up the research process (such as sharing lab notes or negative results). In turn, some other projects require registration in order to access to data. Such is the case of CSIR-OSDD (Box 7). This may imply that the the content is not searchable through general search engines like Google resulting in a tight control of the data (Årdal & Røttingen, 2012).

Open collaboration

To enable collaboration, some projects use collaborative platforms. For example OSM (Box 2) has a website that gives access to the lab notes and records from experiments done by any collaborator. It also uses GitHub for collaboration that has the "to do list", a way to modularize tasks so participants know what needs to be done next and what has already been done. In OSM project they also use a wiki and platforms such as Google plus and Facebook for diffusion.

Projects often impose some entry barriers to ensure that only interested individuals contribute and others do not sabotage the process. Simpler barriers can be registration forms with a mandatory email address and automatic approval. More extensive registration forms may require to state one's qualifications. The registrations are checked manually, by members or project staff. Whether such barriers violate the definition of open source is up to debate.

Qualification is another barrier to collaborate in drug discovery. Although not only highly qualified people could participate, in practice, most OSP projects' participants are professional scientists. However, they are sometimes affiliated to the private sector. For example, TSLS project (Box 1) actively promotes collaboration with the industry and in OSM (Box 2) scientists from pharmaceutical companies and from CRO have contributed to experimental lab work.

In addition, many contributors are students that work in researchers' labs (A. E. Williamson et al., 2016). Matthew Todd told us that doctoral students participated on and off in OSM project (Box 2) with some experimental contributions and there were also undergraduates contributing with molecules. Other non-scientists, from the wider online community, contribute with strategic or technical advice too.

In some cases, contribution is massive which results in significant cost savings. For example, in CSIR-OSDD project (Box 7) there were more than 400 volunteers participating.

Open licenses

There is a tradition amongst software programmers of freely sharing source code. Some OSP projects rely on CC licenses. These licenses help creators to maintain their copyrights while allowing others to copy, distribute, and make use of their work. There are different types of CC licenses so as to be able to deliver a range of permits for the shared work to be used.

All content published in the website by TSLS Project (Box 1) is protected according to the CC Attribution 2.5 License. Results may be utilized by third parties without contracts or royalties. The Pathogen Box (Box 4) is shared with CC Attribution 4.0 License, which allows to adapt the material and to use it commercially. The Malaria Box (Box 3) does not mention any specific CC licenses, but the terms and conditions to sharing are similar to the Pathogen Box.

In turn, Open Insulin project (Box 6) aims at creating a protocol for generic manufacturers to fabricate insulin cheaper, which is ~~then~~ also patent free.

Not all projects revised are fully committed to open licenses. CSIR-OSDD Project (Box 7) has not joined CC license. It allows third parties to patent but it requests them to provide free non-exclusive license to CSIR-OSDD Project so that they could take those molecules "in the drug discovery pipeline and make it available without IP encumbrances".[5] This weak commitment to open licenses made Årdal and Røttingen (2012) to conclude that this project is an example of crowdsourcing rather than OSP.

Outcomes

Many projects have been successful in advancing research in their respective area. TSLS (Box 1) and the Malaria Box (Box 3) are two projects that accomplished their objectives, but the latter did not aim at drug discovery directly but at pushing drug research further. TSLS, managed to develop the off-patent schistosomiasis drug, praziquantel, in enantiopure form, which was the main project goal.[6] The Malaria Box (Box 3) reached their goal of increasing efficiency in drug research through open access and collaboration (Van Voorhis et al., 2016). OSM (Box 2) published intermediate results, revealing explored and unexplor**e**d ~~a~~venues of enquire so that research could be further pursued by the community (A. E. Williamson et al., 2016). CSIR-OSDD (Box 7) has been very productive at publishing: 22 open access articles were produced.

BUSINESS MODEL

Based on the experiences of the aforementioned projects, we use some categories from the management literature to characterize business model in innovation (Chesbrough, 2003; Oskam, Bossink, & de Man, 2017; Wells & Seitz, 2005; Yunus, Moingeon, & Lehmann-Ortega, 2010)[7]:

- Value proposition: to identify the value created for users of project outputs.
- Market segment: to identify users of project outputs and the purpose for which they will be used.

[5] CSIR-OSDD Attribution and Authorship Policy: http://www.osdd.net/about-us/osdd-policies/attribution-authorship-policy, last access 2018 May, 10th.

[6] The Pediatric Praziquantel Consortium is currently working in Phase III to take the drug to the market. See https://www.pediatricpraziquantelconsortium.org/node/28, last access 2018, May 10th.

[7] Although the framework proposed by Chesbrough (2003) was originally developed to characterize the business model of open innovation projects, which as discussed above do not share the principles of OSP, it has been adapted for different purposes. We do so for the context of OSP.

- Value chain: to identify the project position in the value chain that is required to meet the value proposition. This implies to determine the complementary assets that are needed.
- Cost structure and target margins: to identify the project costs and specify the revenue generation mechanisms to cope with them given the value proposition and the position in the value chain.
- Value network: to describe the project position in the larger network of relevant actors, including identification of strategic partners and potentially opposing actors or rivals.
- Competitive strategy: to formulate a road map to move forward towards project value proposition. This implies to identify benefits, make them visible and to early identify challenges.

Value proposition

The value proposition of OSP is its capacity to improve productivity in drug discovery and to target products most needed in the society.

In traditional drug discovery processes a single organization is able to cover all the different steps, from the identification of the objective to the registration of a new therapeutic treatment. Increasingly, key elements in the drug discovery process, are developed outside the firms (Bountra et al., 2017). One of the fundamental values of OSP is precisely that it encourages greater connectivity but, differently to 'open innovation' models, it does so in the open. The adoption of open source approaches allows organizations to share resources such as materials, information and insights. It enhances transparency across the system and thus removes some of the informational asymmetries that explain why huge amounts of resources are invested in projects that are doomed to fail (Bountra et al., 2017). Costs reduce and drugs could be offered at lower price. Besides, as we explained above, when IP rights are out of the way, drug discovery is more likely to target drugs with higher social impact.

In sum, collaboration and openness are the key pillars supporting its value proposition of greater productivity and discovery of most needed drugs.

Market segment

Since drug discovery is the earliest phase of drug production, its immediate market must be organizations that take responsibilities of later phases in drug development. These may be public labs, non-governmental organizations and also pharmaceutical companies.

Value Chain

OSP projects expand and nourish the drug discovery ecosystem by creating a playing field where for-profit and non-profit actors can join efforts while pursuing different strategies. Key actors in their value chain are founders, academic organization and also pharmaceutical companies. In the future, producers of generic drugs may also become key actors in the OSP value chain.

All OSP projects we analyzed have relied on scientific researchers and students' time and have used infrastructure from academic organizations. Many of them also relied on inputs from pharmaceutical companies (Box 3 and Box 4). In fact, OSP facilitates collaboration between academia and industry (Box 1 and Box7).

In turn, most of the OSP projects used funding from government agencies, philanthropic organizations or international organizations.[8] Fewer of them have also started to experience with alternative funding sources, such as crowdfunding (Box 5).

Cost structure

Producing new drugs is very costly, due mainly to three different issues. Firstly, drug discovery is subject to intrinsic failure rate which means that investment must be persistent before reaching any result. Success rates shrank further during clinical trials phases (Mestre-Ferrandiz, Sussex, Towse, & Economics, 2012). Secondly, IP rights increases the costs of research since inputs, both materials and processes, are protected. Licenses must be negotiated or research must take longer roads to circumvent patented knowledge. In turn, the risks of litigations make research financially expensive. Finally, drug development is subject to high regulatory costs related to pre-clinical and clinical trials to show that the drug is effective and safe. Clinical trial costs could be larger than discovery costs (Collier, 2009). They are particularly expensive because several hundreds of patients and control groups must be recruited and because tests must be conducted in locations that fulfill regulatory requirements. In the traditional pharmaceutical industry most drugs only show incremental improvement, thus more patients are needed to find significant results (Collier, 2009).

OSP may be more efficient in drug discovery, since more resources are shared and research is done collaboratively, but yet intrinsic uncertainty remains. When focused on poverty-related drugs, the cost of IP may be lower because some of those rights may be ceded by owners, as part of their corporate social responsibility policy or simply because such research is not profitable for private companies. In turn, trials costs for these drugs may also be lower, because they usually show substantial improvements for patients, thus samples of patients and control groups do not need to be so large to show that the drug is useful (Maxmen, 2016). Matthew Todd from the OSM (Box 2) project argued that because OSP implies open data, the regulatory process should become easier and cheaper at some point: data from previous projects could be re-used and regulatory agencies could value project transparency. Moreover, by involving more people in the design of the clinical trial, researchers can get better advice on how to do it more efficiently.

An additional strategy that benefits cost saving is the reliance on software that is either free or open source. Naturally, this sort of software is often available for other drug discovery models, however, open source projects are friendlier towards the adoption of these tools (Robertson et al., 2014).

[8] For example, 82% of investments in malaria R&D came from the public or philanthropic sectors in 2011 (Moran et al., 2012).

Yet, OSP must cover costs that are irrelevant for traditional pharmaceutical companies. Firstly, OSP initiatives must invest in community development, and this means communications, advertising and software infrastructure. Secondly, they must also cover documentation costs, which is essential for modularization and to make wide collaboration feasible. The grand goal must be divided into several smaller targets, for example, a list of compounds requiring synthesis, so that potential participants may know how to contribute. But for this to work, a clear documentation of what has been done already, for example, information about the identification and characteristics of compounds requiring synthesis must be clearly informed so that others could take on successfully. All participants must document their progress and contributions. Yet someone must fold the information produced worldwide into a story, which can be followed easily by newcomers to the project. In our interview, Matthew Todd referred to this role as the 'storyteller', and there is no such ~~a~~ role in traditional pharma. Although all these costs are small in relation to the grand total of discovery costs, they are essential for OPS and they are normally not included in grant application forms.

In terms of income, while pharmaceutical companies heavily rely on IP rights of marketable drugs and process, OSP projects do not. Although profitability is not a goal, they still need to ensure the necessary funds to cover their discovery and eventually their development costs. Up-to the present, they have relied on public money~~s~~ and donations from philanthropic organizations, since most OSP initiatives seek to develop drugs for the common good. Particularly for clinical trials there are reasons to believe that public money would be better invested in OSP because data quality is better guaranteed due to transparency; and information regarding effects, side effects or counter effects of tried drugs would be open access. Todd explained that it is currently possible to run a clinical trial for a medicine, never publish the results and keep them secret but, in the case of OSP that would never happen. Data will be open and could be re-used in future trials, creating a public good, which additional justifies public investment on OSP trials.

Value Network

There is a wide network of actors who support OSP projects besides those already mentioned in the Value Chain section.

Non-governmental organizations specialized on health and/or development issues, and activist groups fostering social and economic justice and others in the open source community have a key role for OSP projects. They raise awareness on the need to promote scientific commons that could help to reduce poverty, inequality and injustice.

Software developers are very important. ICT products are used in most phases of OSP projects: for distant collaboration, to disseminate information about experiments, to share material, to raise awareness, to disseminate project results, to motivate potential partners, to highlight the perverse effects of IP seeking research.

Moreover, the wider community is also very important in OSP as it is in any open source endeavor. They offer their time voluntarily to support OSP ideas and they could also contribute in defining the target product profile that better suits community health needs.

In contrast, there are other actors that could raise barriers to the escalation of OSP projects. First of all, IP proponents and lobbying groups have been quite successful in

making international regulation ever more promising for patent holders (see for example Trans Pacific Partnership signed by the United States and several countries or the European Union – Mercosur agreement currently (i.e. 2018) being negotiated).

Since OSP community operates in the same ecosystem as traditional pharmaceutical companies, it needs to design strategies to deal with their rules and practices. This means, for example, strategies regarding existent IP rights, to manage and take care of its own developments to avoid illegitimate appropriation, to overcome preclinical and clinical trials, and to commercialize and distribute their drugs.

CONCLUSIONS

The traditional way of discovering drugs is being questioned, in terms of costs, transparency and product targets. Productivity has lowered, data on effects and side effects are encrypted, and lifestyle drugs are being created while those affected large portion of population are not.

We argue here that this may be related to the closed strategy of drug development; a landmark of pharmaceutical industry. OSP is a promising competing idea about how drugs could be discovered and developed. In software, open source strategy competes successfully with proprietary software. Although there are important differences, the general principle of collaborating and sharing may also work in drug development.

OSP embodies many promising elements that make it a working alternative to produce affordable medicines: it is not bound to make profits and for this very reason it could rely on more efficient practices of sharing and collaboration. This makes it a more interesting alternative for the wider community. In the case of drug development for unprofitable markets, such as those of medicines for poverty-related infectious diseases, it may be the only way out. However, for these drugs to be available in the market they must be manufactured normally at large scale. Actors in the generic industry could become good partners. They proved to be able to produce medicines profitably in the absence of IP protection.

Mostly public and philanthropic organizations have invested money in OSP projects so far. We expect this to increase, given their virtuosity in economic and social terms. In fact, health policy should support OSP because it is more efficient and better capable to meet health needs. As a bottom line this implies to create the right incentives so as public labs become committed to OSP.

Yet the challenge is how to create an open source business model that would also invite private actors to invest. Is it possible without secrecy? Do people invest only in highly profitable projects or would they also invest if something important for the common good may turn out? How a reasonable return rate to recoup costs could be ensured for investors in OSP?

It is necessary to think about alternative business model of drug development that could get many on board. Some margins could be obtained through branding. Todd (2015) suggested that granting short-term data exclusivity rights for those investing in clinical trials might be a way to ensure the existence of a financial incentive for OSP. These rights could be understood as a "manufacturing license" rather than IP. This may enable investors to recoup costs for clinical trials without the need of keeping knowledge behind the wall of patents.

Once more OSP projects are able to show their competitive advantage as an alternative pathway in drug development, it may become easier to delineate and communicate their competitive strategy and to attract investors. However, clinical trials costs have prevented OSP drugs to reach the markets. To overcome such bottleneck, investments are required. To break the chicken and egg problem public and philanthropic organization should continue being key players. The wheel must get on moving for OSP to show its value for improving drug development productivity and for developing drugs aiming at improving public health.

Acknowledgements

We are grateful to Gregor Fischer who assisted us on a previous version of this paper. He searched from material and discussed some ideas as part of the activities involved in his six-month student-internship at CENIT. We would also like to thank Matthew Todd for his time and ideas shared with us during the interview.

ANNEX: OSP INITIATIVES ANALYZED BY THE AUTHORS

Box 1: The Synaptic Leap's Schistosomiasis Project (TSLS)

Description and objectives: *The Synaptic Leap's Schistosomiasis Project* started in 2006, led by Matthew Todd. The goal of the project was to create the off-patent schistosomiasis drug, praziquantel, as a single enantiomer.

Funding: In 2008 the project received funding (u$ 330,000) from the World Health Organization (WHO) and the Australian Government.

Collaboration and use of tools: TSLS made use of web tools, the Synaptic Leap website and an open source online laboratory notebook that allowed contributors to enter scientific data more easily than in the website (Årdal & Røttingen, 2012). The posted data from the on-going experiments in the online public-available laboratory notebook and summarized these data on the Synaptic Leap website to disseminate it. They also posted detail progress and descriptions of the next tasks needed, which minimized the time needed from potential contributors. All content may be viewed without a username and password. The funding received allowed them to employ a full-time researcher, who would manage and encourage participation.

Number of contributors: 97 individuals registered on the website and 37 contributed to the TSLS project.

IP Rights: TSLS placed all scientific discoveries in the public domain, limiting therefore patents on their research outputs. All of the website content is copyright protected according to the Creative Commons Attribution 2.5 License unless otherwise stipulated. (Årdal & Røttingen, 2012).

Achievements: The project reached its target in 2011; they produced the off-patent schistosomiasis drug, praziquantel, in enantiopure form.

Source: own elaboration based on www.thesynapticleap.org/ and Årdal and Røttingen (2012)

Box 2: The Open Source Malaria Project (OSM)

Description and objectives: *The OSM Project* is a follow up project for *The Synaptic Leap Malaria* project and is part-funded by *MMVs'* open initiatives. It started in 2010,

carried out by a laboratory team led by Matthew Todd at the University of Sydney. The project ambitious aim was to find a cure for malaria using open source methods. It has started with the aim of developing a compound that could become a preclinical candidate drug to be further developed in Phase I trials and beyond.

Funding: Initially 40-50% came from MMV and the rest from the Australian Government. They were given U$ 500,000 for 3 years by the Australian Government. 30% came from MMV for core activities (one person in the lab).

Collaboration and use of tools: The project begun in 2011 and worked first with the chemicals put into public domain by GlaxoSmithKline (A. Williamson, 2014). All OSM's results are openly available and can be used under the condition that the project is cited. Any drug development project has a high failure rate (around 95%). So far they tried three series of molecules, which were at some point discarded either because they were not successful or because they found other research groups already working on them. In 2017 they were working on their fourth series. OSM project uses several platforms to collaborate that only require a short registration with an email address for editing. For viewing the status of the project no registration is needed. The project has a website (http://opensourcemalaria.org/), with access to the labnotes with experiments recorded from all collaborators; a GitHub for collaboration that has the "to do things", so participants know what needs to be done next and what has already been done; they also have a wiki and the project is also present on platforms such as Google plus and Facebook.

Number of contributors: *250 or more.*

IP Rights: the project places data and lab notes in the public domain, therefore, limiting the possibility to patent them.

OSM Six Laws .

First Law: All data are open and ideas are shared.

Second Law: Anyone can take part at any level.

Third Law:There will be no patents.

Fourth Law:Suggestions are the best form of critique.

Fifth Law:Public discussion is much more valuable than private email.

Sixth Law:An open project is bigger and is not owned by any given lab.

Source: own elaboration based on http://opensourcemalaria.org/ and www.mmv.org

Box 3 The Open Access Malaria Box

Description and objectives: *The Malaria Box* was a project initiated by MMV in 2012 in a bid to catalyse malaria and neglected disease drug discovery and research.

Collaboration and use of tools: *The Malaria Box* was composed of 400 promising compounds with antimalarial activity (200 diverse drug-like compounds as starting points for oral drug discovery and development and 200 diverse probe-like compounds for use as biological tools in malaria research) which they sent out to interested research groups. For example some of the grantees use the Malaria Box to look for new targets to attack in the malaria parasite; other develop new assays, or tests, that can determine very quickly which compounds block transmission of malaria to mosquitoes, etc. The project asked to Malaria Box users to publish and

place their results in the public domain to help continue the virtuous cycle of research.

Funding: from the MMV, and GlaxoSmithKline (GSK). The Gates Foundation, through its *Grand Challenges Explorations initiative*, supported *17 Malaria Box projects*, six of which were awarded a second round of funding.

Number of collaborators: *53 research groups.*

IP Rights: In Malaria Box compounds are available to the wider research community not protected by IP.

Achievements: A collaborative open access paper was published in 2016 (Van Voorhis et al., 2016). The Malaria Box was available free of charge until December 2015. MMV is currently conducting a follow up project called the Pathogen Box.

Source: own elaboration based on www.mmv.org

Box 4: The Pathogen Box

Description and objectives: Following the model of the Malaria Box, the *Pathogen Box* is an initiative from MMV to help catalyse neglected disease drug discovery

Collaboration and use of tools: the Pathogen Box contains 400 diverse, drug-like molecules active against neglected diseases of interest and is available free of charge. *The Pathogen Box* compounds are supplied in 96-well plates, containing 10µL of a 10mM dimethyl sulfoxide (DMSO) solution of each compound. Upon request, researchers around the world will receive a Pathogen Box, and in return, researchers are asked to share any data generated in the public domain. Scientists can use the Pathogen Box website to request the boxes, ask doubts and share results.

Funding: the MMV, and The Gates Foundation (over USD 4 million).

IP Rights: researchers commit to placing the data (meaning final and raw data) resulting from research on the Pathogen Box molecules in the public domain within 2 years after its generation; either via the ChEMBL database and/or by publication in a peer-reviewed journal, with an acknowledgement to the source and supply of the compounds. Publication in an open access journal is strongly encouraged. They request publications under CC Attribution 4.0, without any embargo period

Achievements: By august 2017, 180 boxes have been delivered to scientists around de world, and five articles have been written. These articles present: a novel Antifungal Agent that can fight two of the most common fungal pathogens of humans, together accounting for a staggering 1.4 million infections annually. An approved pesticide with major anthelmintic activity against the barber's pole worm; the discovery of two potential compounds that can fight infections caused by nontuberculous mycobacteria and novel compounds that can fight neospora caninum, which is a major cause of abortion in cattle.

Source: own elaboration based on www.mmv.org and https://www.pathogenbox.org/

Box 5: Project Marilyn

Description and objectives: is a scientific initiative to bring to clinical trial a potential cancer fighting drug called 9-deoxysibiromycin, or 9DS. This is submitting 9DS to a xenograft study ('curing cancer in mice'). The drug candidate 9DS was developed at the University of Maryland, it has shown promise for treating kidney, breast, and skin cancers, and it is also likely to have lower side effects than most chemotherapies.

Since it was not patented, drug companies have not invested in funding expensive clinical trials.

Funding: The project started a crowdfunding campaign in 2014, where individuals donated money to the project. The campaign reached its goal of at least US$ 50,000.

Collaboration and use of tools: *Project Marilyn* is the first project by *Indysci* (http://www.indysci.org/), a nonprofit science research organization whose mission is to fund and conduct socially beneficial scientific projects that challenge aspects of the traditional "science-industrial complex". They believe that pharmaceuticals can be developed without patents, which would result in a better and less expensive healthcare for everyone. The project and the organization are directed by Dr. Isaac Yonemoto.

IP Rights: The drug is open source since it has never been patented. The project asks for the results to be placed into public domain and so consequently reducing the price of the future drug.

Source: own elaboration based on http://www.indysci.org/, fb: @projectmarilyn

Box 6: Open Insulin

Description and objectives: *The open Insulin project* aims at developing an open source protocol to produce insulin. This protocol would then enable generic manufacturers to fabricate insulin cheaper. The cost reduction would then lead to a lower price which in turn would increase accessibility. The project is carried out by a team of biohackers who believe insulin should be freely available to anybody who needs it.

Funding: The project conducted a crowdfunding campaign in 2015 resulting in US$ 16,000 of funding.

Collaboration and use of tools: Fund raising used the platform experiment.com. Currently, donations can be done through their website (http://openinsulin.org/). For collaboration and participation contact is by email. As stated in their website they also organize meetings in the Bay Area, Wednesday evenings at 7 PM at Counter Culture Labs in Oakland.

IP Rights: They argue pharmaceutical companies patent small modifications to previous insulins while withdrawing previous versions from the market to keep prices up. Their aim is to create a protocol so that generic drug companies could make a low-cost insulin avoiding evergreening patents.

Achievements: By 2017 the project was very close to isolating proinsulin in a definitive way.

Source: own elaboration based on http://openinsulin.org/

Box 7: The CSIR Team India Consortium's Open Source Drug Discovery Project (CSIR OSDD)

Description and objectives: *The Open Source Drug Development Project* is an initiative that started in 2008. Its aim is to provide affordable healthcare and discover therapies for neglected Tropical diseases. Currently, their focus lies on Tuberculosis.

Collaboration and use of tools: To achieve their goals, they utilize several websites: an informational website (www.osdd.net) that describes the project, its policies, other platforms and websites of the project, current news, and events between

others. It has an "OSDD Chem" (http://crdd.osdd.net/osddchem/) for volunteers to submitting molecules and project proposals. It also has a Sysborg platform that is OSDD's cyber infrastructure for collaborative research (http://sysborg2.osdd.net). In this platform ideas are shared and contributions are welcome. But to participate and to access any content a registration is needed which then has to be authenticated.

Funding: a US $35 million grant from the Indian government.

Number of contributors: more than 400 volunteers.

IP Rights: Årdal and Røttingen (2012) argue that CSIR OSDD takes a very protective approach of its data so that it is not expropriated by a third party. For now the license language, does not require opening. It allows third parties to patent but, participants must accept the project license agreement, which implies a royalty free and non-exclusive license to CSIR-OSDD on any result obtained. CSIRR-OSDD asserts ownership over its results.

Achievements: the re-annotation of the Mycobacterium tuberculosis genome and the generation of 11 models for prediction of anti-tuberculosis activity.

Source: own elaboration based on Årdal and Røttingen (2012) and http://www.osdd.net/

Artigo recebido em 25/01/2018 e aprovado em 11/04/2018.

REFERENCES

Årdal, C., & Røttingen, J.-A. (2012). Open Source Drug Discovery in Practice: A Case Study. *PLoS Neglected Tropical Diseases, 6*(9), e1827. doi: 10.1371/journal.pntd.0001827

Balasegaram, M., Kolb, P., McKew, J., Menon, J., Olliaro, P., Sablinski, T., . . . Wilbanks, J. (2017a). An open source pharma roadmap. *PLOS Medicine, 14*(4), e1002276. doi: 10.1371/journal.pmed.1002276

Balasegaram, M., Kolb, P., McKew, J., Menon, J., Olliaro, P., Sablinski, T., . . . Wilbanks, J. (2017b). Supporting information for *An open source pharma roadmap*. *PLOS Medicine, 14*(4). doi: 10.1371/journal.pmed.1002276

Bonvoisin, J., Mies, R., Boujut, J.-F., & Stark, R. (2017). What is the "Source" of Open Source Hardware? *Journal of Open Hardware, 1*(1). doi: http://doi.org/10.5334/joh.7

Bountra, C., Lee Hwa, W., & Lezaun, J. (2017). A New Pharmaceutical Commons: Transforming Drug Discovery *Oxford Martin Policy Paper*. United Kingdom: University of Oxford.

Collier, R. (2009). Rapidly rising clinical trial costs worry researchers. *CMAJ : Canadian Medical Association Journal, 180*(3), 277-278. doi: 10.1503/cmaj.082041

Chaudhuri, S., Goldberg, P. K., & Jia, P. (2006). Estimating the effects of global patent protection in pharmaceuticals: A case study of quinolones in India. *American Economic Review, 96*(5), 1477-1514.

DiStefano, J. J., & Maznevski, M. L. (2000). Creating value with diverse teams in global management. *Organizational Dynamics, 29*(1), 45-63.

Dosi, G., & Stiglitz, J. E. (2014). The role of intellectual property rights in the development process, with some lessons from developed countries: an introduction. *Intellectual property rights: Legal and economic challenges for development, 1*.

Franzoni, C., & Sauermann, H. (2014). Crowd science: The organization of scientific research in open collaborative projects. *Research policy, 43*(1), 1-20.

Marden, E. (2010). Open source drug development: a path to more accessible drugs and diagnostics. *Minn. JL Sci. & Tech., 11*, 217.

Maxmen, A. (2016). Busting the billion-dollar myth: how to slash the cost of drug development. *Nature, 536*, 388-390.

Mestre-Ferrandiz, J., Sussex, J., Towse, A., & Economics, O. o. H. (2012). *The R and D Cost of a New Medicine*: Office of Health Economics London.

MMV. (2013). Medicines for Malaria Venture Annual Report 2012.

Moran, M., Guzman, J., Henderson, K., Liyanage, R., Wu, L., Chin, E., . . . Kwong, D. (2012). Neglected disease research and development: a five year review. *Sydney: Policy Cures*.

Osterath, B. (2013). Drug research: thinking inside the Malaria Box, *Deutsche Welle*. Retrieved from http://dw.com/p/1AKrl

Prescrire International. (2015). New drugs and indications in 2014. *Prescrire in English, 24*, 107–110.

Robertson, M. N., Ylioja, P. M., Williamson, A. E., Woelfle, M., Robins, M., Badiola, K. A., . . . Todd, M. H. (2014). Open source drug discovery–a limited tutorial. *Parasitology, 141*(01), 148-157.

Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature reviews Drug discovery, 11*(3), 191-200.

Todd, M. H. (2015). The Economics of Open Source Pharma – What about data exclusivity? Intermolecular Retrieved from https://intermolecular.wordpress.com/2015/02/23/the-economics-of-open-source-pharma-what-about-data-exclusivity/

Todd, M. H. (2017). Why open source pharma is the path to both new and cheaper medicines, *The Guardian*. Retrieved from https://www.theguardian.com/commentisfree/2017/apr/19/why-open-source-pharma-is-the-path-to-both-cheaper-and-new-medicines

Van Voorhis, W. C., Adams, J. H., Adelfio, R., Ahyong, V., Akabas, M. H., Alano, P., . . . Willis, P. A. (2016). Open Source Drug Discovery with the Malaria Box Compound Collection for Neglected Diseases and Beyond. *PLoS Pathogens, 12*(7). doi: 10.1371/journal.ppat.1005763

Williamson, A. (2014). International team of scientists open sources search for malaria cure.

Williamson, A. E., Ylioja, P. M., Robertson, M. N., Antonova-Koch, Y., Avery, V., Baell, J. B., . . . Bhattacharyya, S. (2016). Open source drug discovery: highly potent antimalarial compounds derived from the tres cantos arylpyrroles. *ACS central science, 2*(10), 687-701.

Zobel, A. K., et al. (2016). Does patenting help or hinder open innovation? Evidence from new entrants in the solar industry. *Industrial and Corporate Change, 25*(2), 307-331.