Critical analysis of potentially new ways to the financing of new and expensive medicines
Abstract

This paper has been written in the light of high-income countries struggling to fund premium-priced medicines. Special concern is arising from a certain range of pharmaceuticals that include orphan medicines, personalized medicines, biologics, advanced therapy medicinal products and new generation antibiotics. Goals of this work have been to identify alternative financing approaches for the research and development (R&D) of new medicines; to identify new pathways for effective R&D; to categorize the alternative financing approaches; to critically assess the alternative financing approaches, and to test the alternative financing approaches for feasibility. A systematic review and a pilot stakeholder consultation have been conducted. To the best of author’s knowledge, this is the first study involving systematic review methodology and aiming to investigate ways of financing R&D methods for new medicines, from other than health care payer’s perspective. Five alternative financing approaches have been identified in this study: (1) Health Impact Bonds (HIBs), (2) the Megafund, (3) the Royalty-Based System (RBS), (4) the International Pooled Fund (IPF) and (5) the Health Impact Fund (HIF). Three major new pathways for effective R&D have been identified: (1) academia-based research combined with generic drug maker-like companies; (2) Open Source pathways and (3) managing the public sector’s intellectual property. It was found that none of the alternative financing approaches prohibits an implementation of the concept of delinkage. The Megafund and HIBs would raise the largest amounts of financial resources. However, these two financing mechanisms and especially the Megafund would be characterized by a considerable disruptive nature. The latter has been confirmed through the pilot stakeholder consultation.
Streszczenie

Inspiracją do napisania niniejszej pracy stały się wzmożone wysiłki krajów wysokorozwiniętych, związane z finansowaniem bardzo kosztownych leków. Dotyczą one zwłaszcza leków sierocych, produktów terapii personalizowanej, leków biologicznych, produktów leczniczych terapii zaawansowanej i antybiotyków nowej generacji. Celem niniejszej pracy było zidentyfikowanie alternatywnych sposobów finansowania prac badawczo-rozwojowych (R&D) nad nowymi lekami, zidentyfikowanie nowych szlaków dla efektywnych metod R&D; skategoryzowanie a także krytyczna ocena alternatywnych podejść do finansowania; oraz przeanalizowanie wykonalności wdrożenia alternatywnych podejść do finansowania. Dokonano przeglądu systematycznego oraz przeprowadzono pilotażowe konsultacje z interesariuszami systemu opieki zdrowotnej. Zgodnie z najlepszą wiedzą autorki, jest to pierwsze opracowanie wykorzystujące metodykę przeglądu systematycznego i mające na celu zbadanie sposobów finansowania prac R&D nad nowymi lekami, z perspektywy innej niż płatnika świadczeń opieki zdrowotnej. Zidentyfikowano pięć alternatywnych podejść: 1) obligacje związane z wpływem na zdrowie (Health Impact Bonds; HIBs), (2) mega-fundusz (Megafund), (3) system oparty na tantiemach (Royalty-Based System; RBS), (4) międzynarodowy fundusz wspólny (International Pooled Fund; IPF) oraz (5) fundusz wpływ na zdrowie (Health Impact Fund; HIF). Zidentyfikowano trzy główne, nowe ścieżki efektywnego wspierania R&D: 1) badania oparte na ośrodkach akademickich i związane z firmami podobnymi do generycznych firm farmaceutycznych; (2) ścieżki oparte na otwartym dostępie (Open Source) oraz (3) zarządzanie własnością intelektualną sektora publicznego. Żadne z podejść do alternatywnego finansowania nie koliduje z wdrażaniem koncepcji rozdzielenia kosztów R&D od cen leków (ang. delinkage). Mega-fundusz oraz obligacje typu HIB pozwoliłyby na zebranie największych funduszy. Jednakże wdrażanie obu tych mechanizmów finansowania, a zwłaszcza mega-funduszu, wiązałoby się z wieloma komplikacjami. Potwierdziły to pilotażowe konsultacje wśród interesariuszy systemu opieki zdrowotnej.
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1. Introduction

There are different economic models and business concepts related to financing products or services that bring added value to societies. Here, a selected alternative economic model and several business concepts will be explained before the current state of pharmaceutical innovation and circumstances surrounding it will be described. This is intended as a source for reflection – especially with regard to how Research and Development (R&D) of pharmaceuticals could be financed and how pharmaceutical innovation could be envisioned. It can also serve as an orientation for how to achieve ‘Health in All Policies’ in a broader sense in this world. In Figure 1 a visualization of the diverse concepts described below is proposed.

‘Creating Shared Value’ is a business concept proposed by Porter and Kramer in which it is aimed that businesses create economic value in a way that also society benefits from it. It shall thus connect company success and social progress. It is currently implemented through specific initiatives by companies such as GE, Wal-Mart, Nestlé, Unilever and Johnson & Johnson (Porter & Kramer 2011). ‘Greenwashing’ refers to certain activities such as publishing ‘Corporate Social Responsibility’ reports by which is mainly aimed to give a socially highly responsible image to the public even though in reality there is not much social or environmental responsibility behind the façade (Mahoney et al. 2013). A ‘Social Entrepreneur’ can be defined as somebody “who targets an unfortunate but stable equilibrium that causes the neglect, marginalization, or suffering of a segment of humanity” and who undertakes actions to change it to the better (Martin & Osberg 2007). ‘Economy for the Common Good’ is an alternative economic model that leaves the capitalism and socialism extremes behind and is as an ethical market economy not focused on obtaining as much profit as possible but on cooperating to reach the highest level possible of common good (Felber 2018).

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Figure 1: Modern economic and business concepts in the context of pharmaceutical R&D and innovation practices (author’s own illustration)
The Universal Declaration of Human Rights of 1948 (UN 2018) “declares in its article 25.1 that everyone has the right to health and wellbeing and especially to medical care and necessary social services” (Lavandeira 2002; p.194). As pointed out by Lavandeira in the beginning of this 21st century, “health protection is one of the fundamental principles of modern states” (Lavandeira 2002; p.194). Modern states however, – in Europe (Cohen 2017; Beck 2016; Godman et al. 2015) and beyond (Kelly & Smith 2014) – struggle to fulfil this right to health with increasing prices of pharmaceuticals (Howard et al. 2015).

Public payers are restricted by limited financial resources available but medicines newly introduced on the market tend to be premium-priced and the majority of them add only small therapeutic value if any (Cohen 2017; Antoñanzas et al. 2014) – the phenomenon of the so-called ‘me-too’ drugs (Gyawali & Prasad 2017). Moreover, even high-income countries now struggle funding the premium-priced pharmaceuticals (Godman et al. 2015; Kelly & Smith 2014), which hence presents a threat to the financial sustainability of their healthcare systems (Workman et al. 2017; Godman et al. 2014).

Regarding the financial sustainability of health care systems there is special concern arising from a range of pharmaceuticals that are orphan medicines (Degtiar 2017; Kanters et al. 2014), personalized medicines (Degtiar 2017), biologics (Hirsch et al. 2014; Megerlin et al. 2013; Tu & Samuel 2012) and advanced therapy medicinal products (ATMPs) (Malik 2014). These types of medicines have all been reported to pose challenges to health care payers due to their price or respectively their costs that they present to societies.

Furthermore, antibiotics pose another important challenge to public health professionals since against the existing antibiotics resistances have been developed. Thus, a ‘new generation’ of antibiotics is highly needed (Pasberg-Gauhl 2014).

Regarding the intellectual property of the pharmaceutical industry, there is increasing consensus in that incentivizing innovation through granting patents has important drawbacks (Kameda 2014; Barton & Emanuel 2005) and that the patent-based system does not deliver innovation (European Union 2018; Holman 2006; Baker 2004). Furthermore, it is often found that the pharmaceutical industry is stuck in an innovation crisis (Kudrin 2012) grounded by the fact of shrinking numbers of truly innovative medicines introduced each year into the market (Glaeske & Ludwig 2017). There is thus a need to work on the crucial points that prevent pharmaceutical innovation from happening. Furthermore, the points mentioned above lead to
the question whether there is no other ways of researching and developing new medicines more affordably.

2. Goal

Goals of this work are:

- To identify alternative financing approaches for the research and development (R&D) of new medicines.
- To identify new pathways for effective R&D and product development.
- To categorize the alternative financing approaches.
- To critically assess the alternative financing approaches.
- To test the alternative financing approaches for feasibility.

3. Material and methods

The methodological approach was threefold and consisted of a systematic review on which a pilot questionnaire and pilot interviews were built up on. Beyond this thesis, these pilots will be enhanced and then utilized for a larger stakeholder consultation forming part of a comprehensive scientific project elaborated in cooperation with the Piperska Group. The Piperska Group is a voluntary group of representatives of health authorities, health insurance groups and advisers, across Europe aiming to address and advance topics regarding the pharmaceutical-related financial sustainability of healthcare systems.

Systematic review

Three groups of search terms were created – the first, contained a large variety of search terms all either describing orphan medicines, personalized medicines, biologics, ATMPs or new generation antibiotics; the second, with diverse terms describing financing or economic modelling; and the third contained terms associated with financing but also funding of pharmaceuticals.

Different search combinations were done combining keywords (Annex 1) only, MeSH terms (Annex 2) only or a combination of keywords and MeSH terms. Boolean operators were used to a) connect all the three groups of terms and b) to combine at least two of the three groups to
allow for results that might be highly relevant and meet the terms of two of the groups but not of a third one. Prior to conducting the systematic review, the search terms were discussed with members of the Piperska group in order to include their feedback.

The systematic review was conducted using Medline (PubMed), Econlit and grey literature. Websites of relevant institutions were searched (i.e. Stanford University, European Commission - EC) and other relevant documents were identified through the network of Piperska. Initially, it was planned to also use Embase and Scopus, however, due to the high number of results retrieved from Medline and seen the time constraints that were posed to complete this thesis, the search was limited to the above-mentioned sources of data. The reference lists of relevant articles were examined to find additional relevant information. Duplicate records were removed using the reference management software Mendeley.

Inclusion Criteria have been as follows:
- Language: being published in English, French, German or Spanish;
- Time span: having been published between 2004 and 11\textsuperscript{th} May 2018 – 2004 was taken as starting date as Kelly and Smith had reported in 2014 that medicine prices had “increased by ten-times over the past 10 years” (Kelly & Smith 2014; p.e112), hence, 2004 was found to be a suitable starting point for searching alternative financing models for R&D and new pathways for effective R&D.
- Solution: indicating the solution offered for financing R&D or making R&D more effective with a description of its characteristics and indicating which stakeholders would be involved.
- Clear focus on the financing of R&D for new medicines or on the R&D process itself.

Only the literature that meets the above criteria makes part of the extraction table (Annex 3).

**Stakeholder consultation**

Most participants for the pilot questionnaires and pilot interviews were identified through the Piperska Group. From 22 invitations sent out to fill in the questionnaire, ten filled-in questionnaires were received. The collection of the responses was done using ‘Survey Monkey’ (SurveyMonkey 2018). Survey Monkey is an online survey software. Only in one of the ten
cases the questionnaire was sent by email as there were technical issues. The pilot questionnaire has had 36 questions and average completion time of the online questionnaire was 41 minutes. Based on the ten filled-in questionnaires three semi-structured interviews have been conducted. The semi-structured interview guide can be found in annex 5. Prior to the interviews the interviewees were informed on the ethical characteristics of conducting this interview and were asked to give their informed consent. This study received a positive opinion of the Bioethical Committee of the Jagiellonian University. The pilot questionnaire will serve as the base for a potentially enhanced questionnaire that will be addressed to a larger number of stakeholders in order to reach saturation.

In this thesis the words ‘model’ and ‘mechanism’ will be used interchangeably for the term ‘approach’. Within this work ‘alternative financing mechanisms’ are defined as systems, which allow to finance or to support the financing of research and development (R&D) for new medicines and differ from the current R&D financing model for medicines, which is described hereinafter. The money resulting from applying a financial mechanism or model will be referred to as ‘revenue’ or ‘financial resources’. Thus, the process of collecting the revenue will be called here ‘revenue collection’. The term ‘funding’ will be used to describe how already developed medicines can be made available to those who need them – it thus takes the payer perspective. Whereas the term ‘financing’ will be used to describe how a medicine, which is not yet existing, can be discovered and developed by using certain financial resources and mechanisms – and thus takes the researcher and developer perspective.

The current R&D financing model for medicines
In the private sector R&D activities are financed through “exclusive rights (monopoly rights) over the final product” (UNITAID 2016; p.12). The public’s sector R&D activities are usually financed at national level through public financial resources that are usually derived from taxes (Federal Ministry of Education and Research 2018).

Critical analysis
A critical analysis was conducted to:

a) analyse whether the financial models allow delinkage to act – that is referred to as ‘delinkage feasibility’. Delinkage is defined in this work as acting when R&D costs are decoupled from a medicine’s price.
b) evaluate the degree of disruption that the introduction of the financial models would go along with versus the amount of financial resources that could be raised by these models – that is referred to as ‘disruptive nature vs. financial resources achievable’.

c) determine whether the burden of disease (BoD) would be reduced by a more diverse group of stakeholders versus the number of resulting new compounds – that is referred to as ‘BoD reduction through diverse stakeholders vs. number of resulting new compounds’.

**Delinkage feasibility**

The financial mechanisms found were evaluated with regard to their feasibility for delinkage. To evaluate whether or not a financial model allowed delinkage to act, three categories of assessment were created (see below). The literature was examined based on them in order to allocate the mechanisms to one of the three groups: ‘Clearly Yes’, ‘Possibly Yes’ or ‘No’.

<table>
<thead>
<tr>
<th>It allows delinkage to act:</th>
<th>In the literature it has been clearly stated that the approach enables delinkage or respectively that the price of the medicine is decoupled from R&amp;D costs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly it might allow delinkage to act:</td>
<td>In the literature it has not been clearly stated that the approach enables delinkage or respectively that the price of the medicine is decoupled from R&amp;D costs, but the characteristics of the model seem not to prohibit an implementation of delinkage.</td>
</tr>
<tr>
<td>It does not allow delinkage to act:</td>
<td>In the literature it has neither been stated that the approach enables delinkage or respectively that the price of the medicine is decoupled from R&amp;D costs, nor do the characteristics of the model allow an implementation of delinkage.</td>
</tr>
</tbody>
</table>

**Box 1: Categories of assessment for determining delinkage feasibility**

**Disruptive nature vs. financial resources achievable**

The general criteria for evaluating the disruptive nature were as follows:

i) Making use of capital markets that would be seen as disruptive. It is assumed that the latter would cause scepticism in the public sector and that it would consequently hamper the implementation of the financial model. Whereas if the financial model makes use of taxation, it would not be seen as disruptive.

ii) If the financial model introduces delinkage it would be seen as disruptive. Whereas if the financial model does not introduce delinkage, it would not be seen as disruptive.

iii) Furthermore, concerning the financial resources, the models were evaluated based on making use of capital markets or not making use of it – assuming that by making use of
capital markets more financial resources could be raised. Whereas if the model uses taxation it is assumed that the amount of financial resources that can be achieved would be significantly smaller than by making use of capital markets.

**BoD reduction through diverse stakeholders vs. resulting new compounds**

To evaluate whether the BoD is reduced by a diverse number of stakeholders is based on the types and the number of diverse stakeholders that the financial model involves. Concerning the new compounds, it is assumed that – along with the prior analysis above – if higher resources can be achieved, also a higher number of new pharmaceuticals can be developed.

## 4. Results

On the PRISMA flow diagram (Figure 2) one can see that initially 11,336 records from database searching were retrieved and additional 56 records that were identified through other sources. After records were removed using Mendeley, 7,130 records remained. By title screening 6,656 records were excluded, another 325 records were excluded through abstract screening and finally, after having assessed the full text articles for eligibility 131 records were excluded since they described neither a model for financing R&D for new medicines, nor did they describe a new pathway for effective R&D. The final number of records included for synthesis was 18 records.

Figure 2: PRISMA Flow Diagram describing the process of selecting scientific literature for this systematic review (author’s own illustration)
4.1 Categorization applied

From the information retrieved by this systematic review three categories have been established: (1) alternative financing mechanisms for the research and development of new medicines, (2) new pathways for effective R&D and (3) supportive tools for assuring access. In this chapter the three groups will be explained in detail. An extraction table can be found in Annex 3.

Alternative financing mechanisms

The definition of alternative financing mechanisms has been given in the material and methods chapter. The alternative financing mechanisms have been further divided into ‘capital-market financing mechanisms’ and ‘non-capital market financing mechanisms’.

New pathways for effective R&D

New pathways for effective R&D will in this work be defined as models, which describe how to turn a part or the whole process of R&D more effective.

Supportive tools for assuring access

A couple of supportive tools will be mentioned to locate important existing and other only in theory existing systems or approaches into the whole picture together with alternative financing mechanisms and pathways for effective R&D.

Supportive tools are in this work defined in five simplified groups: i) Reimbursement decision-making tools; ii) Market introducing tools; iii) IP-related tools; iv) Collaborations concerning high-income countries; and v) Collaborations concerning among developing countries.

The supportive tools will only briefly be mentioned as according to the goals of this paper focus is set on alternative financing mechanisms and pathways for effective R&D.

4.2 Related concepts

Before explaining concrete alternative R&D financing mechanisms, first two concepts – delinkage and push-pull combinations – that are very relevant in the context of alternative financing models for R&D will be outlined.
**Delinkage**

According to Knowledge Ecology International (KEI), delinkage “is a term to describe changes in the way we finance R&D” (KEI 2018b). Furthermore, as defined by Unitaid (KEI 2018c) and the Consultative Expert Working Group (CEWG) on R&D Financing and Coordination, delinkage decouples R&D costs from product prices (WHO 2012).

The defenders of this definition of delinkage stated above will briefly be explained here. KEI is a not-for-profit non-governmental organization, which “undertakes and publishes research and new ideas” focusing on “areas where current business models and practices by businesses, governments or other actors fail to address social needs, and where there are opportunities for sustainable improvements“ (KEI 2018a). Unitaid is a hosted partnership of the World Health Organization (WHO) and describes itself as “an international organisation that invests in new ways to prevent, diagnose and treat HIV/AIDS, tuberculosis and malaria more quickly, more cheaply and more effectively” (Unitaid 2018). The CEWG on R&D Financing and Coordination was created following the World Health Assembly (WHA) resolution WHA61.21 (WHO 2012).

Besides the concept of delinkage described above, it must be acknowledged that there are different definitions for what constitutes delinkage. For instance, the pharmaceutical industry describes delinkage in its Davos declaration as “removing the link to sales volumes” while continuing to charge high prices (ReAct 2016). However, for the purposes of this report, the delinkage definition of KEI, Unitaid and the CEWG on R&D Financing and Coordination will be followed.

Love for instance proposes to “to replace the exclusive rights to make or sell a product […] with mega cash prizes that are linked to the impact of the product on health care outcomes” (Love & Hubbard 2009; p.156). Furthermore, Rex proposes delinked rewards for antibiotic innovations (Rex & Outterson 2016).

**Push-Pull Combinations**

It has been argued that combining push and pull incentives may help for instance to advance antibacterial drug development (Ardal et al. 2017; p.1378). “‘Push’ mechanisms are direct investments in basic research, product development or production capacity” (Batson et al. 2006; p.S3/222). According to Mueller-Langer, push mechanisms are meant for “early stage (basic) research” and can be for instance public sector research grants or research institutions, which
are publicly financed (Mueller-Langer 2013; p.185). “‘Pull’ mechanisms provide greater confidence in future sales and their ability to generate a reasonable return on investment, for example by assuring sales volumes or prices” (Batson et al. 2006; p.S3/222).

Combining a push incentive with a pull incentive is said to have the potential to “stimulate research into neglected diseases” (Mueller-Langer 2013; p.185). Mueller-Langer provides an overview of concrete R&D incentive programmes for both types of incentives – push and pull programmes – that can be seen in the figure 3 below.

Some of the concrete incentive programmes listed fulfil the delinkage concept, such as prizes and patent buyouts. As the goal of this work is however to focus on alternative financing models for R&D and new pathways for effective R&D, they will not be explained in detail here, however, the above overview shall serve to better understand the scope of push and pull incentive programmes or combinations of them.

4.3 Alternative R&D financing mechanisms

In this chapter financing models classified as capital market financing mechanisms and non-capital market financing mechanisms will be explained. At the end of this chapter on page 29 Table 2 visualizes the categorization applied consisting of alternative financing mechanisms, new pathways for effective R&D and finally, supportive tools for assuring access.
4.3.1 Capital market financing mechanisms

In the following two sections financing mechanisms categorized as capital market financing mechanisms – Health Impact Bonds and the Megafund – will be explained. Table 1 shows the application of capital market tools to public health challenges.

4.3.1.1 Health Impact Bonds

Rowe and Stephenson resume the origins of applying bonds to social challenges and how bonds finally started to be used to tackle public health challenges. According to them, “impact bonds are instruments for social impact investment currently being trialled in several countries” (Rowe & Stephenson 2016; p.1204). Social impact bonds (SIB) originated in the UK and were used in social program interventions such as to reduce re-conviction rates. Impact bonds go further than pay-by results mechanisms as they “[enable] governments to pay investors retrospectively for programmes that have demonstrated particular outcomes” (Rowe & Stephenson 2016; p.1204-1205).

Health Impact Bonds (HIBs) are financial commodities “[generating] income streams that are linked to reduced future uptake of health and welfare services” (Rowe & Stephenson 2016; p.1205). Thus, through applying impact bonds in social and health settings, immediate and future savings can be made “by sharing the risk of future social problems with the private market” (Rowe & Stephenson 2016; p.1205). Other key characteristics of HIBs are “their stratification of risk exposure, outcome measurement strategies and use of population data to establish counterfactuals” (Rowe & Stephenson 2016; p.1205).

Similar to the SIBs, HIBs “would make the probability of illness tangible through creating a commodity that speculates on the changing health profiles of populations engaged in preventative health programs” (Rowe & Stephenson 2016; p.1206). A HIB would be implemented by a government, which would “determine suitable health programmes for bond finance and engage intermediary actors to market potential investment opportunities” (Rowe & Stephenson 2016; p.1206). The bond-financed program would be administered by healthcare providers. External evaluators would be responsible for monitoring the attainment of the set program goals among the programme participants (Rowe & Stephenson 2016).
Financial mechanism

As SIBs are more established than HIBs (Rowe & Stephenson 2016) the underlying financial mechanism of impact bonds (IB) will be explained here first by taking the example of SIBs and then by resuming the financial mechanism of the first HIBs.

- Explained by SIBs -

The worldwide first SIB was implemented in England in 2010. Called the ‘Peterborough Bond’ it aimed at reducing the reconviction rate of program participants who were compared to a control group. The conditions were as follows: if in 2016 the re-conviction rate of program participants would be at least 7.5% lower than the re-conviction rate in the control group, “the UK Government and [its] corporate partner Big Lottery Fund committed to pay investors a 13% return on their initial investment” (Rowe & Stephenson 2016; p.1205). The returns would be taken from governmental savings thanks to having avoided the cost of imprisoning. Although they missed the goal by 1.6%, this project was the first to connect the tackling of a social challenge with bonds (Rowe & Stephenson 2016).

In Australia the ‘Uniting Care Newpin Social Impact Bond’ gave the first successful example when in 2014 the New South Wales (NSW) Government payed back a 7.5% return to investors. This project, launched in 2013, aimed at enhancing the rate of restoring children to their families to at least 60%. The Newpin Bond promised “a maximum 15% interest rate per annum to investors, to be paid after its full 7-year term” (Rowe & Stephenson 2016; p.1205). But as repayment rates of SIBs – different to government bonds, which are characterized by a fixed rate of return – “are set to fluctuate in correspondence with programme outcomes” (Rowe & Stephenson 2016; p.1205), the final repayment rate was lower than 15% (Rowe & Stephenson 2016).

According to Rowe and Stephenson there are SIB pilots, which entail “the sale of tranches whose minimum repayments are guaranteed” (Rowe & Stephenson 2016; p.1205), and others, which “factored in greater risk for promised return” (Rowe & Stephenson 2016; p.1205). In case of the Australian Newpin Bond however, as in Australia only limited experiences had been made with private investment into public health and welfare, first market confidence had to be created into this new financial mechanism. Hence, the NSW Government “committed to pay a minimum 5% interest per annum on investments for the first 3 years of the programme regardless of its performance” (Rowe & Stephenson 2016; p.1206). Furthermore, full
investments will be returned in 2020 if the restoration rate reached 55% over the total program period (Rowe & Stephenson 2016).

- Explained by first examples of HIBs -

The first HIB, initiated in 2013, was a program running in California, USA, for which bonds were issued and the returns to investors to be paid after a two-year period in 2015 depended on reaching “a 30% reduction in emergency room visits and a 50% reduction in asthma-related hospitalisations” (Rowe & Stephenson 2016; p.1206). Here, “repayments were based on insurance claims data during the programme in comparison with predicted claims based on participants’ previous insurance claims” (Rowe & Stephenson 2016; p.1206).

Furthermore, the Israeli Government made a proposal in 2013 for a HIB for an intervention program aimed at managing type 2 diabetes. Returns for investors for this bond-financed program would be based on “measuring future demand for diabetes treatments, take up of disability related allowances and changing levels of workforce productivity” (Rowe & Stephenson 2016; p.1206). Rowe and Stephenson underline that HIBs “do not necessarily depend on health or illness to produce returns when combined with a range of other investments they can be sorted into categories of risk [and] hedged against other probabilities” (Rowe & Stephenson 2016; p.1211).
Financing the repurposing of generics through HIB

**Background**

Experiences with Social Impact Bonds (SIB) have already been made in projects addressing “recidivism, homelessness, child protection/foster care, and preventive healthcare” (Bloom 2016). Now, Bloom – president and chief officer at ‘Cures Within Reach’ – aims to apply the SIB mechanism to the pharmaceutical sector when aiming to repurpose a developed and commercialized drug for another or several other indications. ‘Cures Within Reach’ is a “US-based global nonprofit focused on repurposing, is preparing to pilot the first SIB for the repurposing of generic drugs in England” (Bloom 2016).

He defends the repurposing principle since it allows to provide patients with treatments significantly faster than having to pass through all discovery, safety and efficacy phases. This would also decrease costs remarkably. Bloom cites an example of the generic drug sirolimus which has shown to be efficacy in another indication, which is autoimmune lymphoproliferative syndrome (ALPS). Sirolimus’ repurposing trial costed less than $500,000. Furthermore, the
repurposing process took only 36 months in total, whereas, the usual duration of developing a
new drug is usually 10 to 15 years. The same medicine was later successfully repurposed for
five other autoimmune indications (Bloom 2016).

He argues that the repurposing of already developed drugs is currently only done with patented
pharmaceuticals. The obstacle for pharmaceutical companies in repurposing generics is usually
that they will find only limited return on their investment into repurposing a medicine. Bloom
however aims to conduct repurposing as well for generics. He argues that the return on
investment “could come from some of the healthcare savings that the repurposed drug’s use
would generate” (Bloom 2016).

According to Bloom, ten projects shall serve as pilots and each of them would be tackling a
different disease. If “repurposing social impact bonds for medicine” is successful it is planned
to implement it “across the whole European Union and then globally” (Bloom 2016).

Financial mechanism/Financial scope

Bloom and his supporters aim to get support “from impact investors such as the Bridges Social
Impact Bond Fund”. On a financial scope, each country, which benefits from a repurposed drug
would pay a certain amount from the costs averted by having applied a repurposed drug. Thus,
if a number of countries joined, the amount to be paid by each country “would be small, but the
total payment ought to be large enough to repay SIB investors and fund the next SIB” (Bloom
2016).

According to Bloom, SIB would allow generic drug repurposing to “access scalable and
sustainable sources of funding that would supplement, rather than compete with, for-profit drug
development” (Bloom 2016).

4.3.1.2 Megafund

Fernandez et al. propose a megafund as “a single financial entity that invests in multiple
biomedical projects” (Fernandez et al. 2012; p.965) of all stages of development and to make
use of the financial instrument ‘securitization’. By having one megafund, which entails a large
portfolio of biomedical projects from early stage of drug discovery to late stages of drug
development, the risk associated with attrition rates of drug candidates decreases overall. Said
differently, key characteristic of the so-called ‘portfolio diversification’ is reducing uncertainty
“achieved by undertaking many programs simultaneously” (Fernandez et al. 2012; p.965).
Fernandez et al. suggest to use ‘securitization’, which defined by Fernandez et al., is “a financing method in which a pool of investment capital is raised by issuing equity as well as several classes of bonds that differ from each other in their risk-reward profile to a diverse population of investors, and in which the funds are used to invest in various assets that serve as the collateral for the bonds” (Fernandez et al. 2012; p.965). This means that the portfolios would be financed through a combination of equity and securitized debt. Here the assets would be the diverse biomedical projects mentioned earlier. This type of investment tool is also called ‘collateralized debt obligation’, which goes beyond asset-backed securities (ABS) as it includes a more diversified range of assets.

By combining equity and securitized debt, and especially by issuing bonds with different maturities the megafund would “accommodate the different investment horizons of various types of investors” (Fernandez et al. 2012; p.965). Hence, a larger amount of capital can be reached. Furthermore, through this financial engineering, R&D will not be interrupted when usually financially driven business deadlines would cut the pursuing of even “genuinely effective therapeutics” (Fernandez et al. 2012; p.965).

Their paper contains a realistic simulation with promising results of the financial performance of a potential cancer megafund. The simulation is “based on historical oncology drug-development databases” (Fernandez et al. 2012; p.967). Fernandez et al. also provide an open source simulation software for calculating different scenarios (Fernandez et al. 2012).

**Cancer megafund simulation: returns to bond and equity holders**

In a publication of Fagnan et al. in 2013 they refer to the earlier publication of Fernandez et al. in which a realistic simulation was presented and extended it to analyse the “impact of [third-party] guarantees on returns to bond and equity holders” (Fagnan et al. 2013; p.408). The latter showed that “even a small (in expected value) third-party guarantee can [substantially] improve the economics of an RBO [(research backed obligations)] transaction” (Fagnan et al. 2013; p.410). RBOs are debt-and-equity financed. In their paper Fagnan et al. compare a cancer megafund simulation between all-equity financed, debt-and-equity financed (RBOs) cases with guarantee and without guarantees of the principal debtor (Fagnan et al. 2013).

Whereas Fernandez et al. presented two simulations of a cancer megafund – one for the early stages (preclinical to Phase II) and another for later stages of drug development (Phase II to New Drug Approval), in Fagnan et al. 2013 they only focus on the first simulation of the early stages (Simulation A), which is the riskier part of the drug development process and this is also
when funding is scarcer. Simulation A shows that the “megafund is almost always profitable” (Fagnan et al. 2013; p.409). It is found that “while the all-equity fund exhibits only a modestly lower probability of negative returns than the RBO equity tranche, it also exhibits a substantially lower probability of very large returns” (Fagnan et al. 2013; p.409). A significant advantage of using RBOs is that this financing structure would lead to financial leverage – because of combining equity securities and debt securities – and thus would result in “almost twice as many compounds – 103 versus 63 – to Phase II” than in case of an all-equity fund (Fagnan et al. 2013; p.409).

**Megafund financing methods for orphan drug R&D (Fagnan et al. 2014)**

Another publication of Fagnan et al. followed in 2014 in which they “explore the applicability of the RBO approach” for the drug discovery for rare diseases (Fagnan et al. 2014; p.533).

Since “RBOs are structured as bonds, they can be designed to appeal to fixed-income investors, who collectively represent a much larger pool of capital than do venture capitalists” (Fagnan et al. 2014; p.533). Fixed-income investors have in the past not been able to make investments into early-stage drug development. Fagnan et al. support the above statement by comparing figures of 2012 of the total size of the US venture capital industry of US $199 billion with the total size of the US bond market, which was US $38 trillion (Fagnan et al. 2014).

The 2014 paper aimed to evaluate the feasibility of the RBO financing technique to the R&D of medicines for rare diseases. They argue that the earlier publications of Fernandez et al. and Fagnan et al. are built on very large portfolios, which in case of orphan diseases might not be possible. They found that even small portfolios of 10 to 22 compounds, which would require less than US $575 million in capital are “sufficiently diversified to yield reasonable returns of RBO investors” (Fagnan et al. 2014; p.534). They admit that the “investment returns of RBOs are positively related to portfolio size owing to the impact of financial leverage” (Fagnan et al. 2014; p.534) but point out that “for certain types of projects the required threshold of assets can be modest” (Fagnan et al. 2014; p.534).

They say that applying portfolio financing to orphan drugs is very feasible since orphan drug development has significantly higher rates of success “compared with those of other disease groups such as oncology or neurodegenerative disorders” (Fagnan et al. 2014; p.534). Also “the success or failure of orphan drug development projects is […] less likely to be correlated across diseases” (Fagnan et al. 2014; p.534), which is according to Fagnan et al. not the case for “other disease groups such as oncology” (Fagnan et al. 2014; p.534). Finally, they say that in the US
context, thanks to the Orphan Drug Act of 1983 orphan drugs are approved faster by the FDA. Also, the overall regulatory success rate of orphan drugs “that entered clinical testing between 1993 and 2004” (Fagnan et al. 2014; p.534) was approximately 22%, whereas “the comparable figure for non-orphan drugs was approximately 11%” (Fagnan et al. 2014; p.534). Fagnan et al. build on another assumption in their simulation, which is that the cost of conducting clinical trials is significantly lower for orphan drugs than for non-orphan drugs (Fagnan et al. 2014).

The simulation results showed that smaller portfolios as only “ten compounds and US $373.75 million of capital - can still be used as collateral for RBO transactions and deliver reasonable investment returns” (Fagnan et al. 2014, p.537).

**Expanding the megafund concept by dynamic leverage**

Montazerhodjat et al. propose a “more efficient structure and higher returns to equity for investors by adding dynamic leverage, a novel securitization technique, to the megafund structure” (Montazerhodjat et al. 2016; p.414) proposed in Fernandez et al. 2012 and Fagnan 2014. By this dynamic leverage concept initially “the portfolio of candidate therapeutic assets is predominantly financed […] by equity” (Montazerhodjat et al. 2016; p.410). Debt is then utilized too when “assets mature and begin generating cash flows” (Montazerhodjat et al. 2016; p.410).

Dynamic leverage is built upon the observation that when a portfolio of biomedical projects has progressed consequently, “its risk should decrease” (Montazerhodjat et al. 2016; p.411). This means that “the amount of debt of a given default probability [the likelihood of the entity being unable to meet its payment obligations on a timely basis] than can be supported by this portfolio, as a percentage of the total invested capital required, should increase” (Montazerhodjat et al. 2016; p.411) and hence, the amount of equity required should decrease. Thus, dynamic leverage “adjusts the amount of debt that a securitization vehicle can sustain, based on parameters of its default probability” (Montazerhodjat et al. 2016; p.411).

There is another important concept connected to dynamic leverage, which is the concept of ‘dynamic risk measurement’. In dynamic risk measurement “the default risk of a bond is periodically measured via certain credit metrics and performance indicators” (Montazerhodjat et al. 2016; p.411). Dynamic leverage and dynamic risk measurement together facilitate the construction of “a time-varying securitization structure that reflects the evolving nature of the portfolio’s assets and optimizes the fund’s capital structure accordingly” (Montazerhodjat et al. 2016; p.411).
In a nutshell thus, dynamic leverage allows the concept of the megafund to be extended “[allowing] for time-varying amounts of debt or ‘dynamic leverage’, which can accommodate the startup phase of a fund focused purely on preclinical R&D and early-stage translational medicine” (Montazerhodjat et al. 2016; p.411).

According to Montazerhodjat, orphan drugs are “particularly well-suited for dynamic leverage because these therapies are relatively new and not likely to be able to generate much cash flow at fund inception” (Montazerhodjat et al. 2016; p.411).

4.3.2 Non-capital market financing mechanisms

In the following three sections financing models categorized as non-capital market financing mechanisms will be explained.

4.3.2.1 Royalty payments

In Workman’s new pathway for effective R&D the financial part consists of the idea that the “academic drug discovery and development units could be sustained in this model by receiving royalties on sales of the [medicines] they originated” (Workman et al. 2017; p.582). Furthermore, they say that setting up “a collection of academic centers with required scale and expertise that would produce significant numbers of drug candidates” (Workman et al. 2017; p.582) […] together with “generics partners or newly created commercial entities will create competition and drive down prices in conventional pharma and biotech” (Workman et al. 2017; p.582).

In Antoñanzas et al. conducted a simulation for an alternative system that is “based on royalty payments [proportional to number of sales] to the patent owner in exchange for the right to market the innovative drugs under competitive conditions” (Antoñanzas et al. 2014; p.618). In the royalty-based system the price would be “equal to the marginal cost” (Antoñanzas et al. 2014; p.619). Finally, they “compare the social welfare yielded by both systems, the patent system and the [royalty-based system]” (Antoñanzas et al. 2014; p.618).

The simulation of Antoñanzas et al. is based on certain proposals that aim to suggest alternatives to the patent system. For instance, Antoñanzas et al. refer to Grootendorst et al. who “described different schemes to facilitate access to new drugs worldwide based on royalties and rewards” (Antoñanzas et al. 2014; p.618). In the scheme based on royalties, “firms would bid for royalty rates, the lowest bid winning the auction” (Antoñanzas et al. 2014; p.618). In the scheme based
on rewards, “rewards would [function] similar to government subsidies aiming to create commercial incentives” (Antoñanzas et al. 2014; p.618) for R&D. They also mention Kremer who suggested “patent buyouts by governments as a mechanism to keep patents in the public domain, with the expectation that they would provide incentives for R&D activities and facilitate market access to innovations” (Antoñanzas et al. 2014; p.618).

The general idea of the prize system is - along with decoupling the cost of R&D from the price of the medicine – to “reward innovations based on their positive impact on health” (Antoñanzas et al. 2014; p.618). Pharmaceutical sales representatives (also called ‘detailing’) “would not be necessary” (Antoñanzas et al. 2014; p.621) and hence, “marketing costs would be saved” (Antoñanzas et al. 2014; p.621). Antoñanzas et al. underline that “detailing costs will not be covered in a competitive setting when the price of the product equals production marginal cost (as it currently happens with generic drugs in developed countries where no marketing efforts are done)” (Antoñanzas et al. 2014; p.621).

The royalty-based system would be implemented through “a planner managing a fund created with contributions from institutions in the North and South” (Antoñanzas et al. 2014; p.621). The contributions going into this fund would be used to pay the patent holder “for allowing the drug to be marketed under competitive conditions” (Antoñanzas et al. 2014; p.621). Naturally, in order to ensure the well-functioning of the new royalty-based system “it should be accepted by all the parties involved” (Antoñanzas et al. 2014; p.621).

They conclude that “if the extra benefits per patient obtained under the royalty-based system are lower than the regulated price, then the patent system is preferred only for high enough values of the shadow price of public funds needed to finance the new system. Otherwise, the system based on royalty payments dominates in terms of welfare” (Antoñanzas et al. 2014; p.625). The ‘shadow price’ is here the “public funds needed to finance the royalties” (Antoñanzas et al. 2014; p.617). As the benefits per patient reached will depend upon the medicine, one cannot generally conclude that the royalty-based system is better or worse than the patent system. Hence, for medicines that reach high benefits per patient and where the total treatment costs and the shadow price is comparably lower, thus, yielding higher social welfare, the new royalty-based system should be used. In the opposite case, thus for medicines, “for which the patent system dominates from a global welfare perspective, some compensatory policies may be needed to facilitate access to […] innovative [medicines]” (Antoñanzas et al. 2014; p.624). In the opposite case, thus for medicines, “for which the patent system dominates
from a global welfare perspective, some compensatory policies may be needed to facilitate access to [...] innovative [medicines]” (Antoñanzas et al. 2014, p.624).

4.3.2.2 International pooled fund

There have been several proposals demanding an international fund for collecting revenues for R&D. The funds proposed differ in their name but differ only slightly in their characteristics. For instance, Outterson et al. propose a pooled fund that is filled by revenues through a “treaty or a WHO regulation” (Outterson et al. 2016; p.2) with “legal and financial commitment mechanisms” (Outterson et al. 2016; p.2). In their proposal “funding should be spent in line with agreed global priorities” (Outterson et al. 2016; p.2). Moreover, they point out, although “most of [the] funding will be under the control of national governments, a substantial proportion should be allocated to a pooled funding mechanism coordinated globally, given that parts of it will need to cover delinkage rewards” (Outterson et al. 2016; p.2).

Furthermore, Outterson et al. state that “complete financial participation from a large number of countries may not be necessary to initiate a new business model” (Outterson et al. 2016; p.2-3). They say that “a contribution of 0.01% of GDP from the Organization for Economic Cooperation and Development (OECD) countries alone could yield between US $4 billion and US $5 billion annually” (Outterson et al. 2016; p.3). Also, Stirner says that in an “International Medical R&D Treaty” (Stirner 2008; p.402) all parties would commit to “spend a percentage of the national income on medical R&D (Stirner 2008; p.402).

In a follow-up report of ‘CEWG on R&D: Financing and Coordination’ they refer to a ‘voluntary pooled fund’ (WHO 2016). They say that such a fund could be financed through contributions from member states, contributions from the private sector or through bonds (WHO 2016). As the CEWG suggests such an international pooled fund could be thus either envisioned by voluntary contributions paid or as Outterson et al. indicated by “legal and financial commitment mechanisms” (Outterson et al. 2016; p.2) that are hence binding. In the following sections one term will be used – that is ‘International Pooled Fund’ – to refer to the types of funds that Outterson et al, Stirner and CEWG suggest since they all have the same main characteristic that is an international fund.
4.3.2.3 Health Impact Fund

According to Banerjee and Pogge, “the current patent monopoly rights under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement have widened the health gap within developing countries as well as that between developing and high-income countries” (Banerjee & Pogge 2010; p.241), they admit though that beyond patent protection and drug affordability there are other factors, which hinder access (Banerjee & Pogge 2010).

In order to react on these access problems Banerjee and Pogge suggest a Health Impact Fund (HIF) “as a complement to the existing intellectual property regime” (Banerjee & Pogge 2010; p.241). The idea is that HIF would function as a global agency, which would be financed through taxes by governments from all around the world. The HIF would “offer pharmaceutical innovators […] to register any new product” (Banerjee & Pogge 2010; p.241). Upon registration the innovator would receive “for a defined period (e.g. 10 years), a share of fixed annual reward pools” (Banerjee & Pogge 2010; p.241). The rewards paid would be “in proportion to their respective contributions to global health […] estimated with a global health impact assessment exercise” (Banerjee & Pogge 2010; p.241). In exchange for the reward payments, the innovator “would agree to sell the medicine wherever it is needed at no more than the lowest feasible cost of production and [cost of] distribution” (Banerjee & Pogge 2010; p.241). Moreover, when the reward period has come to an end, the innovator would offer in the case that patents are still valid, “free licences to enable generic manufacture and sales” (Banerjee & Pogge 2010; p.241).

According to Banerjee and Pogge a “multi-disciplinary group of international experts” (Banerjee & Pogge 2010; p.241) works on defining “the health impact assessment tools that the HIF would use and on designing pilot projects in low- and middle-income country settings” (Banerjee & Pogge 2010; p.241).

In their paper they outline moral arguments “for reforming the existing rules governing pharmaceutical innovation” (Banerjee & Pogge 2010; p.241). They admit that in a free market setting “it would be irrational to undertake the labours of developing a new medicine because innovators could not recoup their research and development expenses, because of competing suppliers who cheaply reverse-engineer their innovation” (Banerjee & Pogge 2010; p.241). Thus, in this sense TRIPS is better. However, they say that “we can do much better still, by the same standard” (Banerjee & Pogge 2010; p.241). They argue that this could be done if we moved from ‘TRIPS-pure’ to ‘TRIPS+HIF’. Thus, in the TRIPS+HIF, the HIF would function as “a complementary reward mechanism” (Banerjee & Pogge 2010; p.241).
Shortly summarized amongst the reasons they give for TRIPS+HIF as an improvement of TRIPS-pure, is that the HIF would manage to “attract more pharmaceutical research toward diseases concentrated among the world’s poor” (Banerjee & Pogge 2010; p.241). Also, HIF-registered medicines “would be sold at the lowest feasible [cost of production and cost of distribution] and would therefore be affordable from day one even to poor patients” (Banerjee & Pogge 2010; p.241). Furthermore, the “HIF would greatly enhance the incentives [for] innovators to create and support the conditions – proper drug storage, diagnosis, prescribing, adherence – that allow their registered product to have its optimal effects” (Banerjee & Pogge 2010; p.241). Banerjee and Pogge argue that the current TRIPS-pure system rewards only the selling of medicines, whereas in the TRIPS+HIF system whereas TRIPS+HIF would give incentives to “ensure that [a medicine is] actually used, to optimal effect, by patients who really need them” (Banerjee & Pogge 2010; p.242) and that an effective and safe medicine actually reaches the patient, which is not a given in developing countries (Banerjee & Pogge 2010).

Banerjee and Pogge say that innovators would have “a powerful profit motive to help overcome any obstacle between this medicine and its optimal health impact” (Banerjee & Pogge 2010; p.242). According to them, innovators would thus “profit maximally if its product were to wipe out the disease completely” (Banerjee & Pogge 2010; p.242).
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4.4 New pathways for effective R&D

In the following sections five new pathways for effective R&D will be described.

4.4.1 Academia-based research combined with generic-like companies

According to Workman cancer medications are often administered to patients without having checked first through biomarkers who of them would benefit from a certain cancer medicine. This drives costs up. Workman et al. say that “biomarkers are critical, as they represent a handle to control drugs costs to society” (Workman et al. 2017; p.580). They demand that regulatory bodies “should set standards for drug approval employing validated and clinically useful biomarkers for patient selection” (Workman et al. 2017; p.580). As a result, this will save costs and “will prevent patients being treated with toxic drugs that do not improve survival and/or quality of life” (Workman et al. 2017; p.580).

Workman et al. underline that much crucial research “that formed the basis for new categories of cancer drugs [was] made by academia” (Workman et al. 2017; p.580) and give many examples for this. They say that “to further develop these academic discoveries, the traditional model of self-supporting research investigators who drive their independent research programs needs to be complemented by concerted multidisciplinary team efforts that are adequately financed and staffed with scientists having all the required expertise to enable drug discovery” (Workman et al. 2017; p.580). They give as key advantage of academic drug discovery “the freedom and indeed incentivization to tackle major challenges that would be viewed as too risky by big pharma and even by many biotech companies” (Workman et al. 2017; p.581). Workman et al. point out a number of reasons why academia could continue to make a remarkable impact in drug discovery (Workman et al. 2017).

Workman et al. also offer three explanations for why academic drug discovery usually stops at “at the stage of clinical testing” (Workman et al. 2017; p.581). First of all there is the quality control “over the large-scale manufacturing of clinical grade drugs and their formulation” (Workman et al. 2017; p.581), which is “not a routine skill of academic groups” (Workman et al. 2017; p.581). The second major problem is funding the significant cost of “performing non-clinical regulatory toxicology studies and clinical trials” (Workman et al. 2017; p.581), which is funds that are hardly attainable “by non-profit organizations” (Workman et al. 2017; p.581).
Finally, academia is “not equipped to handle marketing and sales of approved drugs” (Workman et al. 2017; p.581).

They say that the point when “the interests of large pharma [aiming] to maximize return on investment” (Workman et al. 2017; p.581) and “the typically idealistic motivation that drives most academics […] to solve important problems in oncology” (Workman et al. 2017; p.581) show to be “diagonally disparate” (Workman et al. 2017; p.581) is at the stage of commercialization. However, until today academics are usually “driven into the arms of big pharma after initial proof of concept clinical trials” (Workman et al. 2017; p.581). So far, academic researchers have no means to “influence the pricing of ‘their’ drugs when they reach the market” (Workman et al. 2017; p.581). They say that occasionally there is “charities funding later stage trials, but […] academic drug discovery cannot rely on charity funding only to bring their candidates to patients” (Workman et al. 2017; p.581).

Now, the proposal of Workman et al. next to making increased used of biomarkers consists in “partnering with generic drug makers or new companies” (Workman et al. 2017; p.583) that are similar to the already existing “generic drug makers” (Workman et al. 2017; p.583) in that they are “used to working with lower profit margins” (Workman et al. 2017; p.581). Hence, these companies might be “one potential partner to develop highly innovative, but de-risked, [medicines] from academic drug discovery and development” (Workman et al. 2017; p.581). They argue that “especially when the [medicines] have a strong mechanistic rationale and an associated biomarker of response (key aspects of academic drug development), the registration trials can be small and the success rate much higher than in traditional pharma trials” (Workman et al. 2017; p.581). Consequently, medicine prices could be significantly more sustainable than currently. As the European Medicines Agency (EMA) is “open to novel ways of [medicine] approval” (Workman et al. 2017; p.581) offering an “adaptive licensing program enabling companies to obtain marketing authorization approval on the basis of a small well designed, biomarker supported trial” (Workman et al. 2017; p.581-582).

Workman et al. give two critical points to consider to make this new pathway based on generic-like companies successful. The first point is that “academic organizations will need to abide by their societal responsibility and resist the temptation to sell their drug candidate to the highest bidder” (Workman et al. 2017; p.582). Second, “it will be imperative that agreements on price caps are part of the negotiations with potential investors or with companies that take forward [medicines] arising from academic drug development” (Workman et al. 2017; p.582).
argue that taking the “substantial de-risking achieved prior to commercialization, our model should be attractive to these parties and their investors” (Workman et al. 2017; p.582).

4.4.2 Open Source pathways

The Results for Development Institute (R4D) performed a “high-level review of open source drug discovery projects aimed at neglected diseases” (Ardal & Rottingen 2012; p.2). From this review results a definition for an ‘open source’ project. According to R4D a project must have the following attributes “in order to be considered open source” (Ardal & Rottingen 2012; p.2):

1. The project’s data must be open access, meaning that anyone can view the data free-of-charge.
2. The project must provide a forum for open collaboration (across organizational and geographical boundaries).
3. The project must be governed by a set of rules that mandates the project’s “openness” (Ardal & Rottingen 2012; p.2):

According to Ardal and Rottingen, “three similar concepts [that are…] open access, open innovation and crowdsourcing […] are often confused with ‘open source’” (Ardal & Rottingen 2012; p.2). ‘Open access’ “means that anyone can view, copy or distribute some form of content […] free-of-charge” (Ardal & Rottingen 2012; p.2) while open access does not allow modifying content. Whereas ‘open innovation’ “is […] the use of external sources of R&D” (Ardal & Rottingen 2012; p.2). The latter “may include paying royalties to the innovator” (Ardal & Rottingen 2012; p.2) and besides it “does not necessitate any type of transparency or commons formation” (Ardal & Rottingen 2012; p.2). Finally, ‘crowdsourcing’ according to Ardal and Rottingen is “the use of volunteers to perform a specified task” (Ardal & Rottingen 2012; p.2).

4.4.3 Virtual Knowledge Bank

There is a trend towards adopting “open innovation practices, with sharing of clinical trial data” (Evangelatos et al. 2016; p.211). Evangelatos et al. say that due to the free rider problem however, “clinical trial data sharing among biopharmaceutical companies could undermine their innovativeness” (Evangelatos et al. 2016; p.211). Evangelatos et al. “developed a commons arrangement and devised a model, which enables secure and fair clinical trial data sharing over a Virtual Knowledge Bank based on a web platform” (Evangelatos et al. 2016;
According to them they developed this “based on the theory of public goods” (Evangelatos et al. 2016; p.211). In this approach thus, data is seen “as a virtual currency” (Evangelatos et al. 2016; p.211) and knowledge is treated as a ‘club good’. They refer to knowledge as a club good since the “transformation of information to knowledge requires certain capabilities” (Evangelatos et al. 2016; p.214), thus knowledge “is not a common-pool resource, but rather a club good” (Evangelatos et al. 2016; p.214).

Evangelatos et al. say that “within the strong intellectual property rights environment of the biopharmaceutical industrial sector, sharing of clinical data has mainly taken the form of Public Private Partnerships (PPP) between publicly funded research institutions and private biopharmaceutical companies” (Evangelatos et al. 2016; p.212). According to Evangelatos et al. the European Federation of Pharmaceutical Industries and Associations (EFPIA) also supports “open innovation practices, in the form of clinical trial data sharing” (Evangelatos et al. 2016; p.212-213). However, in the EFPIA approach “clinical trial data is being shared one way, from a biopharmaceutical company to a researcher” (Evangelatos et al. 2016; p.213). Evangelatos et al. argue that “radically advanced open innovation business models, in the form of Private Private Partnerships (PrPrP) between biopharmaceutical companies […] are still missing” (Evangelatos et al. 2016; p.213).

The main driver that has so far hindered pharmaceutical companies from sharing “their R&D data (in the form of clinical trial data) with other companies and benefit from the sharing” (Evangelatos et al. 2016; p.213) is that they are concerned that this would decrease “their intellectual rights, proprietary interests, and competitiveness” (Evangelatos et al. 2016; p.213). Thus, “sharing of clinical trial data could undermine patentability” (Evangelatos et al. 2016; p.213). This can also be “summarized as the risk of free riding on the efforts of others” (Evangelatos et al. 2016; p.213). Hence, open access to a pharmaceutical company’s data “would render [the company] vulnerable to competitors’ free riding on their R&D investments” (Evangelatos et al. 2016; p.213).

Evangelatos et al. argue that „knowledge in the era of Omics and Big Data has been increasingly conceptualized as a public good” (Evangelatos et al. 2016; p.218). Also, “research in the era of Omics (genomics, epigenomics, proteomics, metabolomics, exposomics, etc.) [generates] vast amounts of diverged data in electronic format” (Evangelatos et al. 2016; p.213).

Evangelatos et al. say that advances “in the field of information and communication technology […] have reduced the transaction costs for pooling and sharing information resources to a
minimum” (Evangelatos et al. 2016; p.213). They say that “taking into account the individuals’ self-interested willingness to pay, the main challenge is to devise the appropriate practical arrangements which allow one party to benefit without causing more harm (in absolute terms of value) to the other contracting party” (Evangelatos et al. 2016; p.214).

Thus, in order to overcome the free riding problem they propose “the construction of a web-based platform for the exchange of data (genomics, epigenomics, proteomics, metabolomics, exposomics, etc.) from clinical trials” (Evangelatos et al. 2016; p.214). Therein the web-based platform would work as a Virtual Knowledge Bank (VKB) “where clinical trial data in electronic format is stored as information resources” (Evangelatos et al. 2016; p.214). Depositors would be “private for-profit biopharmaceutical companies entitled to deposit and also withdraw information resources […] from the VKB” (Evangelatos et al. 2016; p.214).

To ensure overcoming the free-rider problem, “transactions will be regulated by applying only one (excludability) criterion: companies will be allowed to download the same amount of data, quantitatively and qualitatively, which they upload” (Evangelatos et al. 2016; p.214). This means that “information resources, in the form of clinical trial data, are being used as a currency for carrying out transactions” (Evangelatos et al. 2016; p.214). Thus, by “treating knowledge as a club good, [their] model facilitates knowledge transfer without an impact on the intellectual property rights of the involved companies” (Evangelatos et al. 2016; p.214). They add that the involved companies “do not patent knowledge in the form of clinical trial data but rather applied knowledge in the form of medicinal formulas, etc.” (Evangelatos et al. 2016; p.214-215).

To make their model work in reality they explain many challenges that will have to be overcome. According to Evangelatos et al. the European Alliance for Personalized Medicine (EAPM) will be working on this and create solutions. One of the challenges mentioned is for instance, that “not all stakeholders who want to benefit from such a Biobank might have the same amount of data” (Evangelatos et al. 2016; p.216). Also there will be security concerns, but these “can be addressed as exemplified by the BioGrid Australia platform where security and encryption is a core part of the implementation” (Evangelatos et al. 2016; p.217).

The BioGrid Australia platform was “designed for sharing of research data” (Evangelatos et al. 2016; p.215). On this platform, “each member can request access to data” (Evangelatos et al. 2016; p.215), however, “each member and collaborator stores and retains control of their data including granting access” (Evangelatos et al. 2016; p.215). Thus, “authorization is given by the ‘key holder’, a person nominated by the owning party of the respective data” (Evangelatos
et al. 2016; p.215). Another important difference to the BioGrid Australia model compared to the envisioned functioning of the VKB is that in the BioGrid Australia model “any member [is allowed] to receive any amount and kind of data within the network based on permission of the owning party” (Evangelatos et al. 2016; p.215). Thus, the BioGrid Australia model “does not include a mechanism to manage depositing data in return for getting access to already stored data” (Evangelatos et al. 2016; p.215).

Evangelatos et al. say that their “model of data sharing is compatible with the moral obligation to treat clinical trial data as public goods without, however, compromising the intellectual property rights of the involved biopharmaceutical companies” (Evangelatos et al. 2016; p.217). They also state that their model “introduces fair trade in the field of clinical trial data sharing” (Evangelatos et al. 2016; p.217) and that “apart from responding to the ethical obligation towards the public good, [their] model fosters innovation in many ways” (Evangelatos et al. 2016; p.217). Evangelatos et al. argue that “regulated sharing of clinical trial data enhances the innovation capacity of the biopharmaceutical companies and promotes the innovativeness of the sector as a whole” (Evangelatos et al. 2016; p.217).

As “every transaction increases the property of the bank […] there are] more possibilities to find […] answers to […] problems” (Evangelatos et al. 2016; p.217) at an affordable cost. Evangelatos et al. assume that “especially small biotechnology companies, the majority of which conduct basic research or clinical trials up to phase II, [will] profit by engaging in transactions over the virtual bank” (Evangelatos et al. 2016; p.217). They say that “large biopharmaceutical companies [would] also benefit since they can acquire data from competitors working on similar areas, a fact that will allow them to reorientate their research efforts accordingly, thus reducing the high attrition rates of the drug development process” (Evangelatos et al. 2016; p.218).

Importantly also “R&D efforts of the past, which did not find their way to the market as a new medicine or diagnostic device, can find new uses as a currency used to acquire data, which are of use for current R&D efforts” (Evangelatos et al. 2016; p.218). Consequently, “R&D costs for the development of a new medicine or devise are in effect being reduced” (Evangelatos et al. 2016; p.218). According to Evangelatos “[their] group in the EAPM is currently working, in cooperation with representatives of the biopharmaceutical industry, to resolve the [challenges mentioned] and to develop the web-based platform” (Evangelatos et al. 2016; p.218).
They say that their model results in a “fair sharing of clinical trial data over the Virtual Knowledge Bank [that] has positive effects on the innovation capacity of the biopharmaceutical industry without compromising the intellectual rights, proprietary interests and competitiveness of the latter” (Evangelatos et al. 2016; p.211)

4.4.4 Open Source Drug Discovery

Similar to the model described by Evangelatos et al. is the pathway described in Bhardwaj et al. The focus is again on the sharing of research data. However, differently from Evangelatos et al, Bhardwaj et al. describe a model for the sharing of data especially for the R&D of medicines targeting diseases that have the highest burden of disease in developing countries (Bhardwaj et al. 2011).

The so-called ‘Open Source Drug Discovery’ (OSDD) project was initiated by the ‘Council of Scientific and Industrial Research, India’ in 2006 and the first project to tackle Tuberculosis “was launched for global participation in 2008” (Bhardwaj et al. 2011; p.480). It is meant to foster “wide participation across geographical borders” (Bhardwaj et al. 2011; p.479) and to bring together “expertise from diverse fields” (Bhardwaj et al. 2011; p.479).

“Since the interventions are community generated, the new chemical entities” (Bhardwaj et al. 2011; p.479) originating from OSDD “will be taken up for clinical trial in a non-exclusive manner [through the] participation of multiple companies with majority funding from [OSDD]” (Bhardwaj et al. 2011; p.479). Hence, the resulting medicines will be available at low-cost. Bhardwaj et al. argue that the major progress OSDD has made over the last years makes it “an alternate model [to the] Intellectual Property Rights (IPR) protected closed-door drug discovery” (Bhardwaj et al. 2011; p.480). OSDD’s aim is “to reduce the risks in the discovery stage by facilitating collaborations between scientists, doctors, technocrats and students through a collaborative platform” (Bhardwaj et al. 2011; p.480).

In their “alternate paradigm of drug discovery process” (Bhardwaj et al. 2011; p.479) a “web-based platform where experts from academia, industry including individuals from varied subject areas can interact and contribute to solve complex problems associated with discovering novel therapies” (Bhardwaj et al. 2011; p.480). Their platform is the ‘SysBorg TB (Systems Biology of organisms) portal’ on which “all data of OSDD are shared with the entire community” (Bhardwaj et al. 2011; p.480). With “all data” they also refer to “methods,
procedures, algorithms and scripts [which] are available for use, reuse and modification for further activities within the purview of [the] OSDD License (Bhardwaj et al. 2011; p.480).

According to Bhardwaj et al. “the information available online on the OSDD portal is regarded as a ‘Protected Collective Information’ by the OSDD sign-in license” (Bhardwaj et al. 2011; p.480). This means that “anyone is free to contribute to or use this community property but the obligation that all improvements and value additions are contributed back to the community” (Bhardwaj et al. 2011; p.480). Hence, different facets from “computational biology, bioinformatics, systems biology, molecular biology, chemo-informatics, medicinal chemistry [and] experimental pharmacology can be integrated into the “drug discovery process without time delay” (Bhardwaj et al. 2011; p.480). Furthermore, the platform also facilitates the “online review of work done and [the] sharing [of] information on both successful and failed experiments among the members of the community” (Bhardwaj et al. 2011; p.480). Then “as the methods and results are […] available, other investigators can modify or improve them in order to achieve better results” (Bhardwaj et al. 2011; p.480).

When a new contribution “is added, the RDF [Resource Description Framework] store also updates the semantic links to different other nodes already in the system” (Bhardwaj et al. 2011; p.480). This way, “credit points are calculated automatically by a micro-attribution algorithm” (Bhardwaj et al. 2011; p.480). Bhardwaj et al. suggest that rewards could be given based on the credit points “accrued over time for all the contributions” (Bhardwaj et al. 2011; p.481).

In Bhardwaj et al’s model when the research part has been completed, the “development work is carried out in countries where the disease is endemic, but where the framework such development at internationally acceptable standards exist” (Bhardwaj et al. 2011; p.481). Clinical trials are conducted with “public funded hospitals in collaboration with doctors, who are willingly joining […] which will bring costs down” (Bhardwaj et al. 2011; p.481) and in collaboration with “CROs [contract research organizations] specialized in clinical trials” (Bhardwaj et al. 2011; p.481) to ensure that all “internationally accepted standards are maintained” (Bhardwaj et al. 2011; p.481).

In the OSDD model data exclusivity is not maintained “and the data from clinical trials [ensuring that all ethical standards are followed] will be made public, bringing openness to [the] clinical trial process” (Bhardwaj et al. 2011; p.481). Furthermore, “contributors can apply and seek intellectual property protection on the condition that these are made available to the developing world through a non-exclusive license” (Bhardwaj et al. 2011; p.481). In order to
have a long-term reach and to facilitate participation “to younger students […] OSDD has adopted 21 university-colleges” (Bhardwaj et al. 2011; p.482). Each of them is called ‘CSIR (Council of Scientific and Industrial Research) Center for OSDD’ (Bhardwaj et al. 2011).

According to Bhardwaj et al. “the OSDD community has posted more than 180 different projects” (Bhardwaj et al. 2011; p.482). Ardal and Rottingen state it has “54 molecules in process” (Ardal & Rottingen 2012; p.4) and explain further accomplishments. The TB research projects were financed by the Government of India spending approximately US $11 million (Bhardwaj et al. 2011).

Ardal and Rottingen point out that critically seen, OSDD is not open source but crowdsourcing since it relies on volunteers (Ardal & Rottingen 2012). However, Ardal and Rottingen analysed another project that is ‘The Synaptic Leap’s Schistosomiasis’ (TSLS) project which they classified as open source project. TSLS aim was “to generate the off-patent schistosomiasis drug, praziquantel” (Ardal & Rottingen 2012; p.7). This project was funded by both the WHO and the Australian Government and completed in 2011 (Ardal & Rottingen 2012).

### 4.4.5 Managing the public sector’s intellectual property

In the context of the introduction of Human Papillomavirus (HPV) vaccine in developing countries, Crager et al. say that the HPV vaccines were developed by Merck and GlaxoSmithKline while the “initial development of currently available HPV vaccines took place at a number of universities and other publicly funded institutions, yet there is little low-cost access to the vaccine in developing countries where access would be most critical” (Crager et al. 2009; p.253). Furthermore, they say that this situation “is the rule rather than the exception with most university-discovered medicines” (Crager et al. 2009; p.253). Crager et al. argue that “universities and other publicly-funded institutions can adopt a number of licensing methods to ensure that vaccines discovered on their campuses are available at low-cost in developing countries” (Crager et al. 2009; p.253).

Mahoney et al. argue that “it has not been well understood why IP management is important and how such management by public sector groups can best be conducted” (Mahoney et al. 2004; p.786). They say that “the public sector needs to increase its sophistication in IP management and needs to identify and implement strategies that will help the public sector to achieve its public health goals” (Mahoney et al. 2004; p.786). According to Mahoney et al. “it is not patents that create monopolies but rather the way in which patents are managed that can
create monopolies” (Mahoney et al. 2004; p.789). They suggest that “with creative licensing strategies the public sector can help to foster competition and prevent the formation of cartels, which, [in their view], is perhaps the best way of reducing prices” (Mahoney et al. 2004; p.789). They believe, “that it is clear that good IP management by public sector research and development organizations is essential to ensuring the availability of safe, effective and affordable [medicines]” (Mahoney et al. 2004; p.791). The UK-based Centre for the Management of IP in Health R&D (MIHR) “will undertake a range of programs to assist organizations involved with health R&D to manage IP to help overcome the inequities of cost and availability” (Mahoney et al. 2004; p.791).

4.5 Supportive tools for assuring access

As the major focus of this work is not on supportive tools for assuring access but on alternative financing mechanisms for R&D and new pathways for effective R&D here the supportive tools will only be explained very briefly.

4.5.1 Reimbursement decision-making tools

MCDA. MCDA “is increasingly used for health technology assessment (HTA)” (Martelli et al. 2016). Also, it can be defined as “a decision-making tool with increasing use in the healthcare sector, including HTA” (Drake et al. 2017).

Cost-effectiveness studies. Cost-effectiveness studies are also referred to as cost effectiveness analyses and they “can help inform policy makers on better ways to allocate limited resources” (Bell et al. 2006; p.1). For instance, the “quality adjusted life year (QALY) is used to compare the effectiveness of a wide range of interventions” (Bell et al. 2006; p.1).

4.5.2 Market introducing tools

HealthCoin. The concept of ‘HealthCoin’ has been developed from the perspective of payer organizations and especially for the US healthcare system context. It concerns payer organizations (i.e. Medicare) in that “even if [the payers] access credit markets to finance the high costs of cures, it cannot exclude other payers to enjoy the benefits of cure if patients decide to change insurance plans. Here, although the original payer is foregoing the subsequent value of cure for these patients, it is not getting anything in return for their upfront investment in the cure” (Basu 2015; p.2).
Hence, “no one payer can appropriate the full value of the cure – a classic ‘free-rider problem’” (Basu 2015; p.2). Basu says that this problem then leads to “under-provision of cures and under-investment in innovation” (Basu 2015; p.2).

Basu et al. say that Health Coin would constitute „a tradable new currency […] that would convert the incremental consequences produced (but not the upfront costs incurred) by curative treatments to a common numeraire, such as health stock units, life-years equivalents, or some other metric“ (Basu et al. 2016; p.861). Consequently, “health plans would give serious considerations to the upfront costs of cures and the returns on their investments in the form of Health Coins, which they can now trade” (Basu 2015; p.3).

**Reinsurance.** Reinsurance “is where insurers seek insurance of their own to cover catastrophic pay-outs. Reinsurance could theoretically offer a short-term option for the first few gene therapies, but concerns were raised at the Policy Forum that commercial reinsurers may look to exclude such high-cost therapies. In addition, stakeholders believe that the reinsurance model will not work well over the long term given how quickly future risk will be priced into the premium” (Hampson et al. 2018; p.20).

**Annuity payments.** Annuity payments are a “mechanism, whereby a constant amount of money is paid to manufacturers per year for a specified period of time (or in perpetuity)” (Jorgensen & Kefalas 2017; p.4). Consequently, “this reduces the annual budget impact for payers, as well as the uncertainty around long-term performance and value” (Jorgensen & Kefalas 2017; p.4). This is also since, “payments can be discontinued if the patient does not sustain the desired response” (Jorgensen & Kefalas 2017; p.4). Hence, “the manufacturer assumes the risk associated with the uncertainty around longer-term claims” (Jorgensen & Kefalas 2017; p.4).

**Amortization.** Amortization is a “mechanism for paying for a large upfront cost by making a number of smaller payments over a period of time […] An example of an amortization mechanism in health care can be found in Spain, where the national government announced low-interest loans for regional payers to fund high-cost HCV therapies” (Hampson et al. 2018; p.21). This mechanism may thus “help to align the cost of the cure with its long-term economic benefits […] payers to fund the treatments whilst balancing their budgets within a single year” (Hampson et al. 2018; p.21).
**Managed-Entry Agreements (MEA).** MEA are “a set of instruments to facilitate access to new medicines, which are now relatively well-established in a number of OECD (Organization for Economic Cooperation and Development) countries” (Ferrario et al. 2017; p.2). Although there is a large variety of MEAs, they can generally be classified into financial agreements and performance-based agreements (also called health-outcome based agreements). The latter are also often referred to as ‘risk-sharing agreements’ (RSA) (Ferrario et al. 2017).

“Despite [the diversity of MEAs], all these agreements have a common objective—to facilitate access to new medicines in a context of uncertainty (around effectiveness and/or use in real-life) and high prices” (Ferrario et al. 2017; p.2). MEAs have been used particularly in an effort of dealing with “high prices for new medicines, [especially] those for cancer and orphan diseases” (Ferrario et al. 2017; p.2), the environment of finite financial resources that payers are exposed to, the “uncertainty regarding the effectiveness of new medicines in routine clinical care (real-life)” [and finally] “the willingness to address unmet need” (Ferrario et al. 2017; p.2).

**Adaptive pathways.** Adaptive pathways “can be defined as a planned, progressive approach to bringing a medicine to patients. It is not a new route of marketing authorisation; it makes use of existing regulatory tools. Under this approach, the medicine will first be authorised in a small patient population that is likely to benefit most from the medicine. Then, additional evidence is gathered over time resulting in progressive licensing adaptations to extend or restrict the previously authorised indications of the medicine” (EMA 2016).

**Priority review vouchers.** Priority review vouchers originated in the US where the “U.S. Congress created the priority review voucher program in 2007 to encourage development of drugs for neglected diseases. Under the voucher program, the developer of a drug for a neglected or rare pediatric disease that is approved by the U.S. Food and Drug Administration receives a bonus priority review voucher for another drug” (Ridley 2017). Priority review vouchers have also been proposed for the European Union. However, different from the US voucher system “a European voucher would also accelerate pricing and reimbursement decisions” (Ridley & Sánchez 2010).
4.5.3 IP-related tools

**Patent-buyouts.** Patent-buyouts sometimes also referred to as ‘auctions’ involve the “buy-outs of medicine patents” (UNITAID 2016; p.52). Consequently, after the buy-out the medicine could be available at marginal cost and thus is a delinkage approach (UNITAID 2016). Kremer proposed an auction system “in which the government purchases most drug patents and places them in the public domain” (Baker 2004; p.3).

UNITAID says that “where the cost of patent buy-out is significant, it may be possible to devise a long-term financing scheme for the buy-out, in the way that governments consider selling bonds to pay for investments in transportation infrastructure […]” (UNITAID 2016; p.52).

**Intellectual property, technology, and know-how (IPTK) bank.** Crager et al. discussed in 2009 a possible framework called ‘Patents, Materials, and Know-how Pool’ (PMK Pool). Later in 2014 Crager proposes an IPTK bank “as a new approach to facilitate widespread access to new vaccines in low- and middle-income countries by efficient transfer of patented vaccine technologies to multiple developing-country vaccines manufacturers” (Crager 2014; p.e85). She explains that an IPTK bank “would bring together the necessary intellectual property rights, manufacturing process information, know-how, and regulatory expertise into a single platform that could be licensed as a package with associated training modules” (Crager 2014; p.e88). Furthermore, “a licensing approach similar to that used by the MPP [Medicines Patent Pool] would be employed to address intellectual property barriers by creating a structure whereby the patented technology could be disseminated to multiple DCVMs [developing-country vaccine manufacturers], each paying royalties to the patent holder. The manufacturing process information, know-how, and regulatory expertise would be brought together through the organization hosting the IPTK bank” (Crager 2014; p.e88).

The **Medicines Patent Pool (MPP).** The MPP was created “with the support of UNITAID in 2009, aims to enable the affordable production of HIV drugs still under patent protection by obtaining voluntary licenses from patent holders and making these licenses available to generic companies in LMICs. Through the MPP, licenses to all patents required to produce a given end product are provided as a package to multiple generic manufacturers on a nonexclusive basis. These manufacturers must meet quality, safety and efficacy standards, and must have access to markets that are large enough to achieve economies of scale and generate major price reductions. Royalties will be paid to patent holders, and generic licenses will be for use only in
LMICs, thereby avoiding infringement upon the main target markets of brand-name manufacturers” (Crager 2014; e87).

**Compulsory license.** A ‘compulsory license’ “is an authorization which is granted by the government without the permission of the patent holder. Most countries have provisions for compulsory licenses, either under their patent law or, as in the US, through anti-trust legislation. Under the TRIPs [Trade-Related Aspects of Intellectual Property Rights] Agreement, countries have the right to issue such licenses. While the Agreement does not limit the grounds - or reasons - for granting compulsory licenses, countries can only use those grounds which are allowed by their national legislation” (WHO 2000). According to the World Trade Organization (WTO), it is “one of the flexibilities in the field of patent protection included in the WTO’s [TRIPS Agreement]” (WTO 2018).

4.5.4 Collaborations concerning high-income countries

**Triple Helix.** By Triple Helix is meant a cooperation for innovation between three different parties – that are government, universities and industry. It requires the active involvement of the three parties in form of a partnership (European Union 2018). “An example of the Triple Helix model of innovation is the development of radiotherapy innovations by the Karolinska university hospital in Sweden, together with other university hospitals, several private companies and government support” (European Union 2018; p.42).

**Joint Procurement.** According to the definition found on the ‘Joint Procurement Fact Sheet’, which was developed by the ICLEI – Local Governments for Sustainability and for the European Commission (EC), Joint Procurement (JP) means “combining the procurement actions of two or more contracting authorities” (ICLEI 2008; p.2) so that finally, “there should be only one tender published on behalf of all participating authorities” (ICLEI 2008; p.2). An example for the joint procurement of medicines is for instance the BeNeLuxA (Espín et al. 2016) that is a joint procurement initiative between Belgium, the Netherlands and Luxembourg and recently Austria joined, too (BeNeLuxA 2018).

4.5.5 Collaborations concerning developing countries

**Public Private Partnerships (PPPs).** According to the World Bank there is no “widely accepted definition” of PPPs (Word Bank Group 2018). The PPP Knowledge Lab defines a PPP as "a long-term contract between a private party and a government entity, for providing a
public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance” (World Bank Group 2018).

The WHO says that PPPs “are seen as an effective way to capitalize on the relative strengths of the public and private sectors to address problems that neither could tackle adequately on its own, in particular in respect of diseases that particularly affect developing countries where research by the private sector is deemed insufficient. Thus the public sector contributes both basic science and funding, and the private sector has strengths in drug discovery and bringing candidate drugs through the trials process to regulatory approval. The lack of incentive is addressed by creating a PPP entity with a well-defined objective relating to the development of a particular product or technology required by developing countries” (WHO 2010).

An example of PPPs are the “Fixed-Dose Artesunate Combination Therapy (FACT) project consortium, which brought together universities, research institutions, public and private pharmaceutical companies, an international NGO and a public interest PDP for the development of two antimalarial fixed-dose combinations recommended by the WHO – artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMQ)” (Kameda 2014; p.102).

Another example is ‘GAVI, The Vaccine Alliance’ whose mission is “saving children’s lives and protecting people’s health by increasing equitable use of vaccines in lower-income countries” (GAVI 2018a). GAVI is partnering with several public and private players, for instance: the Bill & Melinda Gates Foundation, UNICEF, WHO, The World Bank Group, civil society organizations, developing countries’ governments, industrialised countries’ governments, pharmaceutical companies and research and technical health institutes (GAVI 2018b).

On the financial scope it is the World Bank who “is a founding partner to GAVI” who plays a major role. The Independent Evaluation Group (IEG) – which is an independent unit within the World Bank Group (The World Bank Group 2016) – states that the World Bank’s “most significant contribution [in its partnership with GAVI] is […] the establishment and management of two innovative financing mechanisms”: the International Finance Facility for Immunisation (IFFIm) and the Advanced Market Commitment (AMC). According to the IEG, these mechanisms accounted for “one-third of GAVI’s financial resources from 2000 to 2010” (Independent Evaluation Group 2014).
GAVI aims to make immunisation sustainable, which means that “countries enter Gavi support in the initial self-financing phase, where they pay a small amount towards their vaccine costs. When they move to the preparatory transition phase, the price fraction of their co-financing increases by 15% per year, after the grace year. As their GNI per capita grows, they enter the accelerated transition phase – a five-year period when co-financing reaches 100% of vaccine costs and phase-out from our support” (GAVI 2018d). This procedure is visualized by figure 4 below.

**Figure 4: GAVIs sustainability approach (GAVI 2018e)**

**International Finance Facility for Immunisation (IFFIm).** The International Finance Facility for Immunisation (IFFIm) was launched in 2006 and is characterized by donors’ long-term financial pledge commitments (IFFIm 2018). These commitments amount, according to the IFFIM, to “US$ 6.5 billion […] donor contributions over 25 years from the governments of Australia, France, Italy, the Netherlands, Norway, South Africa, Spain, Sweden and the United Kingdom” (IFFIm 2018). The IFFIm financing mechanism is visualized by figure 5.

For GAVI, the “IFFIm issues bonds backed by grants pledged by donor countries and repaid over time” (GAVI 2018c). Hence, the IFFIm “uses long-term pledges from donor governments to sell 'vaccine bonds' in the capital markets”, which makes “large volumes of funds immediately available for Gavi programmes” (IFFIm 2018). This is also referred to as “frontloading”. It allows to align the availability of funds to the demand for vaccines in GAVI eligible countries (GAVI 2018c). The resulting “cash raised through the bonds is used to purchase vaccines, support programmes and strengthen health systems” (GAVI 2018c).
The future donor pledges – so-called ‘GAVI’s proceeds’ – are discounted to their present values. Hence, the actual value of the proceeds is a smaller amount than the monetary amount of future pledges. This means though, that “these amounts are economically equivalent”. Furthermore, “the decision to monetise future pledges is driven by the importance of achieving a health impact today (by frontloading)” (GAVI 2018c).

Hedging – to mitigate the exchange rate risk or to make the financial commitments more secure against exchange loss – is applied in this financing mechanism, also. This means that “all donor pledges are hedged to floating rate US dollars at the time that pledges are signed. As a result, their value is set at that point, reflecting prevailing foreign exchange rates.” Thus, it is “the hedged value of IFFIm grants that determines the amount of frontloading that IFFIm can provide as proceeds to GAVI” (GAVI 2018c).

As the result of the IFFIm financing mechanism and “the World Bank as its treasury manager, [the] IFFIm has leveraged donor pledges to raise more than US$ 5.7 billion over the 2006 to 2016 period” (IFFIm 2018).

**Advance Market Commitment (AMC).** This financing mechanism that similar to the IFFIm is thought to subsidize developing countries by developed countries. However, while the IFFIm that focuses on enabling purchases of existing vaccines, the AMC focuses on the purchase of not yet existing vaccines. The World Bank states that AMC “tackles a longstanding development problem – persistent market failure to develop and produce vaccines needed in poor countries due to perceptions of insufficient demand and market uncertainty” (The World
Bank Group 2018). AMC was first proposed by the Center for Global Development (CDG) in a report on “Making Markets for Vaccines” (Barder 2010).

The WHO defines an AMC as a “legally-binding agreement for an amount of funds to subsidize the purchase, at a given price, of an as yet unavailable vaccine against a specific disease causing high morbidity and mortality in developing countries“ (WHO 2006).

Batson et al. provide a similar definition yet with an additional conditional fragment that is AMC is “a financial commitment to subsidize the future purchase (up to a pre-agreed price) of a vaccine that is not yet available if the vaccine meets pre-defined standards” (Batson et al. 2006). According to GAVI, the pre-defined standards mentioned by Batson et al. are “pre-agreed criteria on effectiveness, cost and availability, and that developing countries demand them” (GAVI 2018c).

Batson et al. also underline that an AMC “is not a purchase guarantee, as industry will only receive the subsidized price if countries demand the product after it has been developed” (Batson et al. 2006).

According to the WHO AMCs could possibly be “designed both for [vaccines] at an early stage of development (such as malaria, HIV/AIDS and tuberculosis vaccines) and for late stage [vaccines] (such as vaccines against rotavirus, human papillomavirus, and pneumococcal disease)” (WHO 2006).

Functioning of AMC mechanism

In practice, “donors […] subsidize the purchase of vaccines by developing countries, up to a fixed number of sales or a fixed total amount” (WHO 2006). The WHO points out that once the “fixed number of sales or total amount has been reached” there are two options for manufacturers, which “benefited from the subsidy”. They would be contractually obliged to […] a) sell to developing countries at a price affordable over the long term” or b) “to license their technology to other manufacturers” (WHO 2006).

The monetary contributions for the AMCs are directed to the World Bank, which calculates the AMC proceeds (GAVI 2018c). The AMC is an implemented mechanism. A first pilot AMC for pneumococcal vaccines (PNV) was launched in 2009. Then in 2010 followed AMC’s real launch delivering its first vaccines (Glassman & McQueston 2013). AMC legal agreements can be found on GAVI’s website (GAVI 2011).
**Pooled Procurement.** Different from Joint Procurement the so-called Pooled Procurement is usually characterized by an external purchasing body (Results for Development Institute 2018) and used in developing countries. An example for this is GAVI (GAVI 2018e) explained above that uses the supply division of UNICEF, which is the body that purchases vaccines on large scale for the GAVI eligible countries (Results for Development Institute 2018).

### 4.6 Stakeholder consultation

In this section the results of the pilot questionnaires and pilot interviews will be shortly presented. First of all, some selected outcomes of the pilot questionnaires will be treated since presenting the results of every single question would lie beyond the scope of this work. In the second section, the main themes that emerged from the interviewees will be described.

#### 4.6.1. Pilot questionnaire

As one can see on Diagram 1 that presents the extent to which participants thought that a delinkage-based system could be implementable in the EU, the majority of participants – 40% indicated that they think that the delinkage system is ‘rather yes’ implementable in the EU and 20% indicated that the delinkage system is ‘fully’ implementable in the EU – whereas the remaining 40% can ‘rather not’ or ‘not at all’ imagine delinkage to be implemented in the EU.

*Diagram 1: Question on delinkage implementation (author's own illustration)*
Diagram 2 presenting the extent to which participants thought that innovation could be rewarded differently in the EU shows that 50% of participants in the questionnaire indicated that they could (‘rather yes’) imagine innovation to be rewarded differently in the EU than currently done based on the patent system. Compared to this, the already above-mentioned degree as to which the participants thought that delinkage could (‘rather yes’) be implemented in the EU was slightly lower at 40%.

The Chart 1 shows the extent to which the participants thought that models based on delinkage have more potential in bringing affordable and clinically effective medicines to the market in the EU than MEAs or RSAs. It results that a majority of 60% believes ‘rather yes’ that models based on delinkage would achieve this better, whereas only 10% believe that models based on delinkage could ‘not at all’ achieve this any better.
Having taken the SIBs as an example for the underlying functioning of the HIBs, the Chart 2 visualizes the degree to which the participants thought that SIBs and thus respectively HIBs could be implementable in the EU. It shows that 50% of participants thought ‘rather yes’ that SIBs are implementable in the European Union, whereas 30% indicated that SIBs would ‘rather not’ be implementable in the EU and finally, 20% indicated that a SIB is not at all implementable in the EU.

To what extent do you think that such a Social Impact Bond is implementable in the European Union?

Chart 1: Question on SIB/HIB (author’s own illustration)
4.6.2. Pilot interviews

In the following, recurring themes arising from the interviewees will be described. They can be resumed through four major topics: financing R&D, the process of public R&D, delinkage and society’s stake. In order to fully maintain the interviewees data protection and anonymity, whenever quotations are given, it will not be indicated who of the three interviewees said it precisely.

Financing R&D

It was said repeatedly amongst the three interviewees that alternative financing models would have to have been shown to work in order to convince important stakeholders so that consequently, an alternative financing model could be implemented. It was suggested that this could be done through macroeconomic modelling and best by some renown economists. It was highlighted that “it would have to be a very convincing model”. It was also mentioned that if the European Commission suggested to introduce a new mode of doing research, it could possibly work.

The future of public-sector R&D

Furthermore, it was put emphasis on that the public sector should be allowed to proceed with its research beyond the preclinical stage. It was pointed out that this would naturally need to go along with more funds distributed on public research projects. Although, at first it may seem that higher levels of financial resources would be required for this, in the end through less-premium priced medicines savings would be made. It was said that it should be aimed that public researchers “would not be dependent to sell these substances but to research them. And then to get the patent”. For the latter, it was highlighted that there would need to be intellectual property specialists. Hence, again for this to happen, financial resources would need to be deployed. It was said that the USA invests substantially more into public research than the European Union.

Delinkage

Regarding delinkage it was said “I don’t admire…I think it’s an excellent idea…”. It was mentioned that in the context of gene therapies delinkage might find implementation due to gene therapies’ expensive and complicated nature. Another area for possible implementation of delinkage was the new-generation antibiotics. As first steps to implement delinkage it was said that political pressure would be needed. It was also said that in order to introduce changes trust-
building instruments are important. According to the interviewee such trust-building instruments are currently initiatives such as the “Mechanism of Coordinated Access to orphan medicinal products” (MoCA) (EURORDIS 2017) and the Medicine Evaluation Committee (MEDEV) (MEDEV 2018).

**Society’s stake**

Also, it was said that society plays an important part of this too. It was highlighted that people are very used to the way of how innovation is done today and can thus not imagine that it could be done differently. It was stressed as well that it is important to inform society about this.

### 5. Discussion

To the best of the author’s knowledge this is the first research, using a set of methods, including a systematic review, for analysing approaches to financing R&D of new medicines. Hanna et al. conducted a systematic review on approaches to funding high-cost medicines taking the payer perspective and looking for suitable funding models for ATMPs. They concluded that a tax-based ‘ATMP-specific fund’ might be the best solution with governments defining “a maximal proportion of GDP allocated to this fund” (Hanna et al. 2018; p.12). Thus, Hanna et al. took the perspective of how payers with limited financial resources can fund an already developed medicine. The present approach is different in that it starts at the very beginning of discovering a new medicine and searches for alternative models to finance R&D. Similar to Hanna et al, Schaffer et al. took also the payer perspective and reviewed innovative payment solutions addressing the affordability issue (Schaffer et al. 2018). Thus, in a certain sense, the whole approach is reversed in the current study and focus is being put on the very beginning of the R&D process instead of focusing on the moment in time when a new medicine has already been discovered.

As a general annotation, the wide range of supportive tools compared to the rather limited number of alternative financing models of R&D shows that payers make huge efforts to cope with the current R&D financing model. It also shows that the emphasis has been so far on searching for ways to cope with it and not on considering alternative financing models for R&D.

**Short statement of results**

The results were divided into three categories: (1) alternative financing mechanisms for R&D, (2) new pathways for effective R&D and (3) supportive tools for assuring access.
Main focus of this discussion will be the alternative financing mechanisms for R&D and new pathways for effective R&D. This discussion will serve to critically evaluate and discuss the approaches found.

**Critical analysis of delinkage**

Delinkage Evaluation

Based on the literature retrieved by this systematic review it has been analysed whether the financial models would allow delinkage to be implemented. It was found that none of the financial mechanisms prohibits delinkage completely. However, not all of the financial mechanisms are clearly designed to allow delinkage. It was found that the Royalty Payment system, the Health Impact Fund concept and the International Pooled Fund clearly enable delinkage. Health Impact Bonds and the Megafund with RBO and dynamic leverage instruments seem to allow for delinkage to be implemented as well. However, the literature did not explicitly state that. The table below briefly summarizes the results of the evaluation. A table with more detailed information can be found in Annex 4.

<table>
<thead>
<tr>
<th>Type of alternative financing mechanism</th>
<th>It allows delinkage to act</th>
<th>Possibly it might allow delinkage to act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Impact <strong>Bonds</strong></td>
<td></td>
<td>Rowe et al. 2016</td>
</tr>
<tr>
<td>Megafund</td>
<td>-</td>
<td>Fernandez et al. 2012</td>
</tr>
<tr>
<td>Royalty payment system</td>
<td>Workman et al. 2017</td>
<td>Antoñanzas 2014</td>
</tr>
<tr>
<td><strong>Health Impact Fund</strong></td>
<td>Banerjee &amp; Pogge 2010</td>
<td></td>
</tr>
<tr>
<td>International pooled fund</td>
<td>Outterson 2016 `t Hoen 2016</td>
<td></td>
</tr>
</tbody>
</table>

As to the concept of delinkage, there is one definition of delinkage that is, as explained earlier in the results, accepted amongst important public health stakeholders. However, what this concept seems to miss to explain is how R&D would really be financed. Would R&D be solely financed through prize rewards? There is actually a clear ‘No’ to this question, since delinkage expressively aims to decouple a medicine’s price from R&D costs. As such, it focuses on providing access to medicines by making them affordable by assuring – through drastic measures such as the proposed auctions – that a medicine’s price will be decoupled from its R&D costs.
Hence, this suggests that delinkage in itself is rather limited as it does not tackle the actual question of how to finance R&D in a sustainable manner. It might however, constitute an important stimulus to develop new pathways for effective R&D that diminish the cost of R&D remarkably and consequently, allow to offer the new medicine as close as possible to marginal cost. Furthermore, it might trigger the development of further creative mechanisms for financing R&D.

**Critical analyses of financial mechanisms**

**Disruptive nature vs. financial resources attainable**

The Diagram 3 and Diagram 4 present the grading applied to the different financial models concerning their disruptive nature and their capacity in raising significant amounts of financial resources.

The evaluation was done taking a scale from 0 to 5. Grade zero meant that there is no capacity in raising financial resources or that there would be no disruption and grade five meant that the financial model has a high capacity of raising financial resources or respectively that the financial model is highly disruptive.

For determining the degree of disruption, the criteria applied were: A) whether the financial model makes use of capital markets – then it would be considered as very disruptive (either grade 4 or 5) – or if the financial model makes use of taxes or contributions paid – then it would not be disruptive. B) whether the financial model would introduce delinkage. If it does then it would be considered as disruptive (grade 1). In describing the results of the evaluation, the grades will be given in brackets.

**Disruptive nature**

The HIB makes use of capital markets (grade 5) but experience has been made with SIBs (grade 4) and the first HIBs (grade 3). Thus, HIBs was given as final grade 3. The Megafund makes use of capital markets (grade 5) but again some experience with capital markets exists already through the SIBs and first HIBs (grade 3). However, the Megafund makes a more deepened use of the capital markets (grade 4) compared to SIBs. Thus, there would be increased scepticism among public health professionals. Hence, as to the degree of disruptive nature the Megafund was given grade 4.

The proposals for a RBS do not suggest to use capital markets (grade 0). But if a system based on royalties was implemented, it would introduce some change since research would be payed
or rewarded based on royalties whose concrete amount would be measured by the number of sales of the medicine (grade 1). Also, the development of the medicine would be conducted by generic drug maker-like companies. Hence, it would introduce a change in the types of companies on the pharmaceutical market (grade 2). Furthermore, the proposals indicated that the RBS would introduce delinkage (grade 3). Thus, for disruptive nature grade 3 was given to the RBS.

For the IPF there is no proposal indicating that the IPF would definitely use capital markets, it is only said that it is a possibility (grade 0). There is many international treaties in other fields (i.e. Kyoto agreement on climate change). Thus, another treaty in itself would not be disruptive. But such an international treaty for financing R&D in order to discover new medicines would introduce some moderate disruption, since financial resources for R&D are usually pooled at national level and not on international level (grade 1). Furthermore, the IPF would introduce delinkage (grade 2). Thus, the IPF was given grade 2 for its degree of disruptive nature.

As the HIF is only suggested as a complementary system it was not attributed the highest grade of disruption. Also, it is proposed to be financed through taxes. It would thus not make use of capital markets (grade 0). However, a global agency would be created (grade 1) from that for several years annual reward pools would be distributed for research fields with the highest global BoD (grade 2). Furthermore, it is supposed to introduce delinkage (grade 3). Thus, the HIF received as final grade for the degree of disruption the grade 3.

**Financial resources achievable**

As the HIB model makes use of the capital market, substantial amounts of financial resources can be achieved (grade 4). The Megafund makes also use of capital markets but so even more comprehensively through combining debt securities and equity securities (securitization technique) (grade 5) than the HIB model. The RBS and the HIF would only rely on taxes or contributions paid (grade 1). Slightly different from them, for the IPF it was indicated that a possibility consists in using bonds besides using taxes. Since this has not been specified further however, only grade 2 was given for financial resources attainable to the IPF – whereas bonds usually would raise substantial amounts of financial resources and hence, a higher grade would be given usually. The evaluation of ‘Disruptive nature vs. Financial resources attainable’ is visualized by Diagram 3.
Diagram 1: Critical analysis - Disruptive nature vs. financial resources achievable (author’s own illustration)

Reducing the BoD through a more diverse group of stakeholders vs. number of resulting new compounds

Reducing the BoD through a more diverse group of stakeholders

Rowe and Stephenson said that by using HIBs the risk of future social problems would be shared with the private market. Hence, by sharing the risk with the private market, the types and number of involved stakeholders increases (grade 4).

As said by Fernandez et al, by using the Megafund’s RBO instrument, a remarkably higher number of stakeholders and also more diverse types of stakeholders (i.e. private market) would be involved in reducing the BoD (Fernandez et al. 2012). Furthermore, thanks to the large portfolio of diverse R&D projects at different progress stages that decrease the overall risk of the portfolio, it can be assumed that investors would be even more attracted than in case of a HIB. Hence, the Megafund would be capable of raising a larger amount of financial resources (grade 5) than the HIB.

Both – the RBS and the HIF – do not use capital markets thus their involved stakeholders would be very limited. However, in both cases it might be that new types of companies would be created and thus new types of stakeholders would join. Hence, regarding the diminishment of BoD through a more diverse group of stakeholders to both the RBS and the HIF grade 1 was assigned. If the IPF was used, the types and number of stakeholders would stay largely the
same. However, if it was decided to use bonds in the design of an IPF, then the type of stakeholders would be more diverse and their number would increase. Thus, the IPF was attributed grade 2 regarding the reduction of the BoD through a more diverse group of stakeholders.

**Number of resulting new compounds**

It can be assumed that if financial resources available rise, the number of new medicines will also rise. Thus, here the same grades have been given as for the element of ‘financial resources attainable’. The evaluation for ‘reducing the BoD through a more diverse group of stakeholders vs. number of resulting new compounds’ is visualized by Diagram 4.

![Diagram 2: BoD reduction through diverse stakeholders vs. the number of resulting new compounds](image)

As one can see on Diagram 4, the highest amounts of financial resources could be raised through – ordered from highest to lowest: 1. the Megafund, 2. HIB, 3. IPF and finally at the same position 4. the RBS and HIF.

On the one hand, the capital market mechanisms – HIB and Megafund – would raise significantly higher amounts of financial resources for conducting R&D for new medicines than the non-capital market mechanisms (RBS, IPF and HIF). On the other hand, however, the capital market mechanisms and especially the megafund, show a high disruptive potential.
Thus, when looking at the disruptive nature of the proposed financing mechanisms, the easiest financial model to introduce based on the above analysis would be the IPF.

Furthermore, regarding the IPF it is important to mention that the WHO has the tools to create an international “R&D agreement”. The WHO’s “constitution (article 19) allows for its 194 member states to negotiate formal international law” (’t Hoen 2016). Thus, there is no major obstacle for the creation of an international R&D treaty. Furthermore, there exists one example of a public health treaty already – that is the ‘Framework Convention on Tobacco Control’ that has been “the first public health treaty negotiated within WHO, which has contributed significantly to global tobacco control efforts” (’t Hoen 2016).

Regarding the HIB, Bloom argues that (he refers to SIBs but his comment is equally valid for HIBs) “it is likely that […] healthcare savings would be greater than the amount needed to repay SIB investors, meaning that the amount of money saved by citizens and governments also would be significant (Bloom 2016). Rowe and Stephenson say that one “subsequent implication of health impact bonds is their preoccupation with accurate measurement of outcomes”. They remark that “establishing intervention and control groups of the required magnitude requires considerable coordination and resources” (Rowe & Stephenson 2016).

The relationship between public sector & capital market

As the above critical analysis on alternative financing mechanisms suggests it is not obvious that the public sector would adopt capital market financing mechanisms quickly. Fernandez et al. reason that it is “natural to question the wisdom of [the approach of securitization]” as securitization “played a role in the recent financial crisis”. They argue that securitization “may have been too effective” in the sense that it allowed “potential homeowners to tap directly into a much larger pool of capital instead of obtaining mortgages from traditional banking institution” where they had been proved on credit-worthiness, which in case of securitization is not needed (Fernandez et al. 2012).

However, Rowe and Stephenson state, along with Bryan and Rafferty (2006), that “sociological accounts of risk and security have often failed to consider the specific ways that contemporary finance rationalises and works with probability, potentiality, uncertainty and risk”. Thus, seeing HIBs as financial instruments, HIBs “translate health risks into universally exchangeable commodities” (Rowe & Stephenson 2016). Also, Fernandez et al. underline that “there is little doubt that securitization was, and continues to be, an effective means of raising capital”
Rowe and Stephenson raise another question. They say that “the alignment of public health and financial markets via [HIB] also leads us to ask, […] how might public health be transformed through its uptake up financialised concepts of risk? How will the ways that various actors create, re-interpret and/or resist the techniques of measurement required by these instruments, be reflected in political pressures upon healthcare into the future?” (Rowe & Stephenson 2016).

Fernandez et al. provide at least a partial response to Rowe and Stephenson’s question. They suggest to avoid potential pitfalls by applying “statistical models of the biomedical portfolio returns [which] should be based on a detailed understanding of the science and engineering underlying the individual projects in addition to an analysis of historical returns”. Also, they say that the valuation of a portfolio “should reflect current market realities at all times rather than hypothetical expectations”. Furthermore, “regulations surrounding the sale of megafund securities – including proper risk disclosure by issuers, suitability requirements for investors and realistic credit analysis – should be strictly enforced” (Fernandez et al. 2012).

Hence, regarding the use of securitization one could conclude since experiences with securitizations have already been made in other sectors, one can learn from them and same or similar mistakes must not be made again. Naturally, frameworks and strategies would need to be developed to ensure that such negative experiences as mentioned above are averted. The bottom line is here however, that securitization presents a very important financial instrument and that it could contribute enormously in advancing R&D for new medicines.

**Comments on new pathways for effective R&D**

The VKB solves the free rider problem and thus as soon as the platform is fully established, a quick adoption of it by pharmaceutical innovators can be expected.

As said in the results, Open Source prevents the duplication of efforts and thus has the potential to decrease attrition rates significantly. Hence, by using Open Source, overall R&D costs will diminish and research in general can be accelerated.
Comments on the stakeholder consultation

The input received from the stakeholders can be commented in the following way.

Civil society’s stake

Ways should be found to inform civil society on that alternative financing models for R&D can function well and that they would enhance the innovation capacity of the pharmaceutical sector. As alternative financing models would have an impact on the capacity of developing medicines that are needed by societies, it can be assumed that society is an important stakeholder in this. Also, the end consumer – the one who might finally benefit from a medicine – is the citizen. Furthermore, if civil society was not informed on alternative financing models, there would be an important asymmetry of information between academia and society. Thus, how and by which communication techniques could civil society be informed and possibly engaged?

Moreover, if civil society was not informed, it might impede a shift in how R&D is financed and rewarded that originates from civil society. Experts in participatory and deliberative democracy (Blacksher 2013) would probably have a say on this and also on how to introduce the results of this work to civil society. Communication experts could also play an important role here.

Financing R&D & the future of public sector R&D

The results of the interviews suggest that delinkage is not perceived as a perfect concept. That goes likely along with that delinkage in itself is not a financing model. It is rather a rewarding model but not in the sense as patents currently reward innovation by granting monopoly situations that naturally result in large profits. Hence, where the current rewarding model is able to cover R&D costs, the delinkage model is not and is also not supposed to. Thus, the delinkage concept would need an accompanying model to finance R&D. That could be a megafund or HIBs or other financial models presented in this work with the important difference in that the megafund and HIBs would be able to raise the largest amounts of financial resources compared to the others. Also, by making use of a megafund and HIBs governments would not need to rely on financial resources coming from taxation. Furthermore, new pathways for effective R&D presented in this work will also be crucial since they will allow to keep costs to a minimum. If more financial resources were available to the public sector, then also intellectual property specialists managing the public’s intellectual property could be employed easily.
Final concluding remarks

The financial mechanisms presented, and especially the megafund and HIBs, present a huge opportunity for developing medicines for conditions for which there is no cure or treatment yet available. New medicines, and frequently cancer medicines, have repeatedly been reported in recent years to add only little clinical benefit. So what if there was finally a break-through therapy found thanks to the discussed financial mechanisms?

Also, for certain orphan drugs for which no cures exist so far, these financial mechanisms are a tremendous opportunity to find appropriate treatments and cures. Last but not least, investments into the R&D for not-yet-existing antibiotics are highly needed. Hence, again there is profound reason to make use of the presented financial instruments.

The question, however, should not be – “what are we waiting for?”, but – “how can we make sure that these financial mechanisms find implementation for financing the R&D of new medicines?” It is rather unlikely that the approaches that are the most capable of raising large amounts of financial resources for R&D (HIBs and Megafund) will be taken up quickly – due to their disruptive nature – if no further convincing work is done.

Certain financial mechanisms presented and especially the Megafund and HIBs go along with reducing the BoD by a more diverse group of stakeholders. As Rowe and Stephenson said (Rowe & Stephenson 2016), this would mean that social or respectively public health challenges that arise are shared with the private market and thus shared with a larger number of stakeholders. Thus, also the risk that research efforts would not result in a new medicine would be shared with the private market. In this way, it connects with the concept of ‘Economy for the Common Good’ in that by raising more financial resources a higher level of Common Good can be reached. Furthermore, the new pathways for effective R&D would also lead to a higher level of Common Good. Whereas the current innovation and financing model creates if any only shared value and is frequently involved in greenwashing activities. This is visualized by Figure 6. One could thus demand that it is time to make use of capital-market mechanisms for enhancing the well-being of societies.
6. Conclusion

The following conclusions can be drawn from this study:

- Five alternative financing approaches have been identified: (1) Health Impact Bonds (HIBs), (2) the Megafund (1 - 2: capital market financing mechanisms), (3) the Royalty-Based System (RBS), (4) the International Pooled Fund (IPF) and (5) the Health Impact Fund (HIF) (3 – 5: non-capital market financing mechanisms).

- Three major new pathways for effective R&D have been identified: (1) Academia-based research combined with generic drug maker-like companies; (2) Open Source pathways and (3) managing the public sector’s intellectual property.

- It was found that none of the alternative financing approaches prohibits an implementation of the concept of delinkage. The Megafund and HIBs would raise the largest amounts of financial resources however, these two financing mechanisms and especially the Megafund would be characterized by a considerable disruptive nature. The latter has been confirmed through the pilot stakeholder consultation.
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## Annex 1: Keywords

### A) GROUP OF KEY-TERMS ASSOCIATED WITH THE TYPE OF MEDICINE

<table>
<thead>
<tr>
<th>Orphan medicines</th>
<th>“orphan drug*” OR “orphan medicine*” OR “orphan molecule*” OR “orphan pharmaceutical*” OR “orphan medicinal product*” OR “orphan therap*”</th>
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</thead>
<tbody>
<tr>
<td>Personalized medicines</td>
<td>“personali* drug*” OR “personali* medicine*” OR “personali* molecule*” OR “personali* pharmaceutical*” OR “personali* medicinal product*” OR “personali* therap*” OR “personali* immunotherap*”</td>
</tr>
<tr>
<td>Biological medicines</td>
<td>“biologic* drug*” OR “biologic* medicine*” OR “biologic* molecule*” OR “biologic* pharmaceutical*” OR “biologic* medicinal product*” OR “biologic* immunotherap*”</td>
</tr>
<tr>
<td>New generation antibiotics</td>
<td>“new generation antimicrob*” OR “new generation antibiotic*” OR “new generation antibacterial*” OR “advanced therapy” AND (drug* OR medicine* OR molecule* OR pharmaceutical* OR “medicinal product*”)</td>
</tr>
<tr>
<td>Advanced therapy medicinal products (gene therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines)</td>
<td>ATMP (gene OR “somatic cell” OR “stem cell” OR “cell-based” OR “cell based” OR cell OR “human cellular”) AND (drug* OR medicine* OR molecule* OR pharmaceutical* OR “medicinal product*” OR therap*)</td>
</tr>
<tr>
<td></td>
<td>(“tissue-engineer*” OR “tissue engineer*”) AND (drug* OR medicine* OR molecule* OR pharmaceutical* OR “medicinal product*” OR product* OR therap*)</td>
</tr>
<tr>
<td></td>
<td>regenerative AND (drug* OR medicine* OR molecule* OR pharmaceutical* OR “medicinal product*” OR therap*)</td>
</tr>
<tr>
<td></td>
<td>HCT/P*</td>
</tr>
</tbody>
</table>

### B) GROUP OF KEY TERMS ASSOCIATED WITH FINANCING - GENERAL

<p>| financing |
| fund* | OR |</p>
<table>
<thead>
<tr>
<th>C) KEY-TERMS ASSOCIATED WITH FINANCING – SPECIFIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>“managed entry” OR MEA OR “risk sharing” OR “risk-sharing” OR rebate* OR discount* OR clawback* OR clawback* OR payback* OR pay-back* OR “outcome* based” OR “outcome-based” OR “outcomes-based”</td>
</tr>
<tr>
<td>“price negotiation*” OR “negotiated price*”</td>
</tr>
<tr>
<td>“tiered price*” OR “tiered pricing”</td>
</tr>
<tr>
<td>“multi criteria decision” OR “multi-criteria decision” OR “multiple criteria decision” OR “multiple-criteria decision” OR MCDA OR MCDM</td>
</tr>
<tr>
<td>“cost-plus price*” OR “value-based price*” OR “value based price*”</td>
</tr>
<tr>
<td>“joint procur*”</td>
</tr>
<tr>
<td>“reimbursement threshold*”</td>
</tr>
<tr>
<td>&quot;open source&quot; OR &quot;open innovation&quot; OR &quot;open collaborative development&quot; OR “intellectual property model*” OR “intellectual property based model*” OR “intellectual property based approach*” OR “IP-based model*” OR “IP-based approach*” OR “patent based model*” OR “patent buy-out” OR “patent buyout” OR “patent validity” OR “research fee*” OR “research tax*” OR “zero-cost compulsory licen*” OR “compulsory licen*” OR “voluntary licen*” OR “non-voluntary licen*” OR auction*</td>
</tr>
<tr>
<td>disinvestment* OR “payer* collaboration*” OR &quot;annuity payment*” OR “annuity based payment*” OR “annuity-based payment*”</td>
</tr>
</tbody>
</table>
healthcoin*
“horizontal innovation*”
“governance for pricing”
“public private partnership*” OR “public-private partnership*” OR PPP
“level* of innovation”
“price correction*”

**Annex 2: MeSH terms**

<table>
<thead>
<tr>
<th>A) GROUP OF MeSH-TERMS ASSOCIATED WITH THE TYPE OF MEDICINE</th>
</tr>
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<tbody>
<tr>
<td>orphan drug production</td>
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<tr>
<td>biological products</td>
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<tr>
<td>genes/therapy</td>
</tr>
<tr>
<td>tissue engineering</td>
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<tr>
<td>stem cells/therapy</td>
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<tr>
<td>cell and tissue based therapy</td>
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<tr>
<td>cells/therapy</td>
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<td>cell engineering</td>
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<table>
<thead>
<tr>
<th>B) GROUP OF MeSH TERMS ASSOCIATED WITH FINANCING - GENERAL</th>
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<tbody>
<tr>
<td>healthcare financing</td>
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<tr>
<td>financing, government</td>
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<tr>
<td>reimbursement, incentive</td>
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<tr>
<td>reimbursement mechanisms</td>
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<tr>
<td>financing, organized</td>
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<tr>
<td>fund raising</td>
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<tr>
<td>financial management</td>
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<tr>
<td>cost allocation</td>
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<tr>
<td>public sector/economics</td>
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<tr>
<td>cost control</td>
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<tr>
<td>costs and cost Analysis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>C) MeSH-TERMS ASSOCIATED WITH FINANCING – SPECIFIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>risk sharing, financial</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td>outcome assessment health care</td>
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<tr>
<td>patient outcome assessment</td>
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<tr>
<td>negotiating</td>
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<tr>
<td>value based purchasing</td>
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<tr>
<td>intellectual property</td>
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<tr>
<td>patents as topic</td>
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<tr>
<td>licensure</td>
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<tr>
<td>public private sector partnerships</td>
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<tr>
<td>diffusion of innovation</td>
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<tr>
<td>technology transfer</td>
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</tbody>
</table>
### Annex 3: Extraction table

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of solution/Type of model</th>
<th>Stakeholders (who for whom?/between which parties?)</th>
<th>Characteristics of the mechanism</th>
<th>Type of medicines</th>
<th>Geographic area for which model is proposed</th>
<th>Theoretic/Implemented (existing)</th>
<th>Author, Year of publication: Title; Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative financing mechanisms</td>
<td>International agreement on R&amp;D: collaboration towards &amp; financing of essential medical R&amp;D.</td>
<td>Among different countries</td>
<td>Financing mechanism would be based on contributions from countries</td>
<td>Diverse, but rather focusing on tropical diseases.</td>
<td>Yet to be defined but it tends to be on international/global level.</td>
<td>Only plans for a possible future implementation of an international agreement on R&amp;D</td>
<td>’t Hoen, 2016: Private Patents and Public Health - Changing Intellectual Property Rules for Access to Medicines; report.</td>
</tr>
<tr>
<td></td>
<td>Royalty payments to the patent owner.</td>
<td>Planner + institutions in the North and South + patent owner</td>
<td>Financed through public funds.</td>
<td>Several types of medicines, i.e. antibiotics.</td>
<td>Medicines for less developed countries.</td>
<td>Simulation for future possible implementation of a royalty-based system</td>
<td>Antoñanzas et al, 2014: Should the patent system for pharmaceuticals be replaced? A theoretical approach.; simulation - highly stylized static model</td>
</tr>
<tr>
<td>Health Impact Fund (HIF)</td>
<td>Governments and pharmaceutical companies.</td>
<td>Financed through worldwide tax contributions</td>
<td>Drugs for neglected diseases.</td>
<td>Especially for low- and middle-income countries.</td>
<td>The health impact assessment tools are currently being defined that the HIF would use &amp; pilot projects are being designed for in</td>
<td>Banerjee et al, 2010: The Health Impact Fund: a potential solution to inequity in global drug access.; not mentioned</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Type of solution/Type of model</td>
<td>Stakeholders (who for whom?/between which parties?)</td>
<td>Characteristics of the mechanism</td>
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<td>Geographic area for which model is proposed</td>
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<td>Author, Year of publication: Title; Study design</td>
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</tr>
<tr>
<td>Social Impact Bond repurposed to medicines.</td>
<td>‘Cures Within Reach’ (a non-profit org.), SIB investors and governments.</td>
<td>Financing the repurposing of drugs by social impact bonds.</td>
<td>Diverse.</td>
<td>Pilot of the first SIB aimed at the repurposing of generic drugs will be in England, then, if successful, planned implementation across EU and worldwide.</td>
<td>Implemented for other types of projects, i.e. recidivism, homelessness, child protection/foster care, and preventive healthcare.</td>
<td>Bloom, 2016: Repurposing Social Impact Bonds for Medicine; not mentioned</td>
<td></td>
</tr>
<tr>
<td>Megafund</td>
<td>Capital market investors &amp; large portfolio of R&amp;D projects</td>
<td>Megafund with large portfolio of early to late-stage biomedical projects &amp; using securitization</td>
<td>Diverse, i.e. cancer medicines.</td>
<td>General, but rather referring to high-income countries.</td>
<td>Simulation of a possible future cancer megafund.</td>
<td>Fernandez et al, 2012: Commercializing biomedical research through securitization techniques.; realistic multiperiod simulation</td>
<td></td>
</tr>
<tr>
<td>Megafund</td>
<td>Capital market investors &amp; large portfolio of R&amp;D projects</td>
<td>Megafund with large portfolio of early to late-stage</td>
<td>Diverse, i.e. cancer medicines.</td>
<td>General, but rather referring to high-income countries</td>
<td>Simulation of a cancer megafund as in Fernandez et al, 2012 and extending it by an</td>
<td>Fagnan et al, 2013: Can Financial Engineering Cure Cancer?: A New Approach to Funding</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Type of solution/Type of model</td>
<td>Stakeholders (who for whom?/between which parties?)</td>
<td>Characteristics of the mechanism</td>
<td>Type of medicines</td>
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<td>Author, Year of publication: Title; Study design</td>
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<tr>
<td>Megafund</td>
<td>Capital market investors &amp; large portfolio of R&amp;D projects</td>
<td>Megafund with large portfolio of early to late-stage biomedical projects &amp; using securitization</td>
<td>Orphan drugs</td>
<td>General, but rather referring to high-income countries</td>
<td>Simulation of applying the megafund characteristics to the drug discovery for orphan diseases.</td>
<td>Fagnan et al, 2014: Financing drug discovery for orphan diseases.; Simulation.</td>
<td></td>
</tr>
<tr>
<td>Megafund</td>
<td>Capital market investors &amp; large portfolio of R&amp;D projects</td>
<td>Megafund with portfolio theory and dynamic leverage instead of securitization</td>
<td>Diverse, i.e. orphan drugs.</td>
<td>General, but rather referring to high-income countries</td>
<td>Simulation of incorporating dynamic leverage into the megafund concept</td>
<td>Montazerhodjat et al, 2016: Financing drug discovery via dynamic leverage.; Simulation.</td>
<td></td>
</tr>
<tr>
<td>Treaty or a WHO regulation</td>
<td>Different countries.</td>
<td>Legal &amp; financial commitments.</td>
<td>Antibiotics</td>
<td>General, because of antibiotic resistance worldwide concern.</td>
<td>Not existing. Explaining how the delinkage concept could be applied for R&amp;D in</td>
<td>Outterson et al, 2016: Delinking Investment in Antibiotic Research and Development from Sales</td>
<td></td>
</tr>
</tbody>
</table>

- **Stakeholders**: Capital market investors & large portfolio of R&D projects
- **Type of mechanisms**: Orphan drugs
- **Geographic area**: General, but rather referring to high-income countries
- **Theoretic/Implemented**: Simulation of applying the megafund characteristics to the drug discovery for orphan diseases.
- **Author, Year of publication**: Fagnan et al, 2014: Financing drug discovery for orphan diseases.; Simulation.
- **Study design**: Simulation.
<table>
<thead>
<tr>
<th>Category</th>
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<th>Type of medicines</th>
<th>Geographic area for which model is proposed</th>
<th>Theoretic/Implemented (existing)</th>
<th>Author, Year of publication: Title; Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Impact Bonds (HIB)</td>
<td>Capital market investors &amp; governments &amp; service/product providers</td>
<td>Bonds issued on capital markets.</td>
<td>General, referring to experiences made with SIB &amp; HIB.</td>
<td>General but referring to experiences made in UK, US and Israel.</td>
<td>SIBs are implemented. The first HIBs are also implemented.</td>
<td>Revenues: The Challenges of Transforming a Promising Idea into Reality.; essay.</td>
<td></td>
</tr>
<tr>
<td>Voluntary pooled fund</td>
<td>Member states (+private sector)</td>
<td>fund could be financed through contributions from member</td>
<td>R&amp;D for diseases mainly prevalent in</td>
<td>Both developed and developing countries.</td>
<td>Not implemented.</td>
<td>Stirner, 2008: Stimulating research and development of pharmaceutical products for neglected diseases.</td>
<td></td>
</tr>
<tr>
<td>WHO, 2016: Options for Sustainable Funding of a Voluntary Pooled Fund to Support Health</td>
<td></td>
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<tr>
<td><strong>Category</strong></td>
<td><strong>Type of solution/Type of model</strong></td>
<td><strong>Stakeholders (who for whom?/between which parties?)</strong></td>
<td><strong>Characteristics of the mechanism</strong></td>
<td><strong>Type of medicines</strong></td>
<td><strong>Geographic area for which model is proposed</strong></td>
<td><strong>Theoretic/Implemented (existing)</strong></td>
<td><strong>Author, Year of publication: Title; Study design</strong></td>
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<tr>
<td><strong>New pathways for effective R&amp;D</strong></td>
<td>Open source, open access, open innovation, crowdsourcing.</td>
<td>Researchers, students, etc. + online platform SysBorg (for OSDD) / Synaptic Leap website + open source online laboratory notebook (for TSLS)</td>
<td>states, contributions from the private sector or through bonds</td>
<td>developing countries.</td>
<td></td>
<td></td>
<td>Research and Development</td>
</tr>
<tr>
<td></td>
<td>Open Source Drug Discovery. Here also called ‘open innovation’ (Ardal &amp; Rottingen, 2012) however said that</td>
<td>Government of India + Council of Scientific and Industrial Research (CSIR) +</td>
<td>Medicines to combat diseases that disproportionately affect the poor.</td>
<td>Medicines to combat tropical diseases like tuberculosis, malaria,</td>
<td>Developing countries</td>
<td>Implemented: One of example of open source (TSLS) and one example of a crowdsourced (CSIR OSDD) project are analysed.</td>
<td>Ardal &amp; Rottingen, 2012: Open source drug discovery in practice: a case study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implemented: Open Source Drug Discovery Project for tackling TB was launched for global participation in 2008.</td>
<td>Bhardwaj et al, 2011: Open source drug discovery—a new paradigm of collaborative research in</td>
</tr>
<tr>
<td>Category</td>
<td>Type of solution/Type of model</td>
<td>Stakeholders (who for whom?/between which parties?)</td>
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<tr>
<td></td>
<td>technically it is crowdsourcing).</td>
<td>Researchers, students, etc. + online platform SysBorg</td>
<td>leshmaniasis, etc.</td>
<td></td>
<td></td>
<td></td>
<td>tuberculosis drug development.; review</td>
</tr>
<tr>
<td></td>
<td>Materials and know-how in university technology transfer policy – licensing methods</td>
<td>University-based researchers’ intellectual property</td>
<td>Human Papillomavirus (HPV) vaccine</td>
<td>Developing countries</td>
<td></td>
<td>Crager et al, 2009: University contributions to the HPV vaccine and implications for access to vaccines in developing countries; addressing materials and know-how in university technology transfer policy.; not mentioned</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‘Virtual Knowledge Bank’ (VKB) for secure and fair clinical trial data sharing – solving the free rider problem</td>
<td>Among biopharmaceutical for-profit companies. Researchers/companies + the web-based platform</td>
<td>Biopharmaceuticals</td>
<td>Not expressively mentioned, but as it is for biopharmaceuticals, it can be assumed that the whole biologics market is meant.</td>
<td>Not yet implemented: Working on solving challenges &amp; developing the web-based platform.</td>
<td>Evangelatos et al, 2016: Clinical Trial Data as Public Goods: Fair Trade and the Virtual Knowledge Bank as a Solution to the Free Rider Problem - A</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Type of solution/Type of model</td>
<td>Stakeholders (who for whom?/between which parties?)</td>
<td>Characteristics of the mechanism</td>
<td>Type of medicines</td>
<td>Geographic area for which model is proposed</td>
<td>Theoretic/Implemented (existing)</td>
<td>Author, Year of publication: Title; Study design</td>
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</tr>
<tr>
<td>Sophisticated IP management by public sector research and development organizations</td>
<td>'Virtual Knowledge Bank’ (VKB)</td>
<td>Public sector institutions and organizations</td>
<td>Vaccines</td>
<td>Developing countries</td>
<td>Not implemented, it is only suggestions.</td>
<td>Mahoney et al, 2004: The introduction of new vaccines into developing countries. III. The role of intellectual property.; not mentioned</td>
<td></td>
</tr>
<tr>
<td>Academia-based research combined with generic drug maker-like companies</td>
<td>Academia-based researchers + 'commercial partners': generic drug maker-like companies, new</td>
<td>Royalty-based system: academic drug discovery and development</td>
<td>Anti-cancer medicines</td>
<td>Not exclusively, but focus is rather on high-income countries.</td>
<td>Not implemented, it is a suggestion for the future.</td>
<td>Workman et al, 2017: How Much Longer Will We Put Up With $100,000 Cancer Drugs?; commentary</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Type of solution/Type of model</td>
<td>Stakeholders (who for whom?/between which parties?)</td>
<td>Characteristics of the mechanism</td>
<td>Type of medicines</td>
<td>Geographic area for which model is proposed</td>
<td>Theoretic/Implemented (existing)</td>
<td>Author, Year of publication: Title; Study design</td>
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<td></td>
<td>companies + contract research organizations (CROs)</td>
<td>units to be sustained by royalty payments on sales of the drugs.</td>
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</tbody>
</table>
## Annex 4: Critical analysis to assess delinkage feasibility

<table>
<thead>
<tr>
<th>Type of alternative financing mechanism</th>
<th>It allows delinkage to act</th>
<th>Possibly it might allow delinkage to act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Impact Bonds</td>
<td>-</td>
<td>In case of bonds, the investors would be paid back with a certain interest rate. This sum is not necessarily equal to the cost of R&amp;D, especially not if there is a large portfolio with different R&amp;D projects.</td>
</tr>
<tr>
<td>Rowe et al. 2016; p.1205:</td>
<td></td>
<td><strong>Rowe et al. 2016; p.1205:</strong></td>
</tr>
<tr>
<td>HIBs are financial commodities</td>
<td></td>
<td>“[generating] income streams that are linked to reduced future uptake of health and welfare services”</td>
</tr>
<tr>
<td>Megafund</td>
<td>-</td>
<td>Fernandez et al. 2012; p.965:</td>
</tr>
<tr>
<td>“A pool of investment capital is raised by issuing equity as well as several classes of bonds that differ from each other in their risk-reward profile to a diverse population of investors, and in which the funds are used to invest in various assets that serve as the collateral for the bonds”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royalty payments</td>
<td>Workman et al. 2017; p.582:</td>
<td>“The academic drug discovery and development units could be sustained in this [pathway] by receiving royalties on sales of the drugs they originated”</td>
</tr>
</tbody>
</table>
“Generic drug makers are used to working with lower profit margins. They and [new companies specifically formed to enable this new pathway] may be one potential partner to develop highly innovative [...medicines] from academic drug discovery and development”.

**Antoñanzas 2014; p.618:**
“Based on royalty payments [proportional to number of sales] to the patent owner in exchange for the right to market the innovative drugs under competitive conditions”. In the royalty-based system the price would be “equal to marginal cost”.

| Health Impact Fund | Banerjee & Pogge 2010; p.241: Upon registration of their new product, innovators would receive “for a defined period (e.g. 10 years), a share of fixed annual reward pools. In exchange, the registrant would agree to sell the medicine wherever it is needed at no more than the lowest feasible cost of production and distribution”.

|"- |"
<table>
<thead>
<tr>
<th>International pooled fund</th>
<th><strong>Outterson 2016; p.2:</strong> A “substantial proportion should be allocated to a pooled funding mechanism coordinated globally, given that parts of it will need to cover delinkage rewards”.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>’t Hoen 2016; p.131:</strong> “innovation models based on delinkage of the cost of R&amp;D from the price of the end product”</td>
</tr>
</tbody>
</table>
Annex 5: Semi-structured interview guide

<table>
<thead>
<tr>
<th>Semi-structured interview guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>How have you first heard about delinkage?</td>
</tr>
</tbody>
</table>

(Regarding Q4) Has there been any debate in politics on the approach of delinkage particularly in your country or other countries?
   - If there was a debate, who participated?
   - And what was the development of this debate?
   - And what were the results or conclusions of this debate?

What would you say is needed to implement a delinkage system?
   (What would there need to be to make delinkage for rewarding innovation feasible?
   How could that, what is needed, be reached?)

What do you think, would need to be the first steps to implement a delinkage system?

What are the obstacles to implement a delinkage system?

How do you think that delinkage could find best serious consideration for implementation?

By which stakeholders should it be put forward (defended)?
   (policy-makers, politicians, other stakeholders)

What role do you think plays civil society in this?

To what degree do you think that (the demands of) civil society could introduce a major shift that would be needed to make a change in the system of rewarding innovation?

(Regarding Q5) To what extent do you think that an innovation system based on delinkage would be capable of bringing truly innovative medicines to the market?

How do you see an innovation system based on delinkage compared to the current innovation system in relation to bringing truly innovative medicines to the market? Is one of them more capable?

(Regarding Q21) Could you please give some examples, if you know of any push-pull combinations, triple helix models or Social Impact Bonds that are implemented in your country or in other countries?

   - If examples are given, ask:
     - Who participated in these push-pull combinations or triple helix models?
     - How/by whom were they financed?
     - To what extent would you say that they have been successful?

(Regarding Q36) Depending on individual answer.

Thank you very much for your time.