Policy Brief on

Reducing Pricing Pressures of Orphan Drugs While Continuing to Incentivize the Innovation

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STUDENT FORUM MAASTRICHT

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Executive summary

The problem statement formulated for this policy brief is: How can high prices for orphan drugs be reduced while continuing to incentivize the innovation in this field? After looking into the complexity of the issue the working group has come up with three ideas which all approach the problem from different angles and range from quick short-term solutions to long-term solutions that also need some changes in the current system at place. Namely, the three ideas which the working group would like to propose to the European Commission are the Transferable Priority Review system, the utilisation of data in decision-making and starting a phase III clinical trial venture fund.

Transferable Priority Review:

Pharmaceutical companies are rather reluctant to invest money in orphan drugs. In order to give them incentives to invest the United States uses the system of priority review of regular non-orphan drugs pharmaceutical products that still have to enter the market. Each company that produces a drug for an orphan disease, regardless of the company's size, receives a voucher for one transferable priority review. This provides more opportunities for companies to invest. This system is not yet implemented in the European Union, but it might have potential in the EU as well with the current framework.

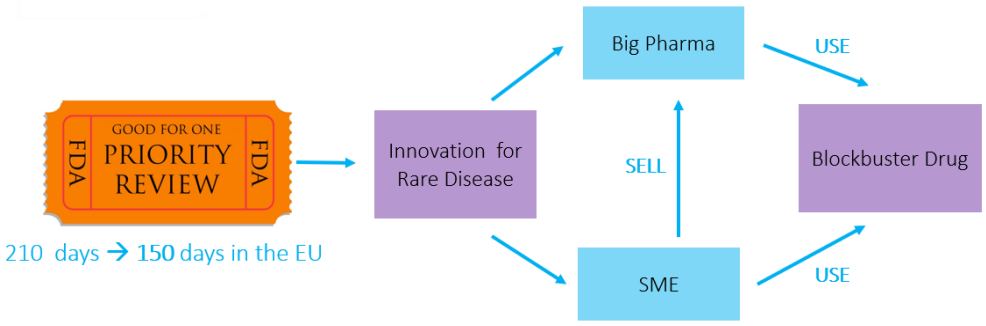

Figure 1: Introducing the Transferable Priority Review in the EU

*SME – Small and Medium-sized Enterprises'

Using Big Data:

There is a need for collaboration between public and private sector in the light of the big data revolution in health care, creating an opportunity for the European Commission to act in the digital revolution that is occurring in the pharmaceutical market. The existing strategies and legal frameworks prevent an overarching data base for rare diseases in Europe. However, this proposal suggests regulated ways in which big data can be used in the orphan drug industry, summarized in Figure 2.

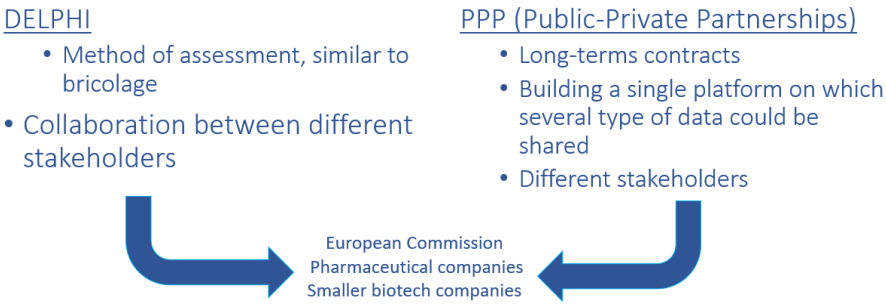

Figure 2: European Commission as an actor in the digital revolution brought by Big Data

Setting up a Venture Fund:

In the pharmaceutical sector Small and Medium-sized Enterprises (SMEs) are usually financially overburdened when it comes to the immense costs that are induced by advanced clinical trials. The here proposed intervention envisions an EU public venture capital fund (for orphan drugs) that supports innovators at this critical stage allowing them to stay independent from big pharmaceutical players. As a result, the market size increases, leading to more competition, transparency over research and development (R&D) expenditures and finally to lower reimbursement prices.

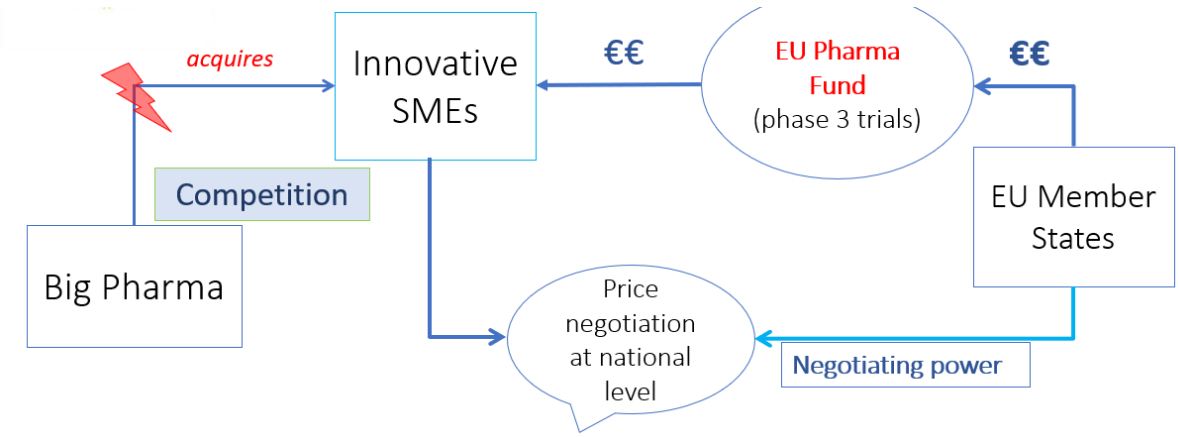

Figure 3: EU Public Venture Capital Fund (for orphan drugs)

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Introduction

The term 'orphan drugs' (OD) refers to medication for rare diseases which are defined as affecting 5 in 10,000 people in the European Union (EU). It is estimated that about 30 million European citizens collectively suffer from about 6,500 classified rare diseases (EMA, 2007). The development and supply of orphan drugs is by default a highly unprofitable business for pharmaceutical companies due to the small market for each individual rare disease. The lengthy and cost-intensive development of drugs and high levels of uncertainty add to the lack of attractiveness for pharmaceutical investment in orphan drugs (Drummond, Wilson, Kanavos, Ubel, & Rovira, 2007). Simultaneously, a substantial share of healthcare expenditures continues to be allocated to patients with rare diseases. Oftentimes, treatment expenditure can add up to several tenth of thousands of Euros annually and several million Euros over the course of a lifetime for just one patient (von der Schulenburg & Frank, 2015). Currently, EU legislation on OD mainly focuses on the promotion of innovation, providing perks for pharmaceutical companies including methodological simplifications, administrative assistance when going through the authorization procedure with the European Medicines Agency (EMA), as well as financial incentives including market exclusivity for the rare disease. While the promotion of OD innovation was intended to counteract the high costs caused by the treatment of rare diseases, member states are often burdened with high prices for ODs (Denis, Mergaert, Fostier, Cleemput, & Simoens, 2010), because the mere designation of 'orphan drug' leads to pharmaceutical companies issuing higher prices (Simoens, 2011).

Following the EU principle of equitable access to high-quality and affordable healthcare for every EU citizen, the EU has taken measures to incentivize innovation in the field of orphan medication. This includes EU Regulation 141/2000 on orphan medicinal products, which inter alia simplified statistical requirements or granted market exclusivity in addition to a patent if pharmaceutical companies work on the development of ODs. Further, cross-border collaboration in the field of ODs was promoted by EU Directive 2011/24 on the application of patients' rights' in cross-border healthcare, by Council Recommendation 2009/C 151/02 on an action in the field of rare diseases and by the Council Conclusion of 17.06.2016 on strengthening the balance in the pharmaceutical systems in the EU and its member states, mainly with regard to information sharing and voluntary alignment of health technology assessment (HTA). We also applaud the Commission's proposal for a regulation on HTA released on 31.01.2018 which is expected to enhance the clinical assessment of ODs. Thereby, EU member states are provided with standardized reliable information that can be used as a foundation for national pricing negotiations (Morel et al., 2013).

Since 2000, EU action has certainly led to improvements in the field of OD innovation and availability; however, to provide effective and affordable treatment for the complex variety of rare diseases, further action is needed - especially regarding affordability of OD. The development, authorization and patent protection of ODs taking place on EU level in accordance with EU competences is only the first part of enabling provision; the second part of providing patients with ODs is bound to pricing and reimbursement practices on national level in accordance with national competence. Hence, this proposal focuses on policy suggestions on EU level.

Taking into account previous efforts of the EU and remaining challenges, the problem statement formulated for this policy brief is: How can high prices for orphan drugs be reduced while continuing to incentivize the innovation in this field?

Policy Briefs

1. Transferable Priority Review

Introduction to the Transferable Priority Review

In addition to the orphan drug fast track approval we propose to implement a voucher for the priority review of another drug of the company's choice. This will incentivize companies to invest in orphan drug research without directly increasing the costs of orphan drugs. The idea is already implemented in the United States (US) but has not yet been implemented in the European Union. There is, however, leeway in current legislation which would enable its implementation. There are numerous advantages for companies to get a faster approval by the EMA, mainly more profit as the commercialization period under patent is longer. Nevertheless, the US model is only an inspiration and before implementing the transferable priority review in the EU the model need some changes to avoid pitfalls already identified by scholars. This a short-term idea which could shift some of the reimbursement burden of the current system in place for orphan drugs.

The current European system legislation and how to implement the priority review voucher program

In the regular system it takes about 210 days for a drug to be approved by the Committee for Medicinal Products for Human Use (CMPH). Pharmaceutical companies may apply for a fast track procedure if they believe that the drug will be a game-changer when it comes to treating this specific disease (EMA, 2018). The legal basis for the accelerated assessment procedure flows from regulation 726/2004 on the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use (Regulation 726/2004, 2004). An accelerated assessment would be possible on the basis of Recital 33 juncto Article 14(9) of regulation 726/2004 if several conditions are met. These conditions are that the drug is meant to have a major public health interest and also has a great deal of therapeutic innovation. Meeting the requirements and also gaining approval from the CMPH would lead to a reduction of the market approval time to 150 days, so approximately a reduction of two months (art. 14(9) Regulation 726/2004, 2004).

Article 14(9) sets out clear limitations as to what drugs qualify for an accelerated procedure, namely the drug is supposed to have a major interest from the point of view of public health and the entire request has to be approved by the CMPH (Regulation 726/2004, 2004). The explanatory note of art. 14(9) of the regulation provides us with information about the interpretation of the term "major interest from the point of view of public health", which provides us that there is no uniform definition of this term, which leaves us with a possible broad interpretation of the term. (Explanatory note on article 14(9), 2016 p.4) The applicant for the accelerated procedure should provide why he thinks that he would justify for the faster procedure. (Explanatory note on article 14(9), 2016) With the arguments brought and the information provided about the drug it is up to the committee to approve the application for an accelerated procedure or not. (Explanatory note on article 14(9), 2016).

Defining the transferable priority: The FDA voucher incentive and its advantages

If we take a look at the US process of getting a drug approved, we can see similarities to Europe. The normal process of getting a drug approved takes around 10 months; this

process is only shortened if a product promises major improvements in effectiveness or safety. However in comparison to Europe; US applied the voucher incentive in 2007. The goal of this incentive was to encourage development of new drugs for neglected or rare (paediatric) diseases. The manufacturer does not only receive priority review for the orphan drug they moreover receive a 'voucher' to get priority treatment on another drug of their choice. In the US the voucher is not company bound, which increases the value of the voucher itself. It enables small companies to sell their vouchers to other companies (Ridley & Régnier, 2016).

Looking into this analogy it is notable that there are two things that could be to our potential interest in setting up a European equivalent to the priority review system established by the US Food and Drug Administration (FDA) voucher incentive. There is a broad interpretation of the term major public interest, which allows us some leeway as to when the application may be effective. Also, there is a case-to-case analysis by the CMPH into who will be eligible for the fast track procedure, so it is ultimately up to the discretion of the CMPH to decide who gets to receive the advantage of quicker market approval.

This could mean that there is a possibility for pharmaceutical companies to be awarded a fast track procedure for a potentially profitable drug whilst at the same time still operating within the legal framework that was set out. A broader application to the article and the use of a broader interpretation of the terms in this article is advisable. Mostly to create incentive for the pharmaceutical companies to invest in orphan drugs research by giving them the possibility of having faster market approval for other drugs that are being developed by them.

Positive effects for manufacturers

Implementing this system would have three positive effects for manufacturers: a competitive effect, a time value effect and an exclusivity effect. The competitive effect ensures the company a big market share as they can bring their product sooner to the market then their competitors. The time value effect entails that the costs that have been made in the manufacturing process can be earned back a couple of months earlier than in the normal process. The exclusivity effect describes the exclusive position the drug enjoys on the market. As it was introduced earlier to the market it has to deal with less competition.

Potential problems of the FDA voucher incentive and improvements for the European model

However, there are also hurdles and problems that need to be addressed. A problem that was identified by Mullard (2015) was that these voucher were used by companies who wanted to bring an already approved drug to the American internal market. The objective of encouraging new innovation is thus lost. Hence, for the application in European countries it might be beneficial to consider a slight redesign of the American system. Instead of enabling companies to use the vouchers for any drug, criterion could be implemented to restrict it to a certain group of drugs e.g. to drugs with a high level of invention. Another potential flaw could be that vouchers might delay the entry of a generic drug by a few months. This is an unfortunate consequence as prices will stay higher for a longer time, nonetheless the added benefit of the new drug for the orphan disease compensates this slight delay in the arrival of generics.

Another limitation is that the drugs that get an accelerated review due to the voucher may be using resources that should be dedicated to the accelerated approval of more important drugs. In the USA, the FDA asks for a fee for using the voucher

(Kesselheim, 2008). This fee is to pay for the added resources that the agency needs to spend on doing the fast approval and to ensure that enough resources remain for the actually high track medicines. Furthermore, the FDA requires a 90 days' notice before the use of a voucher. Applied to the European context, Ridley and Sánchez (2010) propose that the EMA could ask for a fee of 1 to 2 million euros to cover the additional costs of accelerated review.

2. Big & Rare: Big Data and Orphan Drugs

Introduction

For this intervention, the focus is on how the European Commission should use and regulate Big Data for Orphan drugs, to steer innovation, control costs and improve access to drugs for patients with rare diseases. The basic idea behind the hereby proposed model is that, while Article 168 of the Lisbon treaty poses severe restrictions on the ability of the Commission on setting incentives by acting on prices; big data and information could be used as "*currency/facilitator too*l" by the commission to increase their negotiation/contracting power. From a legal point also maybe reiterate that they have a shared competence in this field together with the Member states. Legal basis is art. 168 *juncto* art 4 TFEU, (general competence in art. 4 specific competence in art. 168).

Landscape analysis:

Who are the stakeholders? What is the current legal framework?

General Data Protection Regulation

The General Data Protection Regulation (GDPR) aims to protect the data of EU citizens. For this proposal Art. 5 of the regulation is relevant, as, it points out principles used to process personal data, namely consent, purpose limitation and data minimization. Moreover, it is essential to mention the overarching principle of transparency, in order to assure symmetric information of parties.

Due to the enormous number of data that will be collected, it is important to stress the right to be forgotten (Art. 17) that needs to be read in accordance with the essential principle of the EU. Make sure to also look into Art. 9(1) *juncto* 9(2)(h), this gives you the permission of using medical data since this is a special type of data. Art. 5 does indeed point out the general principles regarding the usage of data, but more specific categories are also mentioned for data that needs special protection.

Use of big data by private pharmaceutical industries

The existing evidence shows that most pharmaceutical companies are adapting their business model to the rise of Industry 4.0 and use of "Big Data" (SNSResearch, 2017). Data analytics represent a ground-breaking tool for pharmaceutical business models, with application ranging from discovery and development, to risk management and marketing (PEX). *Novartis* (Novartis, 2016), shows how the private sector is implementing digital transformation to drive efficiency in the life cycle of drugs and ultimately to improve patient's quality of life. Within McKinsey, big data are seen as a promising tool for predicting modelling of biological process, appropriate identifications of patients for clinical trials, real time monitoring of data, and fast and easy transfer of data between functions (Court, Aaser, Ariker, Brown, & Coyles, 2015). Nonetheless, the collection, integration, and organization of the large variety of data remains the major challenge commonly identified by pharmaceutical companies (Tormay, 2015). This is particularly true for rare diseases and orphan drugs, where information is segmented

and thus, severely impairs drug development (Day, 2010). In this regard, the use and elaboration of existing platforms might represent an optimal solution.

Building on existing platforms with integration of case studies
Among the various existing platforms which aim to store data of rare diseases, EURD and IMI2, stand out as their setup is comparable to the proposed model.

1. *European Platform for Rare Diseases (EPRD)*

Currently there are 600 rare disease registries across Europe, however no uniform accepted standards which govern the collection. This means that often more than one registry exists for the same rare disease, or that registries exist for only 20% of rare diseases. For now, there are multiple projects which tackle this issue, but there is no single European platform. However, the EU believes that patient registries and databases not only improve the development of clinical research through pooling the data and increasing the sample size, but also effectively improve the patient care.

2. *IMI2*

The Innovative Medicine Initiative (IMI) launched the project "Big Data for Better Outcome" (BD4BO) with the aims to catalyse and support sustainable health care system in the EU. Moreover, it seeks to exploit the opportunities offered by big and deep data sources in a few representative disease areas (Szócska et al., 2017). Additionally, this project aims to put together a methodological framework to guide big data research and to invite stakeholders to discuss the future of health systems shaped by big data.
There are different programs supported by the BD4BO, namely BigData@heart (focusing on heart disease), Harmony and a similar project of prostate cancer.

Due to the design of the project and the similarities with rare disease, we decided to focus on Harmony. Harmony aims to deliver a series of benefits for patients, healthcare providers and manufacturers within the hematologic malignancies. The limitation of data on this disease, due to the rarity of this condition and the diverse health care practice across EU, is problematic for policy-makers. Indeed, the lack of comparable data made the creation of a uniform policy, and benchmarks difficult (Szócska et al., 2017)

One of the key elements of this project is the partnership of different stakeholders, such as pharmaceutical industry, universities and EU/National agencies.
Our idea is to combine the use of big data, and European Platform for Rare Diseases, in order to create a new platform that aims at developing strategies to improve the R&D and innovation of orphan drugs. In this project, the Commission will have a role of supervision and will steer the project.

Effect: How does this idea tackles the problem?

Innovation in orphan drugs: data to steer orphan drug R&D
The use of big data could change the paradigm of Innovation in the pharmaceutical industries, indeed it could advance the frontier of medicine and boost R&D productivity in discovery, development and safety (Court et al., 2015). As stated above some pharmaceutical industries are already using big data to steer innovation.

Novartis was the first one to open the door to the use of big data with the intention to boost the research and to save exceeding cost.

Indeed, the McKinsey Global Institute estimated that applying big data strategies to better inform decision making could generate up to 100$ billion in value annually across the US healthcare system. The use of big data will improve the efficiency of

research and clinical trials, and will build new tools for physicians, consumers, insurers, and regulators to meet the promise of more individualized approaches.

As mentioned before, clinical trials are costly and time inefficient, especially phase three trials. With the use of big data, trials can be monitored in real time to "identify safety or operational signals requiring action to avoid significant and potentially costly issues such as adverse events and unnecessary delays" (Cattell, Chilukuri, & Levy, 2013).

This is only one of the uses and of the advantages that big data would bring in the field of orphan drugs. However, Tormay (2015) identifies the collection and processing of various data to be the major challenge for the pharmaceutical industries with regards to innovation and big data. This is particularly true in the field of rare diseases where information is fragmented and difficult to collect, as seen before for the hematologic malignancies. Nevertheless, the commission could facilitate and regulate the collection and processing of relevant data.

Role of the European Commission

The role of the Commission in protecting clinical and patient data is vital throughout the Big Data Revolution, and technological advances of the private sector must be monitored, however also used as a tool for collaboration. According to the McKinsey report 'The Big Data Revolution in health care' (Cattell et al., 2013), technological advances in health care allow data to be exchanged more easily, ensuring transparency, making it easier to 'clean data' and to protect patient privacy. For instance, new programs can remove names and other personal information, to prevent it from going from the records into the large data bases.

Conditions and steps to make it happen

This section examines the strategy which build upon the process of innovation in orphan drugs in the time of the 'big-data' revolution. The strategy is structured in two steps; firstly, an analysis of stakeholders' intentions and space for action through *Delphi method*. Both stages aim at building a common platform for action through which the commission could eventually set incentives to steer innovation and improve access to and affordability of orphan drugs based on the use and provision of data.

1. *The Delphi method*

The Delphi method is a method of assessment, similar to the technique of *bricolage*, where one uses whatever resources and repertoire one has, to perform whatever task one faces (Huber & Glick, 1993). It is a method for group communication, in areas of limited research, in order to forecast certain scenarios, and to derive general consensus among various stakeholders. By using questionnaires and surveys the Delphi method is used to identify the range of opinions on particular matters, to test questions of policy or clinical relevance, and to explore (or achieve) consensus on disputed topics (The Psychologist, 2009). In the light of our proposal, this method can be seen as a method of collaboration between various stakeholders. The stakeholders here being the Commission, the major pharmaceutical companies, as well as the smaller biotech companies and universities, which work together on the big data platforms; for instance, in IMI2.

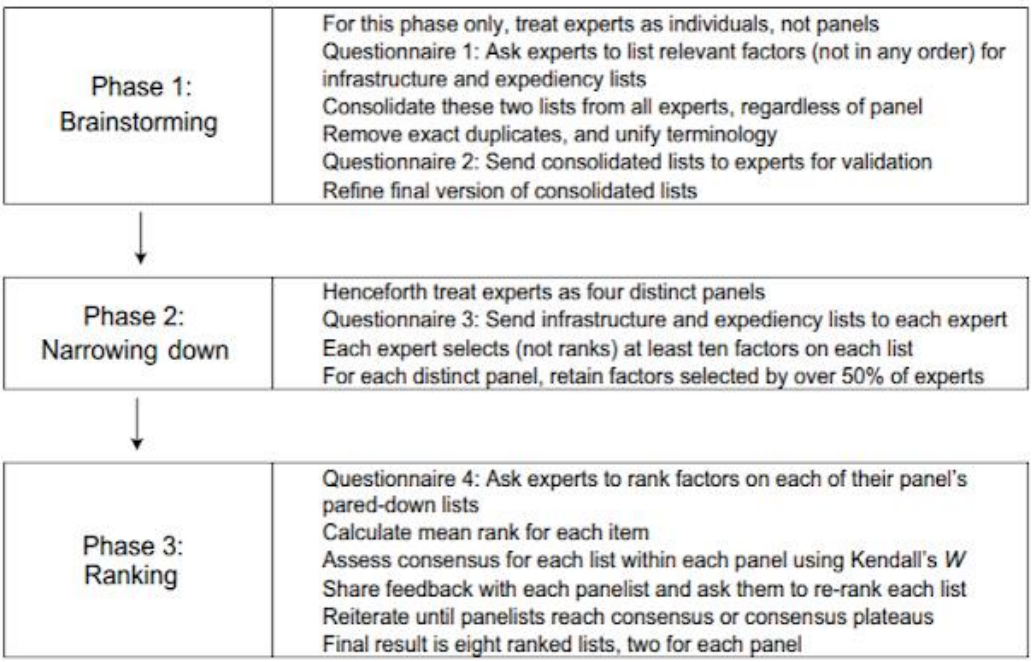

Figure 4. Delphi Study administration process
Source: Okoli and Pawlowski, 2003

2. Public-Private Partnerships (PPP)

Public-Private Partnerships (PPP) are long-terms contracts, wherein the public partner, therefore a government entity, delegates some of its own responsibilities to a private partner. These contracts can last 15 to25 years, and therefore need to be flexible in their nature in the case of unforeseen events. The core goal of a PPP is to create a set of incentives and penalties towards other actors.

Similarly, to the Delphi method, in this case there is a collaboration between the stakeholders, which work together on the same platforms. The current proposal elaborates on the idea of a PPP for data management and analysis in the field of orphan drugs development. The PPP should aim at building a single platform on which several type of data could be shared. Reliable evidence does not always have to come from clinical trials (Day, 2010). The typologies of data and ownership of data varies extensively within the pharmaceutical industry spectrum (Figure 5). The platform should incorporate and structure all the relevant data and consequently make them available for companies that aim at investing in rare diseases. Moreover, health data are considered *sensible data* and their use is extensively regulated in the Directive on Data Protection. Therefore, the partnership should be based on two elements:

1) the ownership of data should be in the hands of the commission, and
2) the use of the data should be transparent and predefined.

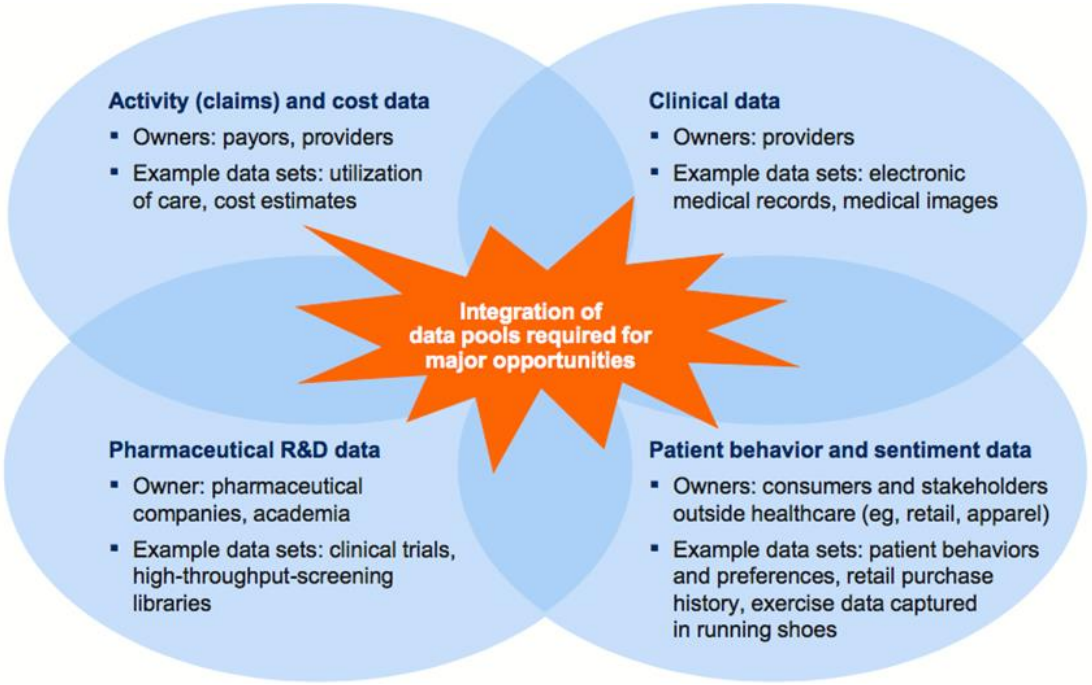

Figure 5. Primary data pools are at the heart of the big-data revolution in Healthcare. Source: *McKinsey, 2013*

Since pharmaceutical companies face major issues in accessing comprehensive and quality data (Tormay, 2015), they might be interested in the development of a EU platform with data on rare diseases. The current digital revolution offers EU decision-making bodies the opportunity to strategically redeploy themselves within the field of orphan drugs. However, the window for action might be narrow and aligning the interests of all the actors in such a short time frame might be challenging. Further research is needed to evaluate the specificities of the partnership and to elaborate the structure and components of the platform.

3. Public Venture Capital Fund

Introduction to the idea of an EU public venture capital fund for SMEs

The intervention envisions an EU public venture capital fund aiming to support small and medium-sized enterprises (SMEs) which are innovating in the pharmaceutical field. These may include biotechnological as well as bioengineering and biomanufacturing companies. The funding should be comprised of contributions by the member states of the Union, supplied in a proportional manner and similarly to existing EU funds for certain initiatives, such as Horizon 2020, the EU's biggest Research and Innovation programme. The fund will be granted to companies after a successful application and evaluation process according to specific criteria defined in advance. These should be inspired by the Eligibility and Evaluation Criteria of Horizon 2020, but extended by aspects in order to introduce and guarantee a research focus on orphan drugs.

Focus on the third phase of clinical trials

The focus of the capital supplied by the fund should rest with the third phase of the clinical trials and be performed in collaboration with an independent governmental or non-profit institute. The motivation to engage at this stage of the clinical evaluation is twofold: first, it can be argued that a significant portion of the overall trial costs are

produced here and are likely to be ever increasing because of advanced standards (English et al. 2010 / Sertkaya et al. 2016). Second, a successful execution of the first and second trial phases enables an assessment of the potential of a new drug with a limited amount of risk (Wong, Siah, & Lo, 2018). In addition, risk will be diversifying funding over a range of different companies and projects.

Further, the majority of such trials is currently funded by large pharmaceutical industries (Ehrhardt, Appel, & Meinert, 2015), generating a bias in trial results to show more successful outcomes in comparison to those conducted by public institutions (Chopra, 2003). The proposed fund model tackles this issue, as the supply of capital is made contingent on performing the trials with independent research institutions.

Framework and mode of operating the fund

The intervention is applicable to medicinal drugs in general as well as to orphan drugs, specifically, and is compatible with the current framework of incentives for either. However, it does not depend on the current incentives for orphan drugs, such as market exclusivity, to function, since research into this area can be designated as one criteria to gaining access to the fund.

The intervention strives to prevent the continuous consolidation of the market due to the practice by large pharmaceutical companies of acquiring many small companies with promising innovations. These acquisitions can involve tremendous takeover costs, that in the end must be reimbursed and therefore drive up prices. However, in the current system, smaller companies rely solely on these financial means of big pharmaceutical entities to stem the high phase III trial costs. The proposed fund model offers an alternative. Small innovators using the fund are able to stay independent, rather than selling their company for a fraction of its eventual value and contribute to enlarging the market and fostering price competition.

In addition, the involvement of public institutions facilitates more objective trial results and increases transparency regarding the structure and magnitude of trial costs, which are heavily debated in literature (Adams & Brantner, 2006). Having access to additional data on R&D costs decreases the information asymmetry and provides the Union's member states with more expertise on the value of the drug. Thus, it gives the Union's member states a stronger bargaining power in price negotiations at the national level, eventually leading to lower prices. To make asymmetric information even less of a problem, access to the fund can be linked to a further sharing of information on already existing R&D expenditures. Anyhow, the existence of more innovative companies will increase competition, also resulting in pricing pressure. The application of different innovations for the fund, and the selection of those by a committee representing the entire EU, furthermore ensures that the Union sets the priorities for research, for example to favour orphan drugs. Consequently, the fund model secures that the needs of all EU citizens are taken into account equally

In summary, the intervention will increase the size of the pharmaceutical market and thereby competition, thus decreasing drug prices, while simultaneously fostering innovation, also in priority areas such as orphan drugs, and increasing transparency.

To assess its success and further possibilities for improvement, an evaluation of the fund is recommended. The fund could be rolled out sequentially, starting with a smaller budget which then increases in its size. There is even room to extend funding to phase II trials, involving higher risks, while bearing an even higher potential for desirable competition effects and lower reimbursement prices.

Discussion

The aim of this proposal was to determine how the high prices for orphan drugs can be reduced while continuing to incentivize the innovation in this field. The field of drug development is a complex one with many stakeholders involved.

Several ideas were rejected in the progress as new information came to light. First, it was considered to bring generic drugs sooner on the market, so consumers were able to buy the off-brand medication sooner. However, to bring generic drugs on the market the patent of the original drug has to expire. Thus, it is not possible to bring generic drugs sooner on the market. Second, it was considered to extend exclusivity on the pharmaceutical market. This idea was rejected because the European Union already has initiatives which do this exact same thing. Third, HTA harmonization was considered as a topic. Due to the recent publication of the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU which discussed our ideas in detail, it became superfluous to mention it in this paper. We applaud this report! However, we would like to stress the importance of orphan drugs. In our opinion it would be beneficial for further innovation and research to mention them in more detail in the finalized report. Fourth, several ideas targeted the reimbursement and pricing of the drugs itself. Yet, we did not go deeper into the topic because of Article 168 of the Lisbon Treaty which states that health related matters lie in the hands of each individual member state. The European Union has no legal competence in the area of health and thus not in the pricing and reimbursement of medicinal products.

Multi-Speed Europe as a Solution?

Since it can be rather difficult to have all of the Member States work together on the topic of Orphan drugs other approaches to harmonisation have also been discussed. A possibility would be to create an Enhanced Cooperation between a certain amount of Member States in the European Union. In order to use the chapters in the Treaty on European Union (TEU) and Treaty on the Functioning of the European Union (TFEU) regarding Enhanced Cooperation we need at least nine Member States working together on the topic at hand. What we would create in this way would be the idea of Multi-Speed Europe, in this way the development would still continue, but not on an equal speed all over the Union. The largest advantage would be that we still continue the development and the Member States that opted out at the beginning still have the possibility to join in at a later stage if they wish to. However, the disadvantages also weigh in relatively heavy, namely the Member States would have the feeling that they are left out in the potential development of the system as such and also it is a politically very heavy measure to use for Member States, this because it shows the potential flaws of the European Union. Therefore it has not been used that often yet and it has only been successful in for instance the field of divorce law (Rome III regulation) and Unitary patent.

Using the Enhanced Cooperation can only happen when it is not an exclusive competence of the Union. This is not the case in the field of Public Health, where the shared competence comes from art. 4 *juncto* art. 168 TFEU. Therefore, using it in this field has potential, but it is a heavy measure that is only used if no consensus can be found on the topic that it addresses.

Conclusion

The three proposed models provide promising insights in mechanisms that may lead more incentives to develop orphan drugs whereas as the same time aiming to reduce the costs of these drugs. It should be noted that the proposed models are complementary to each other and potentially reinforce their effects. For example, providing smaller companies with the possibility of selling their transferable priority vouchers and to give them access to support for phase III trials may both make them a better match to the bigger players on the market. In additions, the use of big data analytics may increase efficiency in researching, possibly reducing costly clinical trials (especially phase II and III trials).

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