Technological Forecasting & Social Change 161 (2020) 120333

Contents lists available at ScienceDirect

Technological Forecasting & Social Change

journal homepage: www.elsevier.com/locate/techfore

Opportunities and barriers for innovation and entrepreneurship in orphan drug development

Olga A. Belousova*, Aard J. Groen, Aniek M. Ouendag

University of Groningen, University of Groningen Center of Entrepreneurship

ARTICLE INFO

Keywords:
Healthcare innovation
Orphan drugs
Rare diseases
Responsible innovation

ABSTRACT

Orphan diseases pose both a challenge to the global medical community and an opportunity for it to focus on global peace engineering and innovation. Where, any single orphan disease is rare, when taken as a whole they affect more than 250 million people throughout the world. This number by comparison is larger than the global number of cancer and AIDS patients. We add to the literature by mapping the available knowledge in the orphan drug development field and exploring the tensions at play for innovation and entrepreneurship in this field. We further add to the literature by providing a framework to review this field based on social systems theory. Our review highlights the gaps in research and proposes a path forward in understanding of and learning from the orphan drug development field.

INTRODUCTION

Rare diseases pose a challenge to society on a global scale. Although most of these diseases have a prevalence of less than 10 patients per 1 million inhabitants (Aymé and Hivert, 2011), together they affect at least 250 million people around the world (Grossman et al., 2014). However, for nearly 7000 rare diseases, fewer than 5% have at least one approved pharmacotherapy (Hechtelt Jonker et al., 2020; Wood et al., 2013). This means that most of the individuals affected by these diseases are being deprived of basic needs, such as proper diagnosis, treatment, and a cure (Certo and Miller, 2008), thus offering opportunities for global peace engineering and innovation.

For those of the rare diseases, where medical treatment or cure are possible, challenges for developing them include the limited knowledge available for most diseases, the difficulties of generating adequate efficacy and safety data in small populations and the risk of financial unsustainability for both developers and health-care systems (Hechtelt Jonker et al., 2020). Although governments intervene, their efforts alone are not sufficient to close the market gap that results from the on average small market potential of each rare disease. Orphan drug (OD) development is an area where governments, patient communities, knowledge institutes, and private actors such as foundations and social impact–oriented enterprises actively work together on socially acceptable, sustainable, and desirable innovation to overcome this global challenge.

With this paper we offer a critical review of the current academic literature about OD development. Drawing on social systems theory (Groen, 2005; Parsons, 1964;1977), we develop an analytical framework to identify main themes and contributions in the goal setting, adaptation, integration, and pattern maintenance mechanisms of the OD field. We then discuss the extent to which this literature reflects the recent changes in the field and propose a path forward for future research.

Our results show that the current debate in the literature relies heavily on an economic logic of analysis, which would benefit from reframing into more systemic thinking in order to include the needs and voices of a broader range of stakeholders. We further note that existing narratives in scientific, regulatory, and public discussions "*established a locus of responsibility for orphan drugs in the … government*" (Grossman, 1984, p.151) while overlooking alternative solutions currently being implemented by the stakeholders of the rare disease community. Applying a multi-level deconstruction to the publications in the OD field, we note important gaps in the research. Among others, future research could explore the roles and boundaries of the stronger and more visible participation from the patients and patient communities, acknowledge the antecedents and impact of technological advances for novel business models, and study the mechanisms of governance of multilateral stakeholder collaboration networks. These trends may augment the measures already offered by governments and stimulate new opportunities for peace engineering and innovation thus contributing to solving this global challenge and furthering the goals of a sustainable and peaceful society.

* Corresponding author. Olga A. Belousova, Kadijk 4, 9747 AT Groningen, The Netherlands.
E-mail address: o.belousova@rug.nl (O.A. Belousova).

https://doi.org/10.1016/j.techfore.2020.120333
Received 27 March 2020; Received in revised form 30 June 2020; Accepted 15 September 2020

METHODOLOGY

Review method

We followed the planning, execution, and reporting procedure for systematic literature review of Tranfield et al., (2003). During the planning stage, we defined the objectives of the research and identified the key data source. Our objective was to describe and systematize the academic publications and discussions on OD development. For this purpose, we searched the ISI Web of Knowledge Social Sciences Citation Index (SSCI) database for relevant studies in journals published in English. This database was selected because it is one of the most comprehensive databases of peer-reviewed journals in the social sciences. As we are interested in innovation and entrepreneurship in the drug development process for rare diseases, the search items were: "orphan drug" and "rare disease drug." We did not conduct searches for individual technologies, components, or any of the 7000 specific diseases.

The search was conducted in November 2017 and resulted in 477 records from all years and journals registered in the database. We further focused on double-blind review papers and excluded open-access articles and conference abstracts, assuming they represent the dominant discussions within the field. The refined sample contained 179 records. Next, as the search triggered results on drug use among orphans, we excluded categories such as "rehabilitation," "substance abuse," "toxicology," and "immunology" reducing number of records by 23. After screening the abstracts and full texts, we manually removed further 26 articles that did not deal directly with rare diseases, which left us with a sample of 130 articles.

The selected articles had appeared in 70 outlets ranging from medical to law and economics journals, with a majority of the outlets having only one or two articles. Nine articles appeared between 1984 and 1995, 18 articles between 1996 and 2006, 43 articles between 2007 and 2012, and 60 between 2013 and 2017.

Analytical framework

To structure our analysis of innovation and entrepreneurship in the development of ODs, we drew on the structural-functional sociological theory of Talcott Parsons (Parsons, 1964,1977) and its adaptation to entrepreneurship by Groen (2005). Social systems theory allows an understanding of developments in society (Parsons, 1977), and the adaptation to entrepreneurship can shed new light on the growth of entrepreneurial developments and the adoption of new technology (Groen et al., 2008; Heuven and Groen, 2012; Leloux and Groen, 2007; Middel et al., 2007; Pullen et al., 2012).

A social system was originally defined as "*a plurality of individual actors interacting with each other in a situation, which has at least a physical or environmental aspect, actors who are motivated in terms of a tendency to the 'optimization of gratification' and whose relation to their situations, including each other, is defined and mediated in terms of culturally structured and shared symbols*" (Parsons 1964, pp. 5–6). Following this definition, the four functional requisites of any system of action include: (A) adaptation or optimization of processes, (G) striving for goal attainment, (I) integration through interaction between actors, and (L) latent pattern maintenance of culturally structured and shared symbols (Groen, 2005; Murphy, 2005). This framework is traditionally thought to be pretty intuitive: A viable system needs to *adapt* to the changes in the external world, while defining, achieving, and defending its *goals* regarding which the members of the system interact and communicate to come to a sustainable level of *integration* and build order and maintain this in a *latent* pattern maintenance dimension of the social system. These mechanisms known as AGIL lay the basis of our multi-dimensional framework to analyze the viability of the OD development space.

Furthermore, to introduce a multi-level perspective we grouped the contributions into three levels – macro (global, national, and international issues), meso (industry, market, technology), and micro (individual actors). The definitions adopted here thus differ from the more traditional socio-institutional understanding of micro-, meso-, and macro- within healthcare field (Smith et al., 2019). Our approach builds instead on the ideas of the socio-technical dynamics models (Clark, 1985; Rip and Groen, 2001) and specifically, the perspective of "many visible hands," (Rip and Groen, 2001) where, instead of having market or government dominance in the development process, a multitude of actors is assumed to develop the innovation and its application, leading to an embeddedness approach (Granovetter, 1985; Laumann and Pappi, 1976). This approach offers a higher promise for the purpose of understating of the mechanisms for innovation and engineering of a peaceful, sustainable society.

Analysis of the contributions

Combining these two approaches, we read the full texts of the articles in the review and coded them according to the unit of analysis, and the main mechanism of interaction, following the AGIL model.

Adaptation. Here we grouped articles that describe how social systems cope with their external boundary conditions, such as their resource base, physical environment, and territory (Groen, 2005). As economic activity often serves to solve problems of adaptation, at a macro we looked for articles covering national budget instruments and concerns about national and societal budget impact of rare diseases. Articles covering the economic activity of markets, common business (revenue) models and pricing strategies were coded as adaptation on *meso* level. At a firm (micro) level, we coded articles reporting individual cases of drugs or firms.

Goal attainment. The goals of any social system have to be defined, prioritizing some over others, determining resource allocations, and directing social energies. Political activity organizes and directs the goal attainment on a macro level. Hence, issues of legislation, prioritization, and ethical implications of rare diseases were coded into this category. At the same time, a plurality of actors, including institutional systems, define the order, power, and hierarchy at the market and industry (*meso*) levels. At the micro level of an individual firm, goal attainment is reflected in the power of an organization "*to decide on goals and to control resources and other actors to attain them*" (Groen, 2005).

Integration. All of the adaptive efforts of social institutions within a society need to be integrated into a cohesive and harmonious system. Individual actor networks form the micro level, while stakeholder relationships and interactions reside at the *meso* (industry or regional) level, and international relations and collaborations determine integration on the macro level.

Latency. The pattern maintenance function creates a state of (temporary) order in a symbolic system of values, norms, beliefs, assumptions, symbols, rule sets, and artifacts and it must be maintained and renewed (Groen, 2005). It allows for learning and change and, at the same time, makes up the identity and culture of a system (Groen, 2005). Fiduciary systems such as families, schools, and churches solve these problems of pattern/tension management at a societal level. Industry level standards and regulations set up the norms and rules on the *meso* level, and reflect the technological trends by embracing (or not) novel technologies and changes they bring. Knowledge accumulation, products, and the norms of an individual actor reside at the micro level.

Table 1. presents the overview of the results of the analysis.

RESULTS

We present the main findings along the AGIL model dimensions.

Adaptation

Out of 130 contributions, only 22 discuss the adaptation (economic) mechanism of ODs. We could identify the following main lines of

Table 1
Summary of the literature review results.

	Adaptation	Goal attainment	Integration	Latency
Macro (global, national)	(12) Budget impact & Societal outcomes of ODs; Financial incentives for biopharma; Assessment of reimbursement dossiers of OD across countries; Cost effectiveness thresholds for HTA	(29) Legislation; Patient access; Prioritization; Decision making on national level; Distributive justice; Ethical, legal and social implications of rare diseases	–	(34) Evaluation of policies across countries; Influence of values on HTA decisions; Alternative frameworks on prioritization; Change in the regulation; Role of FDA in pharmaceutical safety; OD regulations impact
Meso/Macro	(1) Prevent abuse of ODA by changing vocabulary	(1) Effect of patents on OD development in 3rd world countries		(5) Legitimate mechanisms for assessing value; Regulatory intervention and application; Treatment guidelines, processes
Meso (market, industrial, technological, regional)	(6) Focus on subsets of drugs/technologies; Business models, repurposing, clinical trial data sharing; Extraordinary pricing	(16) Market attractiveness for business; Opportunities for non-profits; Decision making in specific diseases/areas	(1) Social network analysis for community partnerships for health in Wisconsin	(12) Emerging technologies; Evidence of clinical and economic value; Advancing knowledge, diagnosis; process; Shared understanding / definition
Micro/Meso	(1) Venture philanthropy as a new model of research funding	(1) Case of patient group changing corporate practices	(2) Cases of building a Facebook or religious community	(1) Involvement of patients and parents in the whole cycle of drug development
Micro (individual players)	(3) Pricing of a specific drug; Cases of fraud	(2) Motives and incentives to go in OD space		(3) Experience of patients ``and not to be rare''

discussion: (a) the macro issues of ODs' impact on public budgets, reimbursement, and expenditures; (b) the *meso* issues of profitability and of companies entering the OD field; and (c) micro-level analysis of the costs of specific drugs.

First and foremost, in the discussion of the impact that ODs have on public budgets, there seems to be implicit consensus that, with the stimulation of OD development and the value-based (often, very high) pricing used, ODs can become an unbearable burden on society (Benjamin et al., 2017; Michel and Toumi, 2012). Some technological trends further reinforce this concern: With the adoption of pharmacogenomics, precision medicine will allow many more medications to qualify under OD regulations, which could further increase this impact on the budget (Danzon and Towse, 2002; Loughnot, 2005) and have even larger societal consequences.

However, other contributions in the review show that only a few ODs enjoy very high sales and around 90% of this sales volume comes from "common disease" patients and not patients with a rare disease which is possible for ODs with non-orphan indications (Divino et al., 2016). Furthermore, Maresova et al., (2016) show that ODs influence between 2 and 11% of the budget impact and do not represent an immediate threat to the system of public health insurance. Similarly, Schlander et al., (2015) assessed both existing and still in the pipeline drugs for ultra-rare diseases and concluded there will be no threat for the next 10 years. Hence, there are two distinct lines of discussion in the literature. While some authors alert for the possible threat of OD for the public budgets, others seem to argue that facts do not support these fears.

The second major discussion within the macro economics of the ODs focused on the effectiveness, profitability, and methods used to assess the value of ODs. Bruyaka et al., (2013) found that the rare disease market is capable to generate two-digit growth and allows for innovations in the treatment of more common and widespread diseases to be reused, thereby increasing the return on investment. Grabowski and Vernon (2000) observed that drugs from the late 1990s included more blockbusters with higher reimbursement rates per treatment, or combining OD status for some indications with approval for other non-orphan indications. Approximately one-fifth of the FDA approved drugs in the past 20 years have designations in orphan and non-orphan indications, among them Avastin, Opdivo, Enbrel, Herceptin, Humira and Remicade. Lazonick and Tulum (2011) further explore the fact that given the 10–20 year time-frame for developing biotech products and the lack of profitability of the industry as a whole, the US biotech boom should not have happened. They report that thanks to the existence of the speculative stock market venture capitalists in US biopharma are able to generate returns on their investment in ODs through IPO before the product was marketed, even if it was not brought to the market at all. This discussion stands in surprisingly stark contrast with the idea that ODs are unprofitable and unattractive for business. Are there circumstances under which ODs can be a basis for sustainable business model?

The insights from the market (*meso*) level analysis and show there may also be a dark side to the OD business practices. Here, many researchers signal the unfair play that allows niche-buster profits to be reaped, such as relabeling to expand patient categories (Berlin, 2009), stratification ("salami slicing") (Abramowicz, 2011; Boon et al., 2008; Goldman, 2000; Loughnot, 2005), or the manipulation of reimbursement negotiations (Coyle et al., 2014; Hemphill, 2010; Rachul et al., 2016). Thus, there is an important ongoing discussion about unethical behavior within the OD field. Which prompt questions for further research on the dark side (and how to eliminate it) of OD business: Has the phase where governments needed to stimulate the involvement of business into OD development passed, and is there now a need to control it instead? This brings us to the discussion of the goal attainment function in the OD.

Goal attainment

We identified 49 articles describing and discussing the goal attainment function in the OD field and analyzing whether ODs is a strategically interesting opportunity for business. The split across levels shows that the researchers' primary concern is the macro level: In total, 29 articles focus on the national level and discuss the role of government and legislation pertaining to ODs, along with ethical questions of societal welfare distribution between rare and common disease treatment development. At the *meso* level, we identified 16 articles discussing the issues of the motivations and roles of alternative actors in the field. Just two articles discuss the micro level. Only one article addressed multilevel issues.

At the macro level, in contrast with the economic discussion, regulatory literature focuses on stimulating drug development in the OD field. The OD market has very high entry barriers. Small patient pools mean limited and weak clinical data at the time of the product launch, and that R&D costs need to be recouped from smaller sales which results in relatively high prices (Boon et al., 2015). This situation led to the enactment of the Orphan Drug Act (ODA) in 1983 in the US and similar subsequent statutes in other countries [Japan in 1993, Australia in 1997, and the European Union (EU) in 1999] (Bruyaka et al., 2013). These regulations provide incentives that include financial support, tax credits, and extended market exclusivity (Murphy et al., 2012) for OD sponsors, where "*there is no reasonable expectation that the costs of developing and making available a drug … will be recovered from sales*" (Arno et al., 1995, p. 234). While OD regulations have proved to be an effective tool in stimulating the development of rare disease therapies (de Vrueh, 2014), they remain under constant scrutiny.

Already early reflections on the ODA have highlighted that, under pressure from the pharmaceutical companies, the "reasonable profit" criteria have been approximated by the size of the affected population, which, in return, has allowed some companies to create blockbuster profit models (Arno et al., 1995). Numerous alternative approaches to market regulation in order to allow compensation for a fair effort while preventing a strain on regulations have been suggested. They include defining what profitability means, as well as the period of time over which profitability is assessed (Denis et al., 2010), introducing a profit cap (Godman et al., 2015), considering differential pricing (Murphy et al., 2012), allowing competitive bids instead of market exclusivity (Abramowicz, 2011), or experimenting with alternative tax credits and price tiers (Kanavos and Mossialos, 1999; Valverde et al., 2012; Villa et al., 2009; Yin, 2008). However, adoption of these measures has been scarce.

Following the discussion about effectiveness of the incentives for entering the OD market, the ethical issues of distributive justice is another dominant theme: Is it justified to sponsor ODs using limited public funds? The combination of substantial prices and high degrees of uncertainty in OD development leads to complex decision making about the approval and reimbursement of ODs (Boon et al., 2015). Indeed, many ODs are so expensive that they fail to meet the standards of HTA cost-effectiveness criteria for reimbursement from public funds. This raises concerns that patients with rare diseases are disadvantaged by the system and questions the use of standard cost-effectiveness criteria for ODs. Many contributions in the review discuss the effectiveness of HTA-based decision-making frameworks (Salas-Vega et al., 2016; Wagner et al., 2016) and solicit societal responses regarding preference for the treatment of rare vs. non-rare diseases (Desser, 2013; Desser et al., 2010; Mentzakis et al., 2011; Wiss et al., 2017). These studies, however, highlight issues of relying on public polls, such as potential biases of societal preference for prioritizing rarity (Desser, 2013), choice under conflict (Tversky and Shafir, 1992), zero-sum framing (Dragojlovic et al., 2015), and the unacceptability of discrimination based on social and biological attributes (Boy et al., 2011), suggesting that this approach is far from ideal to solve the problem.

Furthermore, there seems to be a discrepancy between the macro and micro levels of demands and expectations. While legal and economic incentives established by the regulations improve the economic attractiveness of OD development, "*none of them taken separately is typically sufficient alone to motivate orphan drug development*" (Bruyaka et al., 2013, p.56). Bruyaka et al., (2013) identified that "*Exclusivity is an incentive but it is not what makes firms go into the orphan drug space; rather it is the good match for the technology that company holds*" (p.57). Beyond the economic, legal and technological reasons, the literature also reports the upcoming engagement of families and philanthropies in developing new OD ventures (Davies et al., 2017; Wood et al., 2013).

Latent pattern maintenance

The latency or pattern maintenance function creates a state of (temporary) order in a symbolic system of values, norms, beliefs, assumptions, symbols, rule sets, and artifacts (Groen, 2005). We identified 55 articles distributed over four core themes: (a) content and application of norms and regulations within and across countries (*macro*); (b) knowledge systems and technology dynamics (*meso*); (c) *micro/meso/macro* level discussion of the regulation's implementation guidelines and cross-level collaboration; and (d) patient experiences (*micro*).

The regulatory statutes are a central theme for most (34) of the articles, comparing the content, process, and effects of the legislation within (Moors and Faber, 2007; Pauwels et al., 2015; Wonder and Chin, 2015) or across countries (Blankart et al., 2011; Denis et al., 2010). What becomes apparent is that implementation differs significantly from one country to the next. Even though some authors argue for significant differences between the US and Canada (Herder, 2013), the EU is probably affected the most because of its linguistic, economic, and legislative diversity (Denis et al., 2010; Nicod and Kanavos, 2016; Picavet et al., 2012; Richter et al., 2015). The discussion here often concludes with calls for greater harmonization and integration across regulations in order to create larger markets for firms, facilitate transparent decision making, and ensure better accessibility of drugs for different categories of patients, including low-income, ethnic, high-risk, or late-stage patients (Alqahtani et al., 2015; Iskrov et al., 2012; Rai, 2002; Rosselli et al., 2012).

On the *meso* level, we can observe a separate discussion focused on technological advancement and knowledge accumulation. A large proportion of rare diseases have a genetic origin. Therefore, novel therapies mostly come from technology fields related to genetics, such as biotechnology, gene therapy, and pharmacogenomics (Boon et al., 2008). However, a significant amount of time is still needed for these emerging technologies to reach maturity (Avery, 2010; Boon and Moors, 2008) as their advancement depends on the availability of genetic information (Ferlini et al., 2013). Owing to the huge geographical dispersion of patients and experts, advocacy groups often lack the funds to support individual biorepositories or to locate and participate in existing ones. Hence, most of repositories suffer from duplications, incorrect terminology, platform incompatibility, or are proprietary and not available to all investigators (Benjamin et al., 2017). Nevertheless, this effort is crucial to sharing and exchanging data and to developing studies in a meaningful way (Rubinstein, 2013).

Novel funding schemes are also important when it comes to steering the application of the new technologies to areas of market failure, where multinational companies' market strategies drive the innovation trajectories of life sciences into more profitable streams (Milne and Tait, 2009). Olivier and Williams-Jones (2014) have suggested that research based on pharmacogenomics knowledge and technologies replicates the 90/10 health gap ratio in mainstream drug development and falls short of the promise to help increase justice in global health. Several initiatives are being developed to solve this challenge (Groft and Rubinstein, 2013), and experts suggest that European repositories available to researchers, foundations, and small startups could play a pivotal role (Denis et al., 2010).

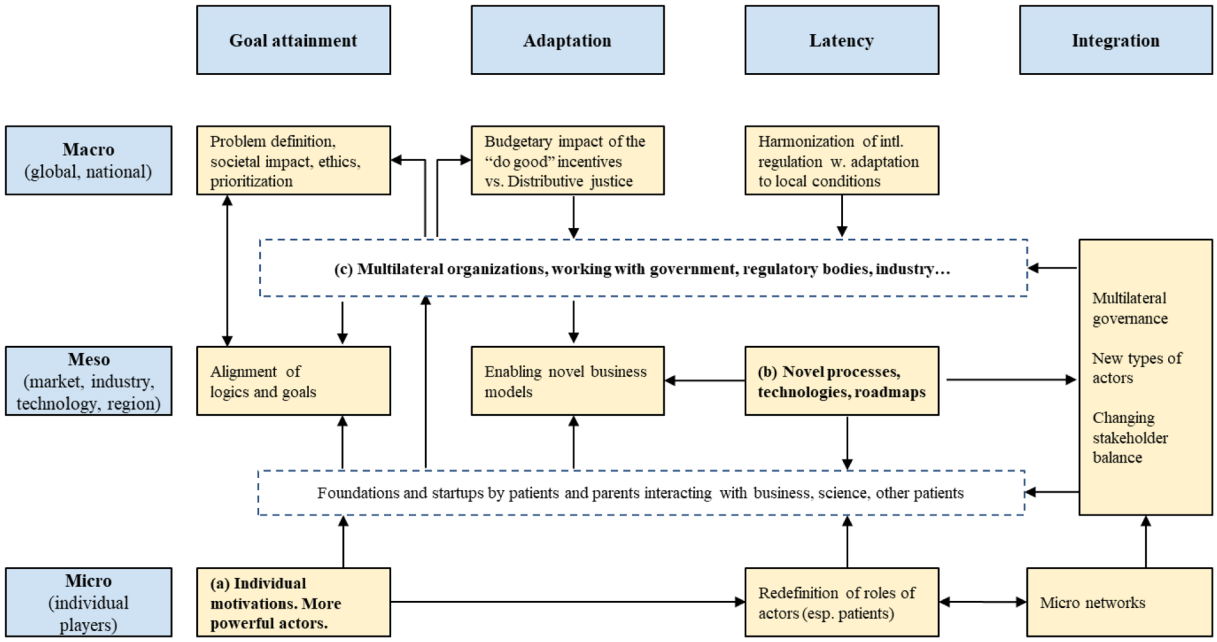

Fig. 1. Areas of development and future research in OD field for responsible innovation and entrepreneurship.

Furthermore, the literature at the *meso* level describes the diverse pathways of developing an OD, including drug discovery, rediscovery, and redirection and identifying potential new uses for compounds that have undergone significant R&D by the industry. By using compounds that have already cleared key regulatory steps, repurposed drugs make it possible to accelerate the pace of therapeutic development. An opposing yet similar discussion is focused on groundbreaking, transformative drugs that, while designed to treat rare diseases, become transformative by opening up new therapeutic pathways or establishing a new understanding of pathology, thereby producing a much greater societal impact than initially expected. Kesselheim et al., (2015) and Groft and Rubinstein (2013) found that public–private partnerships combining publicly funded basic research with further development through collaboration between public and private entities have played a key role in discovering such drugs.

A handful of contributions at the *micro* level of cultural patterns discussion explore the meaning of "being rare." Huyard (2009) and Kesselheim et al., (2015) found that the biggest discomfort of rare disease patients relates to the process of diagnosis and that the search for a cure is not deemed the absolute goal one might have expected it to be. Both research teams acknowledged that their respondents would be satisfied with honest and reasonable efforts to gradually improve their situation. Research of Huyard (2009) highlighted the importance of providing patients and parents with action-oriented and ability-related information, while Kesselheim et al., (2015) reports the readiness of patients to be involved "*beyond the normal understanding of risk*". Similar thinking underlies the works on patient-centered drug approval (Mattingly and Simoni-Wastila, 2017) and evaluation (Kimman et al., 2017; Menon et al., 2015), which explore opportunities for patient involvement to reduce uncertainty in decision making. Some even suggest the leading role of parents and patients in accelerating research and developing treatment for their diseases (Wood et al., 2013).

Integration

Our review noted multiple mentions of the importance of networks, networking, and ecosystems as they allow learning across patient groups, regulatory bodies, and industry (Boon and Broekgaarden, 2013; Boon et al., 2008,2011). For example, realizing the importance of joint effort in developing therapies for rare diseases has resulted in the formation of a cooperative initiative within a national and supranational context among the EU, Canada and the USA, and the International Rare Diseases Research Consortium (IRDiRC) (Ferlini et al., 2013). The many patient-led and governmental networks, such as NORD in the USA, CORD in Canada, EURORDIS in Europe, pan-European networks (ERN), IRDiRC are doing tremendous jobs in educating patient and patient advocacy groups, connecting medical professionals and industry representatives, collecting insights from all of these stakeholders and helping with developing guidelines and roadmaps for future development (Benjamin et al., 2017). Collaborative initiatives further influence decision making through broader stakeholder involvement by seeking comments for refining the scope and nature of HTA projects, considering suggestions of health technology topics, or even deeper involvement such as committee participation in the development of HTA protocols (Douglas et al., 2015). They further highlight the need and importance of doing so at every stage of the OD development (Godman et al., 2015). These activities and networks further make possible novel ways of financing, for example, through venture philanthropy (Davies et al., 2017; Feldman and Graddy-Reed, 2014).

Despite the prominence of the discussion on the need for collaboration and integration, surprisingly few contributions focused on studying the mechanisms underlying and enabling this function in OD development.

DISCUSSION

The multilevel, multidimensional framework

The previous sections have identified the main themes of the review, the main discussions and stumbling points. Fig. 1 combines the four dimensions AGIL framework and the three core levels of analysis (micro, *meso*, and macro) to highlight the expected dynamics of pattern renewal and change in the OD field.

This review allowed us to observe some recent trends. These are: (a) even stronger and more visible participation from the patients and patient communities, leading to more intense interactions across the *micro* and *meso* levels; (b) technological advances making novel processes and business models possible, shifting the relationships at the *meso* level, and requiring broader stakeholder involvement; and (c) the

increasing role of multilateral organizations at the interface of *meso* and *macro* levels that collaborate across different types of stakeholders (governments, industry, science, patients) and steer the future agendas.

The following sections discuss these trends and their implications in the context of broader literature on innovation and entrepreneurship, as well as in the context of the recent trends identified by the Rare2030 project. This project led a series of interviews and focus groups with hundreds of the stakeholders in the field regarding the important trends that were going to affect the rare disease field overall. The working group came up with a set of 12 important trends in political, economic, socio-cultural and technological areas, highlighting their primary drivers and indicators, and outlining the opportunities and threats they present. Although this report is but one of the excellent working documents prepared by the national and international organizations of the rare disease field, its specific foresight orientation provides a great opportunity to formulate future research avenues.

The Rare2030 trends

Among the trends identified by the Rare2030 project, the first one (T1) suggests the rise of the multi-stakeholder networks increasingly collaborating with actors from complimentary fields to advance diagnostics, treatment and care for rare diseases. Two further trends reflect on the economic tendencies of budget strains (T2) and inequality of access due to OD pricing (T3). These trends suggest that as healthcare budgets continue to strain, rare diseases "compete" with more increasingly prevalent diseases. Meanwhile high market prices of orphan medicinal products result in their heterogeneous availability and accessibility.

Trends 4,5,6 and 7 reflect the changes in the socio-cultural dimension, highlighting the longer life span of rare disease patients (T4), push for a more inclusive and solidary society (T5), increasingly empowered rare disease patient and the patient advocacy evolution (T6), and finally, rise in innovation-oriented, multi-stakeholder, needs-led (patient-led) research (T7). As more people with rare diseases are living longer, this creates new challenges such as reproductive choices, transition into adolescent/adult care, comorbidities of aging and age related diseases. This also provides a better understanding of the natural history of many rare diseases. The increased efforts for solidarity and equity on the global scale may lead to the efforts for integration of people living with rare diseases and related disabilities in society, and have thus the potential to counterbalance the inequality of access to ODs. At the same time the lack of disease-modifying treatments and devices for the vast majority of rare diseases suggests continued gaps in design, execution, delivery, and ultimately the outputs of rare disease research. This requires and leads to a globalization of efforts. A rise in needs-led objectives and co-creation are a few of the trends filling these gaps. Together with the increasingly empowered patient and patient advocacy community, the report predicts a new era in patient partnership.

Finally, technological changes reflect on the increasing role of digital health (T8), large data sets (T9), use of AI (T10), advanced technologies and therapeutics (T11), and finally genome sequencing (T12). The potential of large sets of standardized and interoperable data that can help advance understanding of RD and accelerate research is increasingly recognized. Therefore, the ability to share, pool, or at least query data from disparate resources, ideally across borders, is essential. Yet, the rise in the use of AI for diagnostics, treatment and care, opening-up the potential of big data for diagnostics, treatment and care remains limited in the field of rare diseases and still requires significant regulatory attention. New technologies such as gene editing and advanced therapeutics including precision medicine introduce breakthrough opportunities to improve the lives of people living with rare diseases (but also potential undesirable consequences). Finally, with a great majority of rare diseases being genetic, advances in the technology around Next Generation Sequencing (NGS) offer significant promise for unraveling the epidemiology of rare disease, accelerating accurate diagnosis and better targeting treatments. The potential of the novel technologies may be enhanced by the entry of less-traditional, 'disruptive' traditional technology companies to the orphan medicinal product development space, which may see new approaches to bringing drugs to market.

From a wicked problem towards a shared definition

Global challenges are "wicked problems" (Buchanan, 1992; Reinecke and Ansari, 2016). The concerted actions of multiple stakeholders – producers, users, and especially regulators – are necessary to overcome them, but a shared problem definition is a prerequisite for constructive dialog (Moors and Faber, 2007). For the OD field, the problem was initially defined as an inability to obtain a "reasonable profit," which, in its turn, was proxied through a number of patients (Arno et al., 1995). But does this definition still hold? The more recent publications in economic, adaptation, dimension seem to focus on the analysis of the pricing strategies and that "*rare diseases are the industry sector still generating two-digit growth numbers*" (Bruyaka et al., 2013, p.55).

Indeed, our review shows a discrepancy in the understanding of goals across the micro, meso, and macro levels: Regulations at the macro level intend to create conditions of economic sustainability; however, in practice, it is not what motivates companies to enter the OD development space (Bruyaka et al., 2013), and sometimes leads to unethical behaviors, which we call the "dark side" of the OD regulations. Liu et al., (2010) suggested that combining government incentives for drug development, access to treatment, public awareness and registry, and price and purchase mechanisms could foster OD development. Pharmaceutical companies, small and medium enterprises, and governmental and non-governmental organizations could all be engaged in these efforts. Role of patients and caretakers in knowledge accumulation, technology advancement, decision making and fund raising are two of the trends (T6 and 7) that change the landscape of the rare disease field and reinforce proactive, non-economic motivations for businesses (Rare 2030). Stephan et al., (2015) emphasize the importance of simultaneous and complementary public and private initiatives, suggesting that governmental engagement does not "crowd out" private pro-social initiatives such as social entrepreneurship.

At the micro level, individual actors in society – e.g. patients, families, and startups – are merely "small invisible hands" (Rip and Groen, 2001). However, the arrangements created across them can help understand the dynamics of society. As the co-evolution across society and technology (Rip and Kemp, 1998) causes a visible shift along the dimensions of goal attainment dimension toward including a broader range of powerful actors who want to and are ready to be involved, and latency dimension through upstream knowledge creation and adaptation in the form of collective funding schemes. This shift along multiple dimensions of the social system will lead to adaptation of goals and strategic orientations of the field.

Wicked problems, by their nature, "*have no definitive formulation, but every formulation of a wicked problem corresponds to the formulation of a solution*" (Buchanan, 1992, p.16). This means, that every solution is suboptimal and not sufficient to solve the problem, but only to improve the situation. Thus, we argue that a regular cycle of revisiting the formulation of the problem, actors, and goals is needed to make improvements on the aspects not taken into account at the previous review round, make the system more complex and integrated and to fulfill the necessary set of functions – something that moves the entity toward its final state (Van de Ven and Poole, 1995).

Dialog on prioritization of ODs

Regulations of OD development at the macro level translate into practice through the approval procedures for the drugs that subsequently can or cannot enter the market. Our review has shown that the

traditional technical-economic logic of assessing new medication is not transparent and fails both, to provide a legitimate assessment process for ODs, and eliminate arguably unethical behaviors such as extraordinary pricing, multiple indications, and stratification (Franken et al., 2016). The discussion about the legitimacy of the procedures of drug approval is prominent in the reviewed literature. The consequences of OD pricing for access and equality are also highlighted by the stakeholders in the field (T2, T5).

Frameworks combining economic, ethical, innovation, product, and process stage aspects that aim to go beyond the pure effectiveness argument have been suggested (e.g. Wagner et al., 2016). Alternative assessment frameworks call for stimulating transparency, legitimacy, and openness in discussions about OD assessment procedures. This could lead to the elimination of the "dark side" of OD regulations, and to the collective sense of responsibility, where the innovator, as a member of a social group, "*has to ask herself about the wider social and political significance of what she intends to accomplish*" (Grinbaum and Groves, 2013, p.133). This can be achieved by means of an open, transparent, and fair public dialog about health priorities (Ehni, 2014; Reinecke and Ansari, 2016; Tierney et al., 2013).

This dialog should take into account that the current public discourse adopts the "*zero-sum game*" framing and suggests that every dollar assigned to rare disease patients' health care is a dollar the "*general population has not received*" (Dragojlovic et al., 2015). Multiple publications conducting pharmaco-economic analysis suggest, however, that ODs are not necessary presenting an immediate threat to the public budgets (Divino et al., 2016; Maresova et al., 2016; Schlander et al., 2015). The increased efforts for solidarity and equity on the global scale (T5) may help addressing this framing in order to give space to developments to combat rare diseases. The rare disease field is not the first to face such framing issue: Future research could possibly learn from other fields, such as the food versus fuel debate (Breukers et al., 2014; Buyx and Tait, 2011; Thompson, 2012).

Novel technologies and business models for ODs

The emergence of alternative drug development pathways and technologies is another important source of pattern renewal in the OD field. Technological developments drive faster drug research and innovation and make novel business models feasible. Alternative development pathways may include drug discovery, rediscovery, and redirection and identifying potential new uses for compounds that have undergone significant R&D by the industry. Novel technological advancements, such as the promise of genomics, are noted and discussed in the literature. Rare2030 names trends that are going to change the field, among them, the increasing role of digital health (T8), large data sets (T9), use of AI (T10), advanced technologies and therapeutics (T11), and finally genome sequencing (T12). Embracing the possibilities of Big data, internet of things and artificial intelligence may lead to Healthcare 4.0, named so paralleled to the Industry 4.0 (Islam et al., 2020; Marinakis et al., 2017; Tortorella et al., 2020).

However, advancement the technology greatly depends on the involvement of researchers, clinical and patient groups, and private and regulatory actors in providing the data, as well as guidance and financing for the biorepositories and drug commercialization (Feldman and Graddy-Reed, 2014; Ferlini et al., 2013; Godman et al., 2015; So et al., 2013). Numerous efforts by the public and private sector initiatives are targeting creation of such programs and platforms at national, European or even Global level (Godman et al., 2015; Rubinstein and Groft, 2010; Vittozzi et al., 2013). Future research should identify how multi-stakeholder collaborations in creating systematic, usable and accessible registries should be governed and financed to make the technological advancements possible.

Sandler et al., (2002) argue that the coordination of transnational public goods should come from a multilateral organization acting on a consensual basis, such as public–private partnerships that tie together diverse players to develop, fund, and provide new drugs and treatments. Recently, a new type of multilateral organization has been suggested: A mega fund. Fernandez et al., (2012) argued that increasing the scale of investment by pooling a big amount of development initiatives in a single mega fund could address the problem of an over-dependence on state financing. Initially proposed for cancer research, this financial entity amounting to between $5 billion and $15 billion, with the investors committing to make drugs for orphan diseases, could be sufficiently profitable by operating as a meso-macro level platform to develop balanced drug portfolios (Maresova et al., 2016). Future research should identify, when and how OD can be a base for a profitable yet responsible business model.

Collaborative mechanisms across levels

Discussion regarding regulations and their implementation that focused on their diversity across countries makes up by far the largest group of contributions in the review. At the macro level, evaluation and approval procedures across countries create conflicts that can prevent greater harmonization. Yet, each country faces its own set of challenges (Malets and Quack, 2013). While regulatory agencies are doing great work in aligning their processes and decision making criteria, challenges persist (Alqahtani et al., 2015).

At the *meso* level, we see that the multidisciplinary dialog in the area of drug discovery and innovation is driving the pattern renewal. At present, there are more than 7000 rare diseases and a vast geographical dispersion of patients, clinicians, and researchers. It is, therefore, not surprising, that patient associations and foundations are being created to unite efforts around specific diseases and locations. National organizations in US and Canada (NORD and CORD, respectively), and ERORDIS in Europe mediate and guide these efforts on larger regional levels. However, technological developments also empower better and faster communication across borders and stakeholders. Integration, a common vocabulary, an ability to work across different dominant logics (Koelewijn et al., 2012; Lounsbury, 2007), and technological complementarity are key to constructing usable and useful registries and biorepositories in order to make research in this area possible (Denis et al., 2010; Groft and Rubinstein, 2013). At the micro level, patients become more interested in complex solutions that would improve the diagnosis process and are ready to be more involved in the process by actively participating in the drug innovation process (Huyard, 2009; Kesselheim et al., 2015; Wood et al., 2013). This is also supported by the trends observed by Rare2030 (T6, T7). Traditional role distribution may be questioned and redefined by informing the healthcare priorities.

The previous discussion indicates the crucial role of collaborations that are multilateral and those that happen across levels, and how important it is to learn about the "how" and the "who" of multiple stakeholders constituting the ecosystem for OD development. It also highlighted the role of micro networks and the different types of stakeholders entering the scene in OD development. However, as few contributions focused on studying the mechanisms underlying and enabling this function in OD development, it is a current gap in the OD development literature which requires further investigation. With the complexities of the OD development and multi-stakeholder interactions at all times during the development process, this field offers significant opportunities for theory building that could be translated to other adjacent fields and more management theory in general.

Limitations and avenues for future research

This paper is, of course, not without its limitations. First of all, in making this review we have solely focused on OD development. Despite the significant number of contributions and discussions, this search only considers the questions that were raised specifically in relation to OD development. This may, however, overlook the broader policy

measures and discussions in the rare disease field relevant for the discussion. Furthermore, while OD development is an important mission in addressing the societal challenge posed by rare diseases, it is not the only one. Proper and correct diagnosis of rare diseases is one of the major concerns for the patients. However, even accurately diagnosed, patients with rare conditions may be treated by physicians who have little evidence or guidance to help them. Furthermore, for some diseases no disease-modifying therapies are known or are imaginable. Current treatment for these conditions still emphasizes treatment of symptoms and prevention of complications. While these include medications, they could also include nutritional agents, surgical procedures, psychotherapy, physical and occupational therapy, complex medical devices (e.g., sophisticated communication devices), and less complex devices (e.g., braces). Future research could explore the mechanisms of adaptation, goal achievement, integration and latent pattern maintenance in the non-medicinal product and process areas.

In making this review we have further relied on the traditional peer-reviewed publications, leaving a great number of reports that disseminate recommendations provided by the leading national and patient-led organizations and target different areas of rare disease prevention, diagnosis, management and treatment (development and delivery) out of the scope of this review. Future research may compare the insights gained from the traditional and upcoming (open source) and practitioner (gray literature) sources.

Finally, this review has taken the knowledge about the development of ODs as "a stock", highlighting the existing discussions, but not following the dynamics of these discussions over time or across borders. Future research could focus more on the dynamics of the field. For example, by investigating conditions, under which it became more interesting and profitable for big pharma to enter the OD development, and what led to the so-called "dark side" of the OD regulations. As many contributions in this review have extensively compared the state of rare disease drug development, assessment and approval across various combinations of countries and continents, we have opted to not anchor our findings in any specific geographical location. However, as differences exist, the reader may want to assess the applicability of these identified general trends and research avenues for the local situation.

The analysis of the contributions and the discussion above that highlight the research gaps along the goal attainment, adaptation, integration and latency dimensions allow us to identify some directions for future research.

(1) *What are the suitable multi-lateral multi-stakeholder governance models?* Constructive dialog of multiple stakeholders with diverse goals and logics is needed to address any wicked problem. Stakeholders in the rare disease field extensively collaborate with actors from social sciences, health policy, regulatory science, eHealth, big data, -omics approaches, bioinformatics, nanotechnology, etc. (Groft and Rubinstein, 2013). This has resulted in significant advances of the field. What are the underlying governance mechanisms of these collaborations? How do the stakeholder engagement and management strategies reflect the unique challenges of the OD development process? Can these insights inspire solutions to other wicked problems?

(2) *Do deliberative stakeholder involvement strategies differ across fields?* In multi-stakeholder networks, what is a good balance of diversity to ensure that integration, a common vocabulary, and technological complementarity are possible? How do they adjust to the new entrants and changing roles of the existing participants? A.o. Are there special strategies that patients need to keep in mind when engaging in conversation with science, business, and regulatory bodies? Can these insights inform other fields, such as user or open innovation (West and Bogers, 2014), where users change their roles, or Industry 4.0 stream of work that welcomes novel and non-traditional players (Stelzer et al., 2015)?

(3) *What are the limits of patient involvement in OD deliberative democracy?* The shift at the micro level toward greater initiative and more entrepreneurship is very important and meaningful. At the same time, it raises the question of whether one can expect families and patients who are already suffering to assume more responsibility and take charge of new developments. Scherer and Palazzo (2011) have questioned the limits of downstreaming the responsibility (p. 919), but in the field of rare diseases, patients and caretakers have shown that they are ready and able to take on this responsibility by shifting from the role of consumer to that of supplier (Oliveira et al., 2019; Oliveira et al., 2015; Wood et al., 2013). Under what conditions could this be a pathway forward? Furthermore, as patients and patient organizations more often than not focus on their own disease, to what extend can technological advances of Healthcare 4.0 (Islam et al., 2020; Tortorella et al., 2020) stimulate systematic creation of rare disease registries?

(4) *What are the novel business models?* Existing business models rely heavily on the government incentives and possibilities of exploiting existing (matching) technological capabilities. Some studies report unethical business practices that allow niche-buster profits. Under what conditions can business models for ODs be sustainable? Portfolio business models and multilateral funding schemes seem to show promise here. What are the primary enablers and (ethical) consequences of these business models? Are there other novel business strategies that create both economic and social value?

(5) *Does "personalized" mean "prioritized"?* The "4 P's" trend in Healthcare (predictive, preventive, personalized and participatory healthcare) is changing how we embrace healthcare and innovate pharmaceutical treatments (Denicolai and Previtali, 2020; Tierney et al., 2013). A potential research stream focusing on the healthcare trend of the 4P's, ODs and prioritization is an important element in such a discussion.

(6) *What is the price of knowledge?* With the importance of harmonization, collaboration, sharing and transparency in the OD development field another question that comes to mind is the price of knowledge. The concept of an Abundant economy is relevant here. This concept suggests that sharing information does not diminish either the generator nor receiver value (Gary et al., 2020). Future research streams which investigate the changing nature of an I4.0 information-based economy, cryptocurrencies (White et al., 2020) and the value of information sharing in the case of OD development in the light of the 4P's trend in healthcare would be exceptionally valuable research streams.

(7) A final research avenue could explore the idea of the ownership in the OD space. With the importance of mutual efforts of various stakeholders in creating conditions that make OD development efforts possible and sustainable, what is a "reasonable profit" (Denis et al., 2010), and who has the right for the extraordinary (blockbuster) profits from ODs (Godman et al., 2015)? Does the tax, reimbursement and compensation system reflect the shared risk philosophy behind the 4P healthcare system in terms of inappropriate innovations (Radaelli et al., 2017) and risks of transferring medical science to the market (Erzurumlu and Pachamanova, 2020)?

CONCLUSION

Our review shows that 35 years into creating a unique space for OD development, the academic debate is heavily dominated by the discussions on economic stimuli (market exclusivity), economic grounds (cost-effectiveness analysis), cost and expenditure, and the financial malpractices of corporations. In analyzing the issue, the dominance of economic reasoning suggests the problem lies with individual actors' or companies' inability to finance the gap created by a market failure. All of these discussions, despite residing in regulatory or strategic domain are fueled by the economics logic. As government is the main guarantor

of stability and a fair redistribution of public money, it is only natural to look to the government, and great progress has been done in the past years towards elimination of this societal challenge. However, new approaches to accumulate funds or to reduce the need for funding have been suggested as a result of the adaptation and development of the field, and could augment the current efforts and open new opportunities.

Furthermore, analyzing the system from the point of view of social interactions provides additional insight highlighting the importance and potential of involving patients and parents in knowledge accumulation, technology advancement, decision making, and fundraising. However, research needs to advance to better support this development: we still need a better understanding of the mechanisms behind the multi-actor initiatives in the OD field, and how the recent trends in patient and patient advocacy empowerment will influence the governance of the multi-stakeholder collaborations.

Last, as we perform our socio-systemic analysis and reconstruct the field of OD development along the AGIL dimensions, we are able to see the conflict of logics applied with the problems at hand. We are also able to link together solutions coming from different research streams and disciplines that address the similar dimension of the social system through a different disciplinary lens. This provides a balanced tool for analysis of complex developments, such as management of a solution to a global challenge, and a useful lens to identify future avenues for research.

Author statement

All authors have equally contributed to the conceptualization, analysis, validation, visualization and writing (editing) of the manuscript.

REFERENCES

Abramowicz, M., 2011. 'Orphan business models: toward a new form of intellectual property'. Harv Law Rev 124, 1362–1421.

Alqahtani, S., Seoane-Vazquez, E., Rodriguez-Monguio, R., Eguale, T., 2015. 'Priority review drugs approved by the FDA and the EMA: time for international regulatory harmonization of pharmaceuticals?'. Pharmacoepidemiol Drug Saf 24, 709–715.

Arno, P.S., Bonuck, K., Davis, M., 1995. 'Rare diseases, drug development, and AIDS: the impact of the orphan drug act'. Milbank Q 73, 231–252.

Avery, M., 2010. 'Personalized medicine and rescuing "unsafe" drugs with pharmacogenomics: a regulatory perspective'. Food Drug Law J 65, 37–66.

Aymé, S., and Hivert, V. (2011). Report on rare disease research, its determinants in Europe and the way forward: iNSERM.

Benjamin, K., Vernon, M.K., Patrick, D.L., Perfetto, E., Nestler-Parr, S., Burke, L., 2017. 'Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials: an ISPOR COA emerging good practices task force report'. Value in Health 20, 838–855.

Berlin, R.J., 2009. 'Examination of the relationship between oncology drug labeling revision frequency and FDA product categorization'. Am J Public Health 99, 1693–1698.

Blankart, C.R., Stargardt, T., Schreyögg, J., 2011. 'Availability of and access to orphan drugs'. Pharmacoeconomics 29, 63–82.

Boon, W.P.C., Broekgaarden, R., 2013. 'The role of patient advocacy organisations in neuromuscular disease R&D: the case of the dutch neuromuscular disease association VSN'. Neuromuscular Disorders 20, 148–151.

Boon, W.P.C., Martins, L., Koopmanschap, M., 2015. 'Governance of conditional reimbursement practices in the Netherlands'. Health Policy (New York) 119, 180–185.

Boon, W.P.C., Moors, E.H.M., 2008. 'Exploring emerging technologies using metaphors – a study of orphan drugs and pharmacogenomics'. Soc Sci Med 66, 1915–1927.

Boon, W.P.C., Moors, E.H.M., Kuhlmann, S., Smits, R.E.H.M., 2008. 'Demand articulation in intermediary organisations: the case of orphan drugs in the Netherlands'. Technol Forecast Soc Change 75, 644–671.

Boon, W.P.C., Moors, E.H.M., Kuhlmann, S., Smits, R.E.H.M., 2011. 'Demand articulation in emerging technologies: intermediary user organisations as co-producers?'. Res Policy 40, 242–252.

Boy, R., Schwartz, I.V.D., Krug, B.C., Santana-da-Silva, L.C., Steiner, C.E., Acosta, A.X., et al., 2011. 'Ethical issues related to the access to orphan drugs in Brazil: the case of mucopolysaccharidosis type I'. J Med Ethics 37, 233–239.

Breukers, S., Hisschemöller, M., Cuppen, E., Suurs, R., 2014. 'Analysing the past and exploring the future of sustainable biomass. Participatory stakeholder dialogue and technological innovation systems research'. Technol Forecast Soc Change 81, 227–235.

Bruyaka, O., Zeitzmann, H.K., Chalamon, I., Wokutch, R.E., Thakur, P., 2013. 'Strategic corporate social responsibility and orphan drug development: insights from the US and the EU biopharmaceutical industry'. J.Business Ethics 117, 45–65.

Buchanan, R., 1992. 'Wicked problems in design thinking'. Design Issues 8, 5–21.

Buyx, A., Tait, J., 2011. 'Ethical framework for biofuels'. Science 332, 540–541.

Certo, S.T., Miller, T., 2008. 'Social entrepreneurship: key issues and concepts'. Bus Horiz 51, 267–271.

Clark, K.B., 1985. 'The interaction of design hierarchies and market concepts in technological evolution'. Res Policy 14, 235–251.

Coyle, D., Cheung, M.C., Evans, G.A., 2014. 'Opportunity cost of funding drugs for rare diseases: the cost-effectiveness of eculizumab in paroxysmal nocturnal hemoglobinuria'. Medical Decision Making 34, 1016–1029.

Danzon, P., Towse, A., 2002. 'The economics of gene therapy and of pharmacogenetics'. Value in Health 5, 5–13.

Davies, E.H., Fulton, E., Brook, D., Hughes, D.A., 2017. 'Affordable orphan drugs: a role for not-for-profit organizations'. Br J Clin Pharmacol 83, 1595–1601.

de Vrueh, R.L.A., 2014. Why R&D into rare disease matter. In: Bali, R.K., Bos, L., Gibbons, M.C., Ibell, S.R. (Eds.), Rare Diseases in the Age of Health 2.0., Communications in Medical and Care Compunetics, 4 ed. Springer, Heidelberg, Germany.

Denicolai, S., Previtali, P., 2020. 'Precision medicine: implications for value chains and business models in life sciences'. Technol Forecast Soc Change 151, 119767.

Denis, A., Mergaert, L., Fostier, C., Cleemput, I., Simoens, S., 2010. 'A comparative study of European rare disease and orphan drug markets'. Health Policy (New York) 97, 173–179.

Desser, A.S., 2013. 'Prioritizing treatment of rare diseases: a survey of preferences of norwegian doctors'. Soc Sci Med 94, 56–62.

Desser, A.S., Gyrd-Hansen, D., Olsen, J.A., Grepperud, S., Kristiansen, I.S., 2010. 'Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67′. Br Med J 341, c4715.

Divino, V., DeKoven, M., Kleinrock, M., Wade, R.L., Kaura, S., 2016. 'Orphan drug expenditures in the United States: a historical and prospective analysis, 2007–2018′. Health Aff 35, 1588–1594.

Douglas, C.M.W., Wilcox, E., Burgess, M., Lynd, L.D., 2015. 'Why orphan drug coverage reimbursement decision-making needs patient and public involvement'. Health Policy (New York) 119, 588–596.

Dragojlovic, N., Rizzardo, S., Bansback, N., Mitton, C., Marra, C.A., Lynd, L.D., 2015. 'Challenges in measuring the societal value of orphan drugs: insights from a Canadian stated preference survey'. The Patient - Patient-Centered Outcomes Research 8, 93–101.

Ehni, H.-J., 2014. 'Expensive cancer drugs and just health care'. Best Practice Research Clinical Gastroenterology 28, 327–337.

Erzurumlu, S.S., Pachamanova, D., 2020. 'Topic modeling and technology forecasting for assessing the commercial viability of healthcare innovations'. Technol Forecast Soc Change 156, 120041.

Feldman, M.P., Graddy-Reed, A., 2014. 'Accelerating commercialization: a new model of strategic foundation funding'. J Technol Transf 39, 503–523.

Ferlini, A., Scotton, C., Novelli, G., 2013. 'Biomarkers in rare diseases'. Public Health Genomics 16, 313–321.

Fernandez, J.-M., Stein, R.M., Lo, A.W., 2012. 'Commercializing biomedical research through securitization techniques'. Nat. Biotechnol. 30, 964.

Franken, M., Heintz, E., Gerber-Grote, A., Raftery, J., 2016. 'Health economics as rhetoric: the limited impact of health economics on funding decisions in four European countries'. Value in Health 19, 951–956.

Gary, R.F., Fink, M., Belousova, O., Marinakis, Y., Tierney, R., Walsh, S.T., 2020. 'An introduction to the field of abundant economic thought'. Technol Forecast Soc Change, 119796.

Godman, B., Malmström, R.E., Diogene, E., Gray, A., Jayathissa, S., Timoney, A., et al., 2015. 'Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?'. Expert Rev Clin Pharmacol 8, 77–94.

Goldman, L., 2000. 'The billionaire and the orphan drug'. Forbes 168–169 October.

Grabowski, H.G., Vernon, J., 2000. 'The distribution of sales revenues from pharmaceutical innovation'. Pharmacoeconomics 18, 21–32.

Granovetter, M., 1985. 'Economic action and social structure: the problem of embeddedness'. American Journal of Sociology 91, 481–510.

Grinbaum, A., Groves, C., 2013. What is "responsible" about responsible innovation? Understanding the ethical issues. In: Owen, R., Bessant, J., Heintz, M. (Eds.), Responsible innovation: Managing the Responsible Emergence of Science and Innovation in Society. Wiley, Sussex, pp. 119–142.

Groen, A.J., 2005. 'Knowledge intensive entrepreneurship in networks: towards a multi-level/multi-dimensional approach'. J. Enterprising Culture 13, 69–88.

Groen, A.J., Wakkee, I.A.M., De Weerd-Nederhof, P.C., 2008. 'Managing tensions in a high-tech start-up: an innovation journey in social system perspective'. Int. Small Business Journal 26, 57–81.

Groft, S.C., Rubinstein, Y.R., 2013. 'New and evolving rare diseases research programs at the national institutes of health'. Public Health Genomics 16, 259–267.

Grossman, D.B., 1984. 'The orphan drug act: adoption or foster care'. Food Drug Cosmet Law J 39, 128–151.

Grossman, F., Meier, D.M., Steiger, T.S., 2014. The empowered patient in the health system of the future. In: Bali, R.K., Bos, L., Gibbons, M.C., Ibell, S.R. (Eds.), Rare Diseases in the Age of Health 2.0. Communications in Medical and Care Compunetics, 4 ed. Springer, Heidelberg, Germany.

Hechtelt Jonker, A., Hivert, V., Gabaldo, M., Batista, L., O'Connor, D., Aartsma-Rus, A., et al., 2020. 'Boosting delivery of rare disease therapies: the IRDiRC orphan drug development guidebook '. Nature Reviews Drug Discovery.

Hemphill, T.A., 2010. 'Extraordinary pricing of orphan drugs: is it a socially responsible strategy for the US pharmaceutical industry?'. J. Business Ethics 94, 225–242.

Herder, M., 2013. 'When everyone is an orphan: against adopting a US-styled orphan drug

policy in Canada'. Account Res 20, 227–269.
Heuven, J., Groen, A.J., 2012. 'The role of social networks in financing technology-based ventures: an empirical exploration'. Venture capital 14, 131–149.
Huyard, C., 2009. 'What, if anything, is specific about having a rare disorder? Patients' judgements on being ill and being rare'. Health expectations: an international journal of public participation in health care and health policy 12, 361–370.
Iskrov, G., Miteva-Katrandzhieva, T., Stefanov, R., 2012. 'Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria'. Health Policy (New York) 108, 10–18.
Islam, N., Marinakis, Y., Majadillas, M.A., Fink, M., Walsh, S.T., 2020. 'Here there be dragons, a pre-roadmap construct for IoT service infrastructure'. Technol Forecast Soc Change 155, 119073.
Kanavos, P., Mossialos, E., 1999. 'Outstanding regulatory aspects in the European pharmaceutical market'. Pharmacoeconomics 15, 519–533.
Kesselheim, A.S., Tan, Y.T., Avorn, J., 2015. 'The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs'. Health Aff 34, 286–293.
Kimman, M.L., Rotteveel, A.H., Wijsenbeek, M., Mostard, R., Tak, N.C., van Jaarsveld, X., et al., 2017. 'Development and pretesting of a questionnaire to assess patient experiences and satisfaction with medications (PESaM questionnaire)'. The Patient - Patient-Centered Outcomes Research 10, 629–642.
Koelewijn, W.T., Ehrenhard, M.L., Groen, A.J., van Harten, W.H., 2012. 'Intra-organizational dynamics as drivers of entrepreneurship among physicians and managers in hospitals of western countries'. Soc Sci Med 75, 795–800.
Laumann, E.O., Pappi, F.U., 1976. Networks of Collective action: A perspective On Community Influence Systems. Academic Press, New York.
Lazonick, W., Tulum, Ö, 2011. 'US biopharmaceutical finance and the sustainability of the biotech business model'. Res Policy 40, 1170–1187.
Leloux, M.S., Groen, A.J., 2007. 'Business valuation of technology: an experiential model'. Les Nouvelles 478–486.
Liu, B.-C., He, L., He, G., He, Y., 2010. 'A cross-national comparative study of orphan drug policies in the United States, the European Union, and Japan: towards a made-in-China orphan drug policy'. J Public Health Policy 31, 407–421.
Loughnot, D., 2005. 'Potential interactions of the orphan drug act and pharmacogenomics: a flood of orphan drugs and abuses?'. Am J Law Med 31, 365–380.
Lounsbury, M., 2007. 'A tale of two cities: competing logics and practice variation in the professionalizing of mutual funds'. Academy Management Journal 50, 289–307.
Malets, O., Quack, S., 2013. Projecting the local into the global: trajectories of participation in transnational standard-setting. Eds. In: Drori, G., Höllerer, M., Walgenbach, P. (Eds.), Organizations and Managerial ideas: Global themes and Local Variations. Routledge.
Maresova, P., Klimova, B., Kuca, K., 2016. 'Financial and legislative aspects of drug development of orphan diseases on the European market – a systematic review'. Appl Econ 48, 2562–2570.
Marinakis, Y., Harms, R., Walsh, S.T., 2017. 'Monitoring additive manufacturing based products in clinical trials'. Translational materials research 4, 034001.
Mattingly, T.J.I., Simoni-Wastila, L., 2017. 'Patient-centered drug approval: the role of patient advocacy in the drug approval process'. J Manag Care Spec Pharm 23, 1078–1082.
Menon, D., Stafinski, T., Dunn, A., Wong-Rieger, D., 2015. 'Developing a patient-directed policy framework for managing orphan and ultra-orphan drugs throughout their lifecycle'. The Patient - Patient-Centered Outcomes Research 8, 103–117.
Mentzakis, E., Stefanowska, P., Hurley, J., 2011. 'A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: an exploratory study'. Health Economics, Policy and Law 6, 405–433.
Michel, M., Toumi, M., 2012. 'Access to orphan drugs in Europe: current and future issues'. Expert Rev Pharmacoecon Outcomes Res 12, 23–29.
Middel, R., Fisscher, O., Groen, A.J., 2007. 'Managing and organising collaborative improvement: a system integrator perspective'. Int. J.Technology Management 37, 221–236.
Milne, C.-P., Tait, J., 2009. 'Evolution along the government - governance continuum: fDA's orphan products and fast track programs as exemplars of what works for innovation and regulation'. Food Drug Law J 64, 733–754.
Moors, E.H.M., Faber, J., 2007. 'Orphan drugs: unmet societal need for non-profitable privately supplied new products'. Res Policy 36, 336–354.
Murphy, J.M., 2005. AGIL. In: Ritzer, G. (Ed.), Encyclopedia of Social Theory. SAGE Publications, Thousand Oaks, California, pp. , Inc.
Murphy, S.M., Puwanant, A., Griggs, R.C., 2012. 'Unintended effects of orphan product designation for rare neurological diseases'. Ann. Neurol. 72, 481–490.
Nicod, E., Kanavos, P., 2016. 'Developing an evidence-based methodological framework to systematically compare HTA coverage decisions: a mixed methods study'. Health Policy (New York) 120, 35–45.
Oliveira, P., Zejnilovic, L., Azevedo, S., Rodrigues, A.M., Canhão, H., 2019. 'Peer adoption and development of health innovations by patients: national representative study of 6204 citizens'. J. Med. Internet Res. 21, e11726.
Oliveira, P., Zejnilovic, L., Canhão, H., von Hippel, E., 2015. 'Innovation by patients with rare diseases and chronic needs'. Orphanet J Rare Dis 10, 41.
Olivier, C., Williams-Jones, B., 2014. 'Global pharmacogenomics: where is the research taking us?'. Glob Public Health 9, 312–324.
Parsons, T., 1964. The Social System. The Free Press, New York.
Parsons, T., 1977. Social Systems and the Evolution of Action Theory. The Free Press, New York.
Pauwels, K., Huys, I., De Nys, K., Casteels, M., Simoens, S., 2015. 'Predictors for reimbursement of oncology drugs in Belgium between 2002 and 2013'. Expert Rev Pharmacoecon Outcomes Res 15, 859–868.
Picavet, E., Dooms, M., Cassiman, D., Simoens, S., 2012. 'Orphan drugs for rare diseases: grounds for special status'. Drug Dev. Res. 73, 115–119.
Pullen, A.J.J., de Weerd-Nederhof, P.C., Groen, A.J., Fisscher, O.A.M., 2012. 'Open innovation in practice: goal complementarity and closed NPD networks to explain differences in innovation performance for SMEs in the medical devices sector'. J. Product Innovation Management 29, 917–934.
Rachul, C., Toews, M., Caulfield, T., 2016. 'Controversies with Kalydeco: newspaper coverage in Canada and the United States of the cystic fibrosis "wonder drug"'. J. Cystic Fibrosis 15, 624–629.
Radaelli, G., Lettieri, E., Frattini, F., Luzzini, D., Boaretto, A., 2017. 'Users' search mechanisms and risks of inappropriateness in healthcare innovations: the role of literacy and trust in professional contexts'. Technol Forecast Soc Change 120, 240–251.
Rai, A.K., 2002. 'Pharmacogenetic interventions, orphan drugs, and distributive justice: the role of cost-benefit analysis'. Social Philosophy and Policy 19, 246–270.
Reinecke, J., Ansari, S., 2016. 'Taming wicked problems: the role of framing in the construction of corporate social responsibility'. J. Management Studies 53, 299–329.
Richter, T., Nestler-Parr, S., Babela, R., Khan, Z.M., Tesoro, T., Molsen, E., et al., 2015. 'Rare disease terminology and definitions-a systematic global review: report of the ISPOR rare disease special interest group'. Value Health 18, 906–914.
Rip, A., Groen, A.J., 2001. Many visible hands. In: Coombs, R., Green, K., Richards, A., Walsh, V. (Eds.), Technology and the Market demand, Users and Innovation. Edward Elgar Publishing, Cheltenham, UK.
Rip, A., Kemp, R., 1998. Technological change. In: Rayner, S., Malone, E.L. (Eds.), Human Choice and Climate Change 2. Battelle Press, Columbus, OH, USA, pp. 327–399.
Rosselli, D., Rueda, J.-D., Solano, M., 2012. 'Ethical and economic considerations of rare diseases in ethnic minorities: the case of mucopolysaccharidosis VI in Colombia'. J Med Ethics 38, 699–700.
Rubinstein, Y.R., 2013. Biorepositories Are Advancing Research About Rare diseases: Q&A With Yaffa Rubinstein. Available at. https://www.thermofisher.com/blog/biobanking/biorepositories-are-advancing-research-about-rare-diseases-qa-with-yaffa-rubinstein/ accessed 17 May 2019.
Rubinstein, Y.R., Groft, S.C., 2010. 'Driving interest in consolidating resources for the creation of a global rare disease patient registry'. Contemp Clin Trials 31, 393.
Salas-Vega, S., Bertling, A., Mossialos, E., 2016. 'A comparative study of drug listing recommendations and the decision-making process in Australia, the Netherlands, Sweden, and the UK'. Health Policy (New York) 120, 1104–1114.
Sandler, T., Arce, M., G., D., 2002. 'A conceptual framework for understanding global and transnational public goods for health'. Fisc Stud 23, 195–222.
Scherer, A.G., Palazzo, G., 2011. 'The new political role of business in a globalized world: a review of a new perspective on CSR and its implications for the firm, governance, and democracy'. J.Management Studies 48, 899–931.
Schlander, M., Adarkwah, C.C., Gandjour, A., 2015. 'Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe'. Expert Rev Pharmacoecon Outcomes Res 15, 171–179.
Smith, T., McNeil, K., Mitchell, R., Boyle, B., Ries, N., 2019. 'A study of macro-, meso- and micro-barriers and enablers affecting extended scopes of practice: the case of rural nurse practitioners in Australia'. BMC Nurs 18, 14.
So, D., Joly, Y., Knoppers, B.M., 2013. 'Clinical trial transparency and orphan drug development: recent trends in data sharing by the pharmaceutical industry'. Public Health Genomics 16, 322–335.
Stelzer, B., Meyer-Brötz, F., Schiebel, E., Brecht, L., 2015. 'Combining the scenario technique with bibliometrics for technology foresight: the case of personalized medicine'. Technol Forecast Soc Change 98, 137–156.
Stephan, U., Uhlaner, L.M., Stride, C., 2015. 'Institutions and social entrepreneurship: the role of institutional voids, institutional support, and institutional configurations'. J Int Bus Stud 46, 308–331.
Thompson, P.B., 2012. 'The agricultural ethics of biofuels: the food vs. Fuel debate'. Agriculture 2, 339–358.
Tierney, R., Hermina, W., Walsh, S., 2013. 'The pharmaceutical technology landscape: a new form of technology roadmapping'. Technol Forecast Soc Change 80, 194–211.
Tortorella, G.L., Fogliatto, F.S., Espôsto, K.F., Vergara, A.M.C., Vassolo, R., Mendoza, D.T., et al., 2020. 'Effects of contingencies on healthcare 4.0 technologies adoption and barriers in emerging economies'. Technol Forecast Soc Change 156, 120048.
Tranfield, D., Denyer, D., Smart, P., 2003. 'Towards a methodology for developing evidence-informed management knowledge by means of systematic review'. British J. Management 14, 207–222.
Tversky, A., Shafir, E., 1992. 'Choice under conflict: the dynamics of deferred decision'. Psychol Sci 3, 358–361.
Valverde, A.M., Reed, S.D., Schulman, K.A., 2012. 'Proposed "grant-and-access" program with price caps could stimulate development of drugs for very rare diseases'. Health Aff 31, 2528–2535.
Van de Ven, A.H., Poole, M.S., 1995. 'Explaining development and change in organizations'. The Academy Management Review 20, 510–540.
Villa, S., Compagni, A., Reich, M.R., 2009. 'Orphan drug legislation: lessons for neglected tropical diseases'. Int J Health Plann Manage 24, 27–42.
Vittozzi, L., Gainotti, S., Mollo, E., Donati, C., Taruscio, D., 2013. ' A model for the European platform for rare disease registries'. Public Health Genomics 16, 299–304.
Wagner, M., Khoury, H., Willet, J., Rindress, D., Goetghebeur, M., 2016. 'Can the EVIDEM framework tackle issues raised by evaluating treatments for rare diseases: analysis of issues and policies, and context-specific adaptation'. Pharmacoeconomics 34, 285–301.
West, J., Bogers, M., 2014. 'Leveraging external sources of innovation: a review of research on open innovation'. J. Product Innovation Management 31, 814–831.
White, R., Marinakis, Y., Islam, N., Walsh, S., 2020. 'Is bitcoin a currency, a technology-based product, or something else?'. Technol Forecast Soc Change 151, 119877.
Wiss, J., Levin, L.-A., Andersson, D., Tinghög, G., 2017. 'Prioritizing rare diseases: psychological effects influencing medical decision making'. Medical Decision Making 37, 567–576.

Wonder, M., Chin, G., 2015. 'What impact does "conventional" economic evaluation have on patient access to new orphan medicines? A comparative study of their re-imbursement in Australia (2005–2012)'. Expert Rev Pharmacoecon Outcomes Res 15, 843–850.
Wood, J., Sames, L., Moore, A., Ekins, S., 2013. 'Multifaceted roles of ultra-rare and rare disease patients/parents in drug discovery'. Drug Discov. Today 18, 1043–1051.
Yin, W., 2008. 'Market incentives and pharmaceutical innovation'. J Health Econ 27, 1060–1077.

Dr. Olga Belousova is an Assistant professor at the University of Groningen. She received her PhD in Corporate entrepreneurship from the Université catholique de Louvain (Belgium). Olga's research interests include new venture creation processes in both independent and corporate contexts. Her current research explores capabilities and processes for high-tech and knowledge intensive businesses, such as new venture development in healthcare. She has published in Technological Forecasting and Social Change, International Entrepreneurship and Management Journal, Frontiers of Entrepreneurship Research, and others.

Prof. dr. A.J. (Aard) Groen holds a chair position on entrepreneurship and valorisation at the University of Groningen (the Netherlands). His-research focuses on knowledge-intensive entrepreneurship in start-ups and existing ventures across a range of advanced technology sectors. His-papers have been published in the Journal of Management, the Journal of Business Venturing, the International Journal of Small Business, Creativity and Innovation Management, Technovation and elsewhere. Dr. Groen has led multiple European Union funded projects and is presently an advisor to the board of Eurodev, which facilitates international business development and M&A activity.

Aniek M. Ouendag, MSc. After finishing the MSc BA Small Business and Entrepreneurship at University of Groningen, Aniek Ouendag joined the University of Groningen centre of Entrepreneurship. Here she is coordinator of business accelerator VentureLab North. At VentureLab Aniek is in charge of the overall planning and control, as well as expanding and maintaining the network of the accelerator. Her master thesis covered the topic of stakeholder analysis in healthcare, an area of research she still pursues, as well as further healthcare entrepreneurship research, and broader entrepreneurial research related to VentureLab North.