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Addressing the Social and Economic Challenges of Orphan Drugs: A Managerial Perspective

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Abstract

The work aims to investigate the phenomenon of orphan drugs to reflect upon current models at the basis of identify ways and instruments to support decision makers in assessing models able to facilitate their spread in accordance with the principles characterizing the pharmaceutical companies as profit-oriented economic systems.
The paper offers an analysis of the evolution in the managerial approach to orphan drugs and it underlines some possible reflections in order to combine the economic orientation of pharmaceutical companies with the social role of orphan drugs in the perspective of sustainable development.
Some practical and research implications are declined with reference to the possible future evolutions in the management on the investigated phenomenon in order to allow a paradigm shift in the approach to the market based on the common satisfaction of the involved actors (*win-win logic*).

Keywords: Orphan Drugs; Managerial approaches; Literature review; Sustainable perspective.

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1. Introduction

The pharmaceutical sector for its characteristics is very different from other industrial sectors specially for the nature of the drugs as goods and to the existence of a strong interdependence among the various economic and social actors involved into the production and distribution chain (pharmaceutical companies, doctors, pharmacists patients and the State in the role of third-party payer).

The pharmaceutical product has two distinctive features that differ from any other industrial product (D.P.R. 1998/217, p. 8):

- In specific cases, its price is paid by final consumer only in part because there is the participation of the State in the role of third-part payer.
- Its market is 'mediated' because for the majority of marketed drugs the patient is obliged to consult its doctor for a prescription.

These aspects impact on the configuration and dynamics of the whole pharmaceutical system and require appropriate governance and management models.

Two elements, in particular, influence the configuration of the pharmaceutical sector:

- The absence of substitution in the use of drugs for the various therapeutic classes.
- The differences in the markets regulatory system between countries (regulation of prices, distribution channels, access and reimbursement mechanisms).

These elements, combined with the social role that the pharmaceutical sector plays in terms of contribution to the healthcare system, are at the basis of the increasing attention of business and economic studies to this sector (Hepler, Strand, 1990).

In recent years, several literature contributions have analysed conditions, models and tools to improve approaches to protect and preserve collective health without negatively impacting on the economic performance of involved companies (Jackson, Marks, 1994). Specifically, the conditions that allow healthcare sector organizations to operate in respect with the principles of efficiency in order to ensure their survival (Folland et al., 2007) have been under focus. The problem is that companies that do not achieve adequate returns on investments in markets move away from them and create 'empty offering' in all areas not considered profitable although crucial for collective health (Scheinberg, Walshe, 1989).

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A significant example of this path is traceable in the phenomenon of Orphan Drugs. Orphan Drugs are drugs "that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need" (Sharma, Jacob, A., Tandon, & Kumar, 2010). Thus, an orphan drug is a "product that is potentially useful to treat a rare disease, but does not have a sufficient market to repay the costs of its development" (www.osservatoriomalattierare.it). Apparently, companies capable to produce these drugs have no economic interest to enter the market. This decision usually depends on two factors: (1) the process from the discovery of a new molecule to its marketing is long (average 10 years), expensive (several tens of millions of euro) and very uncertain (among ten molecules tested, only one may have a therapeutic effect); (2) the drug that treats a rare disease does not allow recovering the capital invested for its research & development (Scherer, 1993).

The low profitability of orphan drugs is due to the low incidence with which rare diseases occur. To date, however, more than 6000 types of orphan drugs have been identified, and each year 250 new diseases are described (www.eurordis.org). Empirical studies have shown that 25 million people in North America and 30 million in Europe are suffering from one of these diseases (Wastfelt et al., 2006). The majority of patients are children and a third of them dies in the first year of life (Crompton, 2002). Most of these diseases, often chronic, progressive and debilitating, has a genetic origin (70-80%), while the remainder is caused by infections, allergic and autoimmune disorders, poisoning and unknown causes (Rinaldi, 2005).

Table 1: *Orphan Drugs definitions and scenario*

Vela (2010)	**"Orphan drugs are medicinal products intended for diagnosis, prevention or treatment of rare or uncommon diseases. These drugs are recognized as "special" drugs, as a subcategory of legally accredited drugs. The definition of an orphan drug is related to the concept of rare diseases described in the EU Regulations (in special, Regulation (EC) n. 141/2000.4). Rare diseases are – according to the EU Law – those diseases which are life threatening or lead to chronic disability, and prevalence is less than 5 in 10.0005 citizens. In the United States the prevalence is lower: 7.5 in 10.000 (whereas in Japan it is at 4 in 10.000).**

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	According to USA Law, a rare disease cannot affect in the United States more than 200.000 citizens. A disease affecting more people can be considered a rare disease when it is not possible for a pharmaceutical laboratory, to recoup the cost of developing and distribution of this drug when selling it in the national territory" (pp. 217-218).
Abramawicz (2011)	"the distribution of sales of approved orphan drugs is highly skewed, with a small number of orphan drugs accounting for a high percentage of overall revenues" (p. 1393).
Mcguire et al. (2014)	"Orphan drugs are a riskier business venture than seeking new medicines for more prevalent diseases. The high costs of R&D, long lead times to market, legal restrictions and protection of intellectual property rights by patents, all act as barriers to entry of new manufacturers, and could well result in negative net present values. Clinical trials in particular require lengthy time periods before government agencies approvals, which has the effect of accruing significant expenses before earning income from sales, sometimes 10-15 years, which may be beyond an acceptable payback period. These a crude expenses are large opportunity costs which can discourage investment in R&D for other drugs that may have both higher and more immediate return on investment" (p. 5).

It has been noted, however, that "before the Orphan Drug Act, the research community was convinced that there was little chance of receiving FDA drug approval for a product to treat a rare disease. The drug was frequently given in open protocols to treat patients, and to "see if it works". With the stimulation of the Orphan Drug Act, philosophy has shifted. Manufacturers and sponsors are more familiar with developing drugs to treat very small populations; firms have been established primarily to develop orphan drugs; drug companies have become interested in producing treatment for orphan diseases. In some cases, sponsors of orphan products have gained access to funding or capital markets on the strength of an orphan product research grant or designation" (Marlene, 2001, p. 38).

On the basis of this introductory overview, with the aim to highlight the contribution of the managerial perspective to the debate on Orphan Drugs, in next sections the paper proposes: an analysis of the regulatory process of orphan drugs (par. 1.1); a short review of literature contributions on the topic (par. 1.2); an interpretation of the investigated phenomenon from the wider perspective of sustainable development (par. 2) and a first attempt to draw a

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possible conceptual model to support the paradigmatic change required in the management of orphan drugs (par. 3); final remarks on managerial and research implications (par. 4).

1.1 Regulatory of Orphan Drugs

According to European legislation (Regulation (EC) N. 141/2000 of the European Parliament and of the Council of Europe) the criteria for defining an orphan medicine are:

- That the drug is intended for the diagnosis, prevention or treatment of disease that leads to a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the Community [or]
- That the drug is intended for the diagnosis, prevention or treatment of a disease in the Community which involves a threat to the life, and that without incentives, the marketing of that product in the Community would not generate sufficient return to justify the necessary investment.

Considering the relevance of this type of drug and the impact that it has on people health conditions, along time policy makers have tried to define guidelines and criteria to stimulate research and development with reference to orphan drugs (www.orpha.net):

- In 1983 the United States was enacted the Orphan Drug Act. This law defines the ‘orphan’ drug in relation to the prevalence (frequency) of the disease for which has been indicated as a treatment in the American population. The concept of orphan drug in the United States is not limited to just pharmaceuticals or biological, but also covers medical devices and dietary products. It was created an office of orphan drugs in the FDA (Food and Drug Administration): the OOPD (Office of Orphan Products Development). Its task is to assist and encourage the provision of safe and effective products for the treatment of rare diseases. Giving a drug to the statute of ‘orphan’, it allows the promoter (sponsor) to benefit from the incentives for the dissemination of these products. These measures apply to all stages of drug development.
- In 1993, Japan revised the pharmaceutical law by introducing special provisions related to research and development of orphan drugs. According to these new provisions,

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orphan drug status can be granted to a drug, provided it fulfils the following two criteria:

- The disease for which it is required to use the drug must be incurable. There must not be possible alternative treatment, or efficacy and safety provisions of the drug should be excellent compared to other available drugs.
- The number of patients suffering from this disease must be less than 50,000.

- In 1997, Australia has approved the Australian Therapeutic Goods Administration (TGA) to transpose the indications coming from the US Food and Drug Administration (FDA) Orphan Drugs Program. The program establishes a series of fiscal and financial incentives for Orphan Drugs and it establishes that a drug is defined Orphan if intended to treat diseases that affect fewer than 2,000 patients.
- In 2000, Europe has adopted Regulation (EC) No. 141/2000 on orphan drugs whose objectives are:
  - To encourage the pharmaceutical and biotechnology industries to develop and market orphan drugs.

  To create a Committee of Orphan Medicinal Products (COMP) established within the European Medicines Agency (EMEA), responsible for examining applications for designation and to advise and assist the Commission in discussions concerning orphan drugs.

The process of developing and marketing orphan drugs can be divided into three steps (see Mehta, Beck, Sunder-Plassmann, 2006 for a complete description of the process):

- application for designation (a process based on assumption);
- application for protocol assistance (a science-driven process for optimal use of resources and conducting clinical trials);
- application for marketing authorization (a process based on demonstration of evidence).

The regulatory process of Orphan Drugs in Europe in summarized in Fig. 1.

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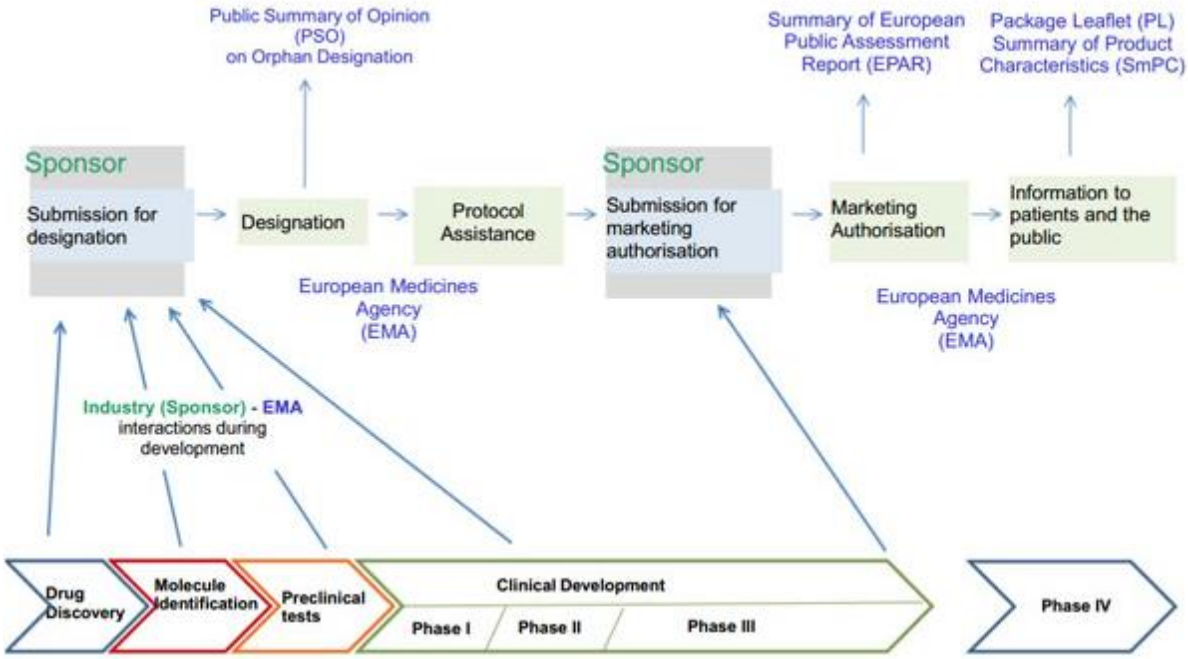
Figure 1: Orphan drug regulatory process in EU



Source: http://www.eurordis.org/it/content/promuovere-lo-sviluppo-di-farmaci-orfani

In Europe, in particular, to promote production and distribution of Orphan Drugs, the European Union has established a range of benefits including (Regulation (EC) n. 141/2000):

- *Exclusive marketing in Europe.* As result of the marketing authorization for an orphan drug by the EMA (European Medicines Agency) cannot be marketed competitive products for 10 years and, in the case of paediatric drugs, exclusivity trade is extended to 12 years.
- *Protocol assistance free.* The EMA provides free pharmaceutical companies that invest in the production and marketing of orphan drugs protocol assistance (scientific advice for orphan products), in the form of scientific advice on the various tests and the clinical trials required for drug development.

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- *Tax cuts.* During the process of approving the marketing of orphan drugs are granted tax breaks and exemptions for new drugs.
- *Research funded by the European Union.* The pharmaceutical companies developing orphan drugs may benefit from specific grants from the EU and from individual Governments.

Table 2: *A comparative overview of regulatory approaches to Orphan Drugs*

	Legal framework	***Affected population (on 10,000 individuals)***	***Exclusive sales***	***Funds for research***	***Technical assistance***	***Tax credit***
Asia	Orphan Drug Act (1983)	7,3	7	NIH programs	Yes	Yes
Japan	Orphan Drug Regulation (1993)		10	Government funds	Yes	Yes
Australia	Policy on orphan drug (1998)		5	No	No	No
Europe	Regulation (EC) N°141/2000 (2000)	6,8	10	National incentives	Yes	Managed by Countries

Source: Elaboration on Orphanet data

Despite the attention of national governments to the issue of Orphan Drugs, access to drugs for patients with rare diseases is still scarce. A study conducted by EURORDIS about the availability of 60 orphan drugs approved in 10 European Union Countries highlights that "in France, Netherlands and Denmark 90% of the 60 authorised OD are available, whereas in Spain, Greece and Romania only one-third of the authorised OD can be found on the market.

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A third intermediate group of countries comprising Italy, Hungary and Belgium have approximately two-thirds available" (EURORDIS, 2012).

1.2 Approaches and guidelines in the management of orphan drugs: a short literature review

The analysis of economic and legislative evolution of orphan drugs highlights the need for governmental intervention to ensure the achievement of collective health through direct intervention aimed to support research and production of those drugs that do not have the requirement of 'affordability' (Sharma et al., 2010).

In this perspective, "any analysis of how scarce resources for orphan-drug research should be allocated is simply a subset of the much larger inquiry into how scarce health-care resources should be allocated. Many moral philosophers have engaged this larger question. Some libertarian analysts who reject compelled redistribution of social goods generally have concluded that there is no social obligation to redistribute health-care resources" (Rai, 2002, p. 254).

Some scholars have stressed the contribution of moral theory in the definition of principles to guide the redistribution of resource in the healthcare sector (Braveman, Gruskin, 2003). They underline the incapability of traditional tools and models to address the need of aligning the economic and social perspectives (Godfrey, 2005); more specifically, they highlight the need of widening the view of consolidated models including in the managerial perspective variables that are not related only to the economic dimensions (Swayne et al., 2012). In this respect, it has been affirmed that "the aim of justice as fairness, then, is practical: it presents itself as a conception of justice that may be shared by citizens as a basis of a reasoned, informed, and willing political judgment" (Rawls, 1993, p. 9); accordingly, the need for a governmental intervention as a third part able to solve the *misalignment* between the interests of society and the economic aims of pharmaceutical companies is highlighted (Brezis, 2008).

It should be considered that the "prices of orphan drugs tend to be high due to a number of reasons. High prices may originate from marketing exclusivity, which gives a monopoly to

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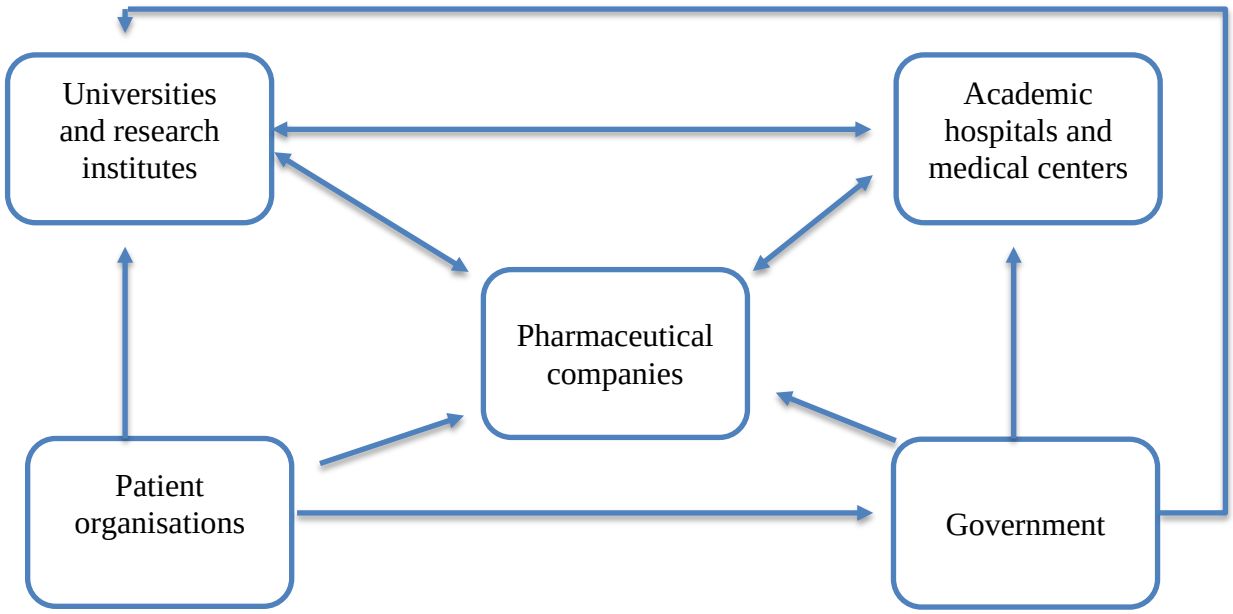
pharmaceutical companies. Also, the costs of research and development have to be recouped from a small number of patients. However, the lack of economic viability can be questioned for certain orphan drugs that have proved to be effective against multiple (sometimes non-orphan) diseases and, thus, target a larger number of patients" (Denis et al., 2010, pp. 177-178).

The processes related to orphan drugs, however, involve many actors engaged in not obly economic interests. Moors and Faber in 2007 propose the following classification:

- Universities and research institutes
- Academic hospitals
- Pharmaceutical companies
- Patients' organizations
- The government

Figure 2: Network of actors involved in the development of orphan drugs



Source: Moors, Faber, 2007, p. 341

A similar classification is a good starting point to analyze the situation from a structural perspective. A deeper analysis of finalities, interests and dominant schemes is necessary, however, to comprehend the logics that motivate and direct behaviours. Such analysis is

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necessary to identify possible areas of convergence and to direct decision makers in the search for possible pathways to combine the economic and the social perspectives.

Three basic categories of solutions have been identified so far (Lavandeira, 2002, p. 196):

1) *Marketing exclusivity* of the orphan drug; sponsors of this drug are granted a given period of marketing exclusivity during which no other drug will be approved for the disease in question;

2) The setting up of *tax credits and research aids*;

3) *Simplification* of and *advantages* in the drugs authorization procedure".

These solutions essentially take the economic perspective of companies and try to identify possible advantages for them to foster investment in the production and distribution of orphan drugs.

The approach then basically moves from an implicit assumption that conditions for sustaining the economic interest must be created. The way to solve the problem essentially follows a 'linear' logic, so limiting, in actual fact, the range of possibilities.

Trying to overcome these limited set of possible solutions, it is our opinion that a change in perspective is required going beyond dominant schemes that seems to necessarily imply the impossibility to identify an other than economic solutions to the problem or their inefficacy.

2. A 'beyond the scheme' interpretation of the Orphan Drug issue

The decision about the budget to spend in research on rare diseases, and on drugs used to treat them, is a moral dilemma (Resnik, 2001). Rare diseases by definition affect only a limited part of the population and the investment of resources for research activities related them could be considered not convenient from the utilitarian point of view because they do not maximize the benefits for the companies (Hernberg-Stahl, Reljanovic, 2013). At the same time, many people claim that public actors have the obligation to help who are suffering of rare diseases (Gericke *et al.*, 2005).

These moral obligations, in addition to the professional medicine aim to advance in scientific knowledge and research through new therapies, impact differently on the research and development of orphan drugs (Gericke et al., 2005).

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Analysing the assessment tools used in the healthcare sector, it is possible to note the dominance of an utilitarian approach oriented to identify indices to measure the impact of the initiatives undertaken on life expectancy and, simultaneously, on the quality of life (*Quality Adjusted Life Years, QALY* or *Disability Adjusted Life Years, DALY*).

No orphan drug would be valid in terms of cost-effectiveness with the application of these evaluation techniques due to:

- The rarity of the diseases to which they are intended (development costs should be recovered from the sale of a limited number of patients).
- The limited data available from clinical trials.

Given the current scenario of Orphan Drugs, therefore, there seems to be no way to reconcile the economic interests of pharmaceutical companies with the public healthcare needs.

Starting from the preliminary reflections proposed above, our aim is to identify key elements of a possible approach to Orphan Drugs that overcomes the limits of a strictly economic view. Of course, we do not simply refer to considering the social view that is at the basis of the whole issue of Orphan Drugs. We intend to focus on the problem of reconciling the different views, highlighting the necessity to widen the perspective to make apparent that dominant approaches may not effectively address the issues of Orphan Drugs and a more radical change is required that involve the way to see business and their role in current socio-economic scenario.

To this aim, we widen our focus bay adopting a view in which the problem of reconciling the economic and social perspectives is central. We refer to the *sustainability* and *sustainable development* view.

A representation of the integrated economic, social and environmental perspectives under the paradigm of sustainability is proposed in Figure 3.

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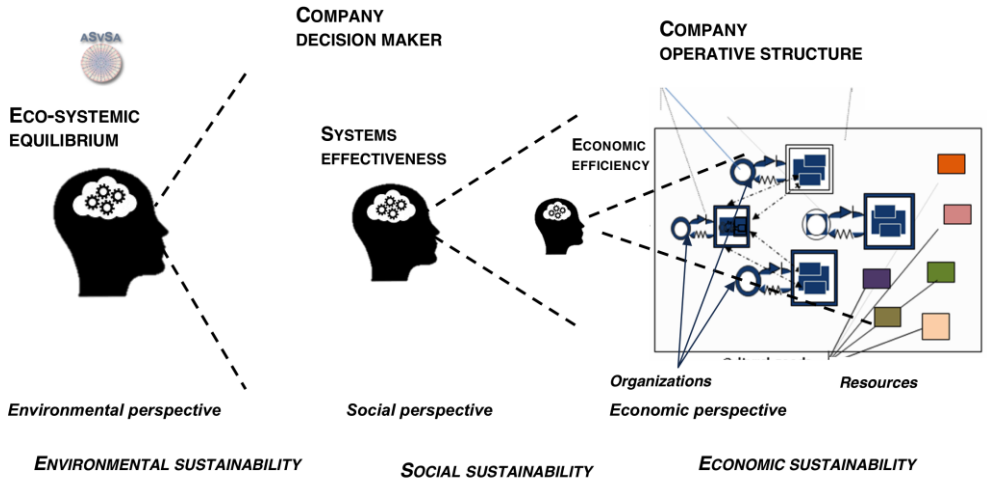
Figure 3: An integrated sustainability perspective of economic, social and environmental views.



Source: Saviano, 2015, www.asvsa.org

As shown in the figure, we think that the economic, social and environmental views that commonly generate trade-offs in decision making processes can be integrated under a wider view of sustainability (Barile et al., 2012; Saviano, 2015).

Regarding, more specifically, the context of Orphan Drugs, we know that major issues related to achieving health conditions for all populations involve pharmaceutical care and, more specifically, the access to drugs.

To clarify our point of view, in next section, we briefly outline fundamental orientations and trends in the context of the new worldwide engagement for Sustainable Development (SD) with specific reference to what is of interest for the pharmaceutical care.

2.1 The challenges of sustainable development to the pharmaceutical sector

The theme of sustainable development, and more generally of sustainability, has became central to multiple governmental, social and economic interests. Scholars, are ever more

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engaged in contributing to the transition towards a sustainable development capable of promoting wellbeing for all populations. Accepting the challenge of a more relevant role in society not only related to the governance and management of economic dynamics, business scholars are engaged as well in this challenge and focus on the issues of reconciling the economic, social and also environmental perspectives. A profound rethinking of current business models appears necessary (Pels et al., 2014; Saviano et al., 2010; Barile et al., 2015).

Sustainable development as construct originated in macroeconomic studies (Hanley 2000) and based on three principles –integrating environmental, economic prosperity and social equity (Barbier 1987; Elliott 2005)– is requiring many changes in the way of considering the approach to the market in order to include the dimension of common satisfaction (Bansal 2002, 2005; Dyllick and Hockerts 2002; Etzion 2007; Figge and Hahn 2005; Gladwin et al. 1995; Goodall 2008; Shrivastava 1995; Springett 2003; Westley and Vredenburg 1996).

Increasingly intense pressure from the international institutions pushes the actions of governments towards the achievement of a set of goals capable targeted to improving the quality of life communities, the equity in access to basic resources, and the careful management of available resources as defined in the *Sustainable Development Goals* framework *(SDGs)* (Bansal 2002).

Specifically, goal 3 of the current framework of SDGs is related to "ensure healthy lives and promote well-being for all at all ages" (https://sustainabledevelopment.un.org/sdg3). This goal is linked to the concept of health and, more generally, to the implementation of measures aimed to ensure equity in access to an adequate standard of living (Saith, 2006). In this regard, the *Osservatorio Italiano sulla Salute Globale (OISG)* underlines that to address a true human development, it is necessary to start from health as a synthesis of all stages of existence: education, work, gender balance, distribution of wealth and access to resources, social protection, self-determination and quality of a democracy.

In this scenario, the problem of Orphan Drugs has several implications not only from the ethical or moral point of view of the specific social issue of access to pharmaceutical care

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but also with reference to a more general involvement of businesses in the implementation of management models able to contribute to the achievement of the new set of SDGs.

The case of Orphan Drugs offers, from this perspective, a context in which new business models can be developed and experimented to identify a more general way to reconcile the multiple perspectives (social, environmental and economic ones ad a basis) involved in SD.

Essentially, Orphan Drugs pose the challenge to combine the rational dimension (profit, efficiency, effectiveness) with ethical and moral dimension (sustainability, equity, health for all) in economic and managerial processes.

In the next section, a possible conceptual framework is proposed to outline the issue of Orphan Drugs within the wider context of a deep rethinking of dominant business models in a changing scenario in which the sole consideration of economic perspective results not only inadequate to meet emerging needs but also ever less satisfactory for business to effectively compete.

3. Towards a possible framework for addressing the challenge of Orphan Drugs

It is widely agreed that business models –and more generally to economic activities– cannot simply pursue the goals of profit and return on capital maximization (Jensen and Meckling, 1976) but must respond to a wider set of expectations of various stakeholders (Friedman, 1970).

The definition of any economic strategy should adequately consider all the following dimensions (Pels et al., 2013):

- *Contextualization* as profound knowledge of market and its needs;
- *Understanding* as process that starting from a market allows the observer to provide its explanation of the phenomena under investigation;
- The *continuous evolution* of the systems operating in the observed context.

The consideration of these dimensions leads to add to the traditional markets strategy – *Market Adaptation*, *Mission Focus*, *Disruptive Innovation* – the *Inclusive Development* strategy (Sheth, Pels, 2013) as a business model in which the primary goal of firms becomes the inclusion of community interest (Figure 4).

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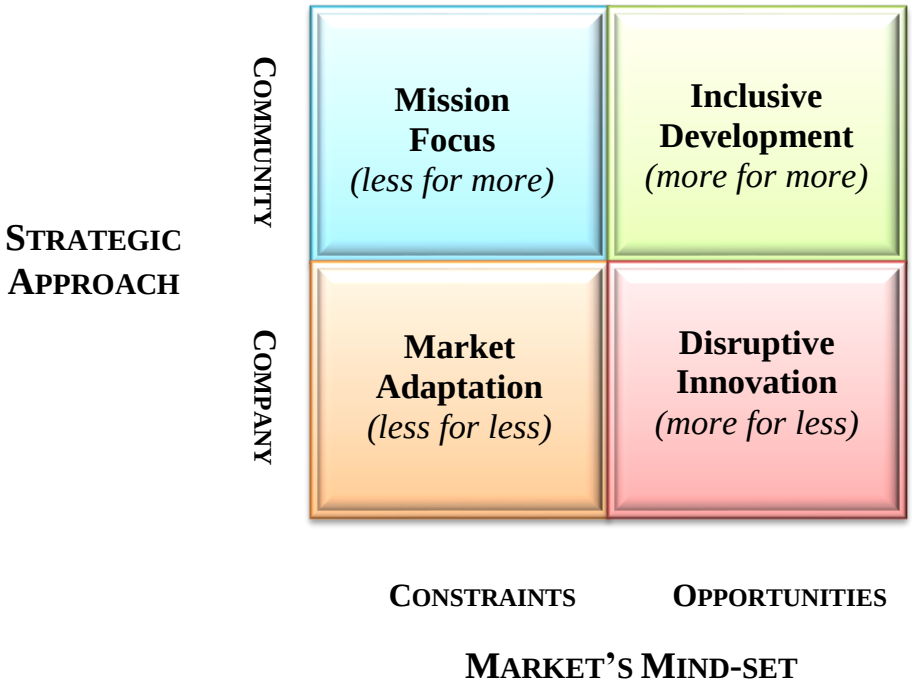
Figure 4: *Market Strategies*



Source: Our Elaboration from Pels *et al.*, 2014, p. 7

The *Inclusive Development* strategy is the result of a change based on the identification of market opportunities deriving from the inclusion of the community perspective. Unlike the *Mission Focus* strategy, it does not focus on specific aspects of the market but the attention is directed to the inter-relationships between the parties. At the same time, the Inclusive Development strategy is similar to *Disruptive Innovation* strategy because it proposes new business models but – differently from Disruptive Innovation – it seeks to harmonize internal resources of company with the resources of context in order to promote behaviours aimed at sharing and value co-creation (Pels et al., 2014).

The paradigm shift on which Inclusive Development is based offers a viable path for the growth and development of the economy as well as for the resolution of ethical-moral problems (such as those related to Orphan Drugs). Significant examples of the validity of

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this strategy can be traced in the economy of 13 States as shown by the data of the study conducted by the Commission on Growth and Development (see Table 3).

Table 3: *13 Success Stories of Sustained, High Growth*

Economy	Period of high growth**	Per capita income at the beginning and 2005***	
Botswana	1960-2005	210	3,800
Brazil	1950-1980	960	4,000
China	1961-2005	105	1,400
Hong Kong, China*	1960-1997	3,100	29,900
Indonesia	1966-1997	200	900
Japan*	1950-1983	3,500	39,600
Korea*	1960-2001	1,100	13,200
Malaysia	1967-1997	790	4,400
Malta*	1963-1994	1,100	9,600
Oman	1960-1999	950	9,000
Singapore*	1967-2002	2,200	25,400
Taiwan, China*	1965-2002	1,500	16,400
Thailand	1960-1997	330	2,400

*Economies that have reached industrialized countries' per capita income levels.
**Period in which GDP growth was 7 percent per year or more.
***In constant US$ of 2000.

Source: Commission on Growth and Development, 2008, p. 20

The adoption of an inclusive development view in the problematic context of orphan drugs (focus is no longer on the individual parts but on the interrelation among them) leads to fade away the differences between businesses, consumers, profit and non-profit sectors, etc. (Prahalad, 2004) allowing to "redefining the contours of the business" (Márquez et al., 2010, p. 318). The change in the approach to market could favour the emergence of a win-win logic based on the "deeper appreciation of societal needs, a greater understanding of the true bases of company productivity, and the ability to collaborate across profit/nonprofit boundaries" (Porter, Kramer, 2011, p. 62). The ultimate goal becomes the generation of

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value for all stakeholders and therefore also the satisfaction of those needs that do not produce profits for companies (e.g. Orphan Drugs). A new horizon is possible as shown by the numerous cases of successful implementation of Inclusive Development strategies as the Nigerian initiative Zidisha (Table 4).

Table 4: *Zidisha - An example of successful inclusive development strategy*

"Zidisha was founded to see how far this idea of using the Internet to make geography irrelevant can go. We use technology to connect internet-capable young adults in the world's poorest places with a global market for person-to-person loans - an eBay-style marketplace where borrowers transact directly with lenders and raise the funding they need to grow their small businesses, limited only by their own track record of responsible repayment. Since we do not outsource loan management to local banks, the cost to borrowers is far lower than what has traditionally been possible for traditional microfinance. As a result, living in an unlucky part of the world need no longer put a ceiling on our members' ambitions. They can connect to Zidisha regardless, using technology to bypass hitherto insurmountable local obstacles. Zidisha is pioneering something radically new, continuously learning and adapting our model as we gain experience. Our community is the work of hundreds of volunteers and thousands of lenders and borrowers in every continent, who are fed up with a world that shuts people out of opportunity because of their location. We've many transformed many thousands of lives through the opportunities created by connecting people to people".

Source: ****

4. Concluding remarks

This paper proposes preliminary reflections of what we have called a 'beyond the schemes' approach to frame the issue of Orphan Drugs as a problem that appears to us emblematic of a far wider necessity emerging from the current socio-economic worldwide scenario.

We essentially suggest to change the way to frame the problem of Orphan Drugs, abandoning a 'linear thought' logic, and highlight the need to rethink traditional business models in the light of emerging trends that appear to direct towards a more radical change. A change towards the adoption of a shared view of a more sustainable and inclusive development. A view that must be shared not only among economic actors, but by them

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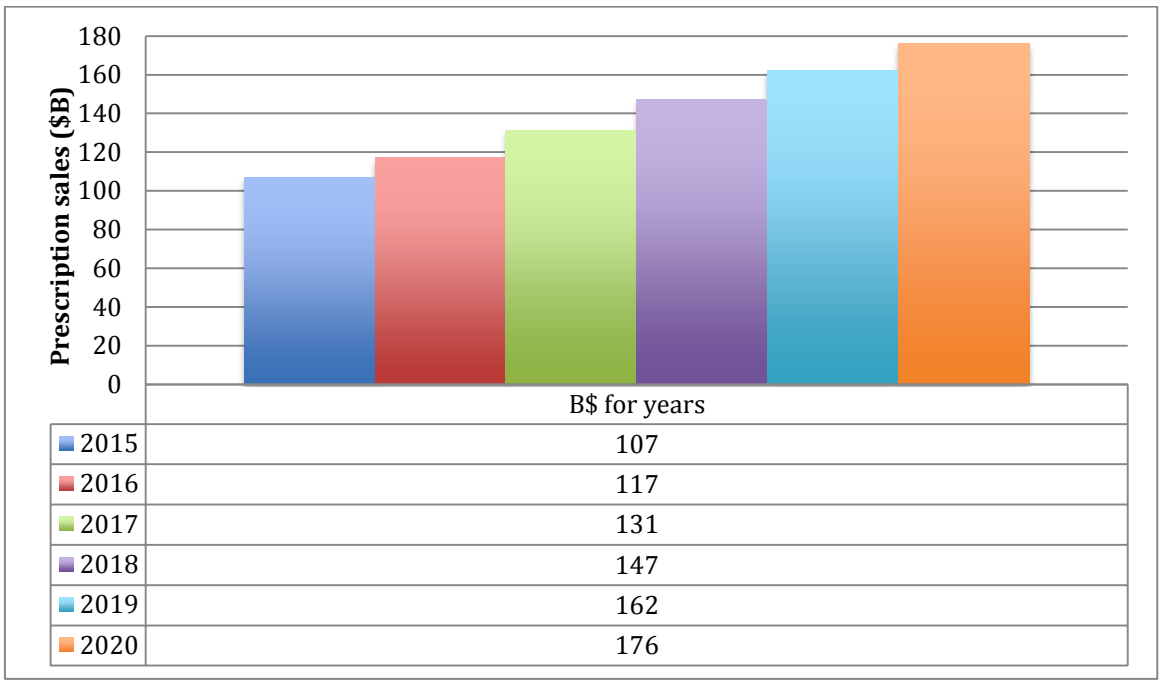
together with governments, the scientific and academic world and the society itself, in the transition from the traditional win-lose logic to a new inclusive win-win logic (Barile et al., 2013; Saviano, Caputo, 2013).

In this perspective, the 'problem' of Orphan Drugs becomes a 'case study' useful to analyze situations in which companies must broaden their perspective combining rational dimension with ethics and morality (Golinelli *et al*., 2012; Saviano *et al*., 2014) but not in traditional aid or philanthropic logics. This view requires further multi-disciplinary research to deeply analyze the conditions for such a relevant change.

As for the economic and managerial implications of our interpretation, opportunities clearly appear considering that, as shown in Figure 5, "the orphan drugs sales will grow at an annual rate of 11% and constitute 19% of the total share of prescription drugs by 2020, totalling 176 billion dollars" (Gerritse, 2015).

Figure 5: *Prevision on Worldwide Orphan Drug sales in Billions of Dollars*



	B$ for years
2015	107
2016	117
2017	131
2018	147
2019	162
2020	176

Source: Elaboration from Vaczek, 2014, p. 10

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Many challenges arise from ongoing changes that requires a deep rethinking of current business models of pharmaceutical companies within the whole socio-economic context of healthcare (Gerritse, 2015):

- Complex and changing national and regional regulations;
- Clinical trial design and finding & keeping patients;
- The lack of a central database designed specifically to list patient registries, which asks for close stakeholder engagement;
- Partnering and establishing financing for future development;
- Establishing a foundation for price that is balanced and sustainable;
- Achieving an efficient and timely access to market with equal access for patients around the world;
- Achieving timely and correct diagnosis to enable higher quality of life and more time and information for developers.

All these challenges, indeed, in the proposed changed perspective, can easily be viewed as opportunities to redefine the role of business in the whole environmental and socio-economic context of our world.

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